Effectiveness of screening for atrial fibrillation and its determinants. A meta-analysis

Pawel Petryszyn\textsuperscript{1}*, Piotr Niewinski\textsuperscript{2}, Aleksandra Staniak\textsuperscript{1}*, Patryk Piotrowski\textsuperscript{3}, Anna Well\textsuperscript{1}*, Michal Well\textsuperscript{1}, Izabela Jeskowiak\textsuperscript{1}, Gregory Lip\textsuperscript{4‡}, Piotr Ponikowski\textsuperscript{2‡}

\textsuperscript{1} Department of Clinical Pharmacology, Wroclaw Medical University, Wroclaw, Poland, \textsuperscript{2} Department of Heart Diseases, Wroclaw Medical University, Wroclaw, Poland, \textsuperscript{3} Department of Psychiatry, Wroclaw Medical University, Wroclaw, Poland, \textsuperscript{4} Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, United Kingdom

* These authors contributed equally to this work.
‡ These authors also contributed equally to this work.
* ppetryszyn@wp.pl

Abstract

Background

Many atrial fibrillation patients eligible for oral anticoagulants are unaware of the presence of AF, and improved detection is necessary to facilitate thromboprophylaxis against stroke.

Objective

To assess the effectiveness of screening for AF compared to no screening and to compare efficacy outcomes of different screening strategies.

Materials and methods

Cochrane Central Register of Controlled Trials, EMBASE and MEDLINE from Jan 1, 2000 – Dec 31, 2015 were searched. Studies employing systematic or opportunistic screening and using ECG or pulse palpation in populations age ≥40 years were included. Data describing study and patient characteristics and number of patients with new AF were extracted. The outcome was the incidence of previously undiagnosed AF.

Results

We identified 25 unique (3 RCTs and 22 observational) studies (n = 88 786) from 14 countries. The incidence of newly detected AF due to screening was 1.5% (95% CI 1.1 to 1.8%). Systematic screening was more effective than opportunistic: 1.8% (95% CI 1.4 to 2.3%) vs. 1.1% (95% CI 0.6 to 1.6%), p<0.05, GP-led screening than community based: 1.9% (95% CI 1.4 to 2.4%) vs. 1.1% (95% CI 0.7 to 1.6%), p<0.05, and repeated heart rhythm measurements than isolated assessments of rhythm: 2.1% (95% CI 1.5–2.8) vs. 1.2% (95% CI 0.8–1.6), p<0.05. Only heart rhythm measurement frequency had statistical significance in a multivariate meta-regression model (p<0.05).
Conclusions
Active screening for AF, whether systematic or opportunistic, is effective beginning from 40 years of age. The organisation of screening process may be more important than technical solutions used for heart rhythm assessment.

Introduction
Atrial fibrillation (AF) is the most common sustained arrhythmia with the prevalence estimated at 2% of the total adult population[1]. Over the last two decades the prevalence of reported AF has increased by 13% and epidemiological studies predict further increases related mostly to the ageing of the society[2]. AF carries a substantial risk of thromboembolism, heart failure and mortality[3]. These risks of complications related to AF can be substantially decreased by introduction of appropriate treatment. This has been repeatedly demonstrated for oral anticoagulants (OACs) and acute ischemic stroke[4,5]. The nonvitamin-K antagonist OACs may further improve outcomes and decrease the risk of intracranial bleeding[6]. Due to lack of symptoms a significant proportion of patients suffering from AF are unaware of their arrhythmia[7].

Screening for AF aimed at early detection of asymptomatic individuals appears to be so important as it enables the implementation of an early intervention and changes the prognosis. According to the current ESC guidelines opportunistic screening for AF is recommended in patients >65 years with the use of pulse-taking or an electrocardiogram (ECG)[8]. The STROKESTOP study findings suggest that systematic screening based on repeated short ECG recordings results in satisfactory yield for AF detection in elderly individuals[9].

It is currently unclear which of these two screening methods is more effective in detecting previously undiagnosed AF. Other factors might also influence the efficiency of the screening process. First, different technical modalities may be employed for the screening, including standard 12-lead ECG, various portable devices recording data other than 12-lead ECG and pulse palpation. Second, organisation of the screening process may vary (GP-led vs. community-based approach).

In this systematic review and meta-analysis we aimed to: (1) assess the effectiveness of active screening for previously undiagnosed AF and (2) investigate various aspects of the screening programme.

Methods
The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram and checklist (S1 Table) [10]. Details of the protocol for this systematic review were registered on PROSPERO and can be accessed at https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017067507

Literature search
Relevant studies were identified by searching multiple databases including Cochrane Central Register of Controlled Trials, EMBASE and MEDLINE (PubMed). Keyword search terms were ‘atrial fibrillation’ AND (‘mass screening’ OR ‘screening’ OR ‘detection’ OR ‘case finding’) AND (‘pulse’ OR ‘electrocardiography’ OR ‘ecg’ OR ‘electrocardiogram’). Embase database was searched as follows: #1 ‘atrial fibrillation [definition]’ OR ‘atrial fibrillation [Title/
Abstract, #2 ‘mass screening’ [definition] OR ‘mass screening’ [Title/Abstract] OR ‘screening’ [Title/Abstract] OR ‘detection’ [Title/Abstract] OR ‘case finding’ [Title/Abstract], #3 ‘pulse rate’ [Definition] OR ‘pulse rate’ [Title/Abstract] OR ‘electrocardiogram’ [Definition] OR ‘electrocardiography’ [Title/Abstract] OR ‘ecg’ [Title/Abstract], #4 ‘#1 AND #2 AND #3’. Search terms for MEDLINE and EMBASE with corresponding publication numbers can be found in the S1 Appendix. The search was constrained to the period January 1, 2000 –Dec 31, 2015. No language or other limitations were applied. Reference lists of all included papers were searched to identify potentially relevant articles, so the Internet handsearching was performed.

Criteria for considering studies
All randomised controlled trials (RCTs) and observational studies comparing screening for AF to no screening were eligible for inclusion. Studies with historical control and in which there was only an intervention arm were also qualified. Case series and review articles were excluded.

Eligible participants were men and women ≥40 years living in community or attending GP practices. People with implanted pacemaker or defibrillator likewise any specific groups like athletes were excluded. Patients with previous stroke or TIA were considered only if they constituted a proportion of the larger population. Patients with the prior diagnosis of AF were excluded from the final number of newly diagnosed AF cases.

Studies eligible for inclusion compared systematic or opportunistic screening programmes to no screening in the control or pre-intervention group. “No screening” was defined as a passive approach towards the diagnosis of AF. The latter indicating that the diagnosis was made either incidentally or following presentation with symptoms of arrhythmia over the study period. “Systematic screening” was defined as screening carried out in all people over a certain age or in a particular sub-group. “Opportunistic screening” was defined as screening performed in patients attending medical professional for another reason. The term “active screening” encompasses both systematic and opportunistic screening and means searching for AF in opposition to passive case-finding in people with symptoms or signs of AF referred to here as “no screening”. Screening might have been led by primary care physicians in their local practices (using their facilities) or taken place in community, i.e. in the form of health program, in which different medical centres participated. A detection method of AF in the intervention group could consist of pulse palpation, ECG (less than 12-lead and 12-lead) and the use of some other wearable devices. The heart rate could be checked only once or repeatedly, and the programme could be designed as a one- or multi-step process. The diagnosis of AF needed to eventually be confirmed using 12-lead ECG interpreted by an appropriately trained GP or a cardiologist.

The primary outcome was the incidence of previously undiagnosed AF as the result of screening or the difference in the incidence between the intervention and control (pre-intervention) group. The secondary outcomes comprised the identification of factors influencing the effectiveness of screening, as well as the eligibility of newly detected AF for stroke thromboprophylaxis (assessed with the use of CHADS2 or CHA2DS2-VASc scales).

Data collection and analysis
Preliminary screening of retrieved abstracts in order to eliminate irrelevant studies was performed by two authors (AS, PP). All except two authors (GL, PPO) assessed full texts for eligibility. Multiple reports from the same study were identified. Data from published reports was extracted using a prespecified data collection form. Data describing study and patient
characteristics, number of patients in intervention and control arm, number and percent of patients with new AF, median CHA\textsuperscript{2}DS\textsubscript{2}-VASc score, percentage of patients scoring ≥2 and data necessary to perform risk of bias assessment were extracted. Risk of bias assessment was performed by two authors (AS, PP). Disagreements were resolved by discussion with all other authors. Randomized controlled studies were assessed according to the Cochrane Collaboration’s tool and in prospective cohort studies the Newcastle-Ottawa Scale was adopted.

For any individual study a risk difference was calculated. In single-arm studies the risk in control group was assumed to be 0. An intention-to-treat analysis to estimate new AF incidence was conducted, the denominator being all patients qualified to (be screened) who were eligible and consented, even if differently assessed in original study reports.

The methodological (study design, quality) and clinical (population, setting, systematic vs. opportunistic screening) heterogeneity was assessed. It was decided to perform meta-analysis to estimate new AF incidence as a result of screening using data collected from all eligible studies and to address the heterogeneity in subgroup and sensitivity analysis. Statistical heterogeneity was evaluated with Cochran’s Q-statistic and quantified with the I\textsuperscript{2} statistic. Whenever tests for heterogeneity revealed that variations between the studies were statistically significant (P < 0.05 or I\textsuperscript{2} ≥ 50%), a random-effects model was used. Subgroup analyses were carried out as follows: cut-off age: >64 vs. <65 years old, setting: GP vs. community, type of intervention: pulse palpation vs. ECG, 12-lead ECG vs. less than 12-lead ECG, systematic vs. opportunistic screening, heart rhythm measurement frequency: repeated vs. only once, randomized clinical trials vs. observational studies. In addition, five potential sources of heterogeneity: age, screening setting, ECG vs. pulse palpation, systematic vs. opportunistic screening and heart rhythm measurement frequency were tested by meta-regression in a multivariate meta-regression model. In sensitivity analysis studies in which recruited participants had to have one of the following: AF or stroke risk factor, heart disease (coronary heart disease, congestive heart failure) were excluded. Egger’s test and Begg’s funnel plot were used to evaluate the publication bias.

All statistical analyses were performed using Statistica version 12.0 (StatSoft, Tulsa, US) and all tested P values < 0.05 were considered statistically significant.

Results

Details of the study selection are presented in Fig 1. Table 1 displays the characteristics and outcomes of included studies. 25 studies that were included came from 14 countries. Participants were recruited from GPs (10 studies) or community (15 studies). Concerning the study design, these included 3 randomized clinical trials [11–13], 4 prospective cohort studies with randomization [9,14–16], 13 prospective cohort studies [17–29], 4 cross-sectional studies [30–33], and one case-control study[34]. The total number of participants was 88,786 with weighted mean age of 58.6 and 46.4% were males. The lower age limit for recruitment varied widely across studies with 13 studies limiting recruitment to >64 years [9,11,12,14,15,17–24,28,30]. In 5 studies [13,18,21,25,26] recruited participants had to have one of the following: AF or stroke risk factor, heart disease (coronary heart disease, congestive heart failure) were excluded. The most common exclusion criteria were: atrial fibrillation or atrial flutter, prior stroke, transient ischemic attack, implantable pacemaker or defibrillator, terminal illness or severe cognitive impairment.

In 14 studies [9,11–16,20,23,26–29,33] screening was conducted systematically, whereas in 13 studies [11,12,17–19,21,22,24,25,30–32,34] it was done opportunistically. In the SAFE study [11] there were two screening arms: systematic and opportunistic. Similarly, in the RCT Morgan 2002 [12] systematic and opportunistic groups were compared. These were analysed separately for the calculation of main outcome in subgroup analysis. Screening modalities differed between studies: in 11 [11,13,16,19–21,23,27,29,33,34] it was a 12-lead ECG; in 9
In total, 1056 articles were found. A primary screen of the abstracts resulted in the exclusion of 947 records. A further 82 were excluded based on the full-text review. This produced 27 articles that met inclusion criteria though representing 25 unique (3 RCTs and 22 observational) studies.

https://doi.org/10.1371/journal.pone.0213198.g001
Table 1. Characteristics and outcomes of included studies.

| Study          | Country       | Study design                  | Population cut-off age (mean); setting                      | Intervention                                                                 | N   | New AF (%) |
|---------------|---------------|-------------------------------|-------------------------------------------------------------|-------------------------------------------------------------------------------|-----|-------------|
| Smyth 2015 [17] | Ireland       | Prospective cohort            | >64 years (75.1); GP                                        | Pulse palpation, repeatedly, opportunistic                                    | 7262 | 55 (0.8)   |
| Svennberg 2015 [9] | Sweden       | Prospective cohort, randomisation | 75–76 years (75.5); community                               | Less than 12-lead ECG, repeatedly, systematic                                | 7173 | 218 (3.0) |
| Bury 2015 [14]  | Ireland       | Prospective cohort, randomisation | ≥70 years (78); GP                                         | Less than 12-lead ECG, only once, systematic                                  | 566  | 12 (1.2)   |
| Turakhia 2015 [18] | USA          | Prospective cohort            | ≥55 years (69); outpatient clinic                           | Less than 12-lead ECG (Zio wearable patch-based device), repeatedly, opportunistic | 75   | 4 (5.3)    |
| Benito 2015 [13] | Spain         | RCT                           | (69), primary healthcare centre                           | 12-lead ECG, repeatedly, systematic (intervention group)                     | 463  | 11 (2.4)   |
| Lowres 2014 [30] | Australia     | Cross-sectional               | ≥ 65 years (76); community                                 | Less than 12-lead ECG, only once, opportunistic                              | 1000 | 15 (1.5)   |
| Javed 2014 [22]  | UK            | Prospective cohort            | >65 years (69.7); GP                                       | Less than 12-lead ECG, only once, opportunistic                              | 6856 | 54 (0.8)   |
| Van Mourik 2014 [23] | Netherlands | Prospective cohort            | ≥65 years (75.5); GP                                       | 12-lead ECG, only once, systematic                                            | 389  | 7 (1.8)    |
| Virtanen 2014 [15] | Finland      | Prospective cohort study, randomisation | ≥75 years (79); community                             | Pulse palpation, repeatedly, systematic                                        | 205  | 4 (1.9)    |
| Clua-Espuny 2013 [16] | Spain       | Prospective cohort, randomisation | >60 years; GP                                             | 12-lead ECG, only once, systematic                                          | 1043 | 23 (2.2)   |
| Rhys 2013 [24]  | UK            | Prospective cohort            | ≥65 years; community                                       | Pulse palpation, only once, opportunistic                                    | 573  | 2 (0.3)    |
| Hendriks 2013 [25] | Sweden       | Prospective cohort            | (69.8); GP                                               | Less than 12-lead ECG, repeatedly, opportunistic                              | 928  | 35 (3.8)   |
| Wiesel 2013 [26] | USA           | Prospective cohort            | >64 years or those with hypertension, diabetes, congestive heart failure, or previous stroke (67); GP | Less than 12-lead ECG (AF-BP monitor), repeatedly, systematic              | 139  | 2 (1.4)    |
| Frewen 2013 [27] | Ireland       | Prospective cohort            | ≥50 years (63.8); community                               | 12-lead ECG, only once, systematic                                            | 4890 | 45 (0.9)   |
| Sanmartin 2013 [28] | Spain        | Prospective cohort            | ≥65 years; community                                       | Pulse palpation, only once, opportunistic                                    | 1532 | 17 (1.1)   |
| Claes 2012 [31]  | Belgium       | Cross-sectional               | ≥40 years (59); community                                 | Less than 12-lead ECG, only once, opportunistic                              | 10   | 167 (1.6)  |
| Schnabel 2012 [33]  | Germany      | Cross-sectional               | (52.2); community                                         | 12-lead ECG, only once, systematic                                            | 5000 | 25 (0.5)   |
| Doliwa 2009 [32] | Sweden        | Cross-sectional               | Community                                                 | Less than 12-lead ECG, only once, opportunistic                              | 606  | 6 (1.0)    |
| Yap 2008 [29]    | Singapore     | Prospective cohort            | ≥55 years; community                                       | 12-lead ECG, only once, opportunistic                                        | 1839 | 16 (0.9)   |
| Kim 2007 [34]    | Korea         | Case-control                  | (49_median); community                                    | 12-lead ECG, repeatedly, opportunistic                                        | 16   | 568 (2)    |
| Fitzmaurice 2007 [11]  | UK           | RCT                           | ≥65 years (75.3); GP                                       | 12-lead ECG, only once, systematic                                            | 4562 | 74 (1.62)  |
| Minami 2007 [19] | Japan         | Prospective cohort            | (51); community                                           | 12-lead ECG, only once, opportunistic                                        | 722  | 5 (0.7)    |
| Scalvini 2005 [20] | Italy        | Prospective cohort            | (61); GP                                                  | 12-lead ECG, repeatedly, systematic                                          | 7516 | 271 (3.6)  |
| Rockman 2004 [21] | USA           | Prospective cohort            | >60 years (70.8); community                               | 12-lead ECG, only once, opportunistic                                        | 610  | 3 (0.5)    |

(Continued)
[9,14,18,22,25,26,30–32] less than 12-lead (1-3-lead) ECG; and in 7 [11,12,15,17,24,28] pulse palpation, usually followed by ECG if the pulse was irregular. In 17 studies [11,12,14,16,19,21–24,27–33] there was only one heart rhythm measurement performed, while in 10 [9,11,13,15,17,18,20,25,26,34] studies the rhythm was taken several times within a certain time period.

Risk of bias in included studies

Overall quality of non-randomized studies was moderate, according to the Newcastle-Ottawa Scale. In four studies [18,21,25,26] the population was not representative of the average population. In one study [15] it was not possible to objectively confirm whether screening actually took place. In two studies [27,34] it was possible to include patients with already known AF in the main outcome assessment. In three studies [18,31,32] the diagnosis of AF was not confirmed in an objective or blinded fashion, i.e., by the 12-lead ECG interpreted independently by a cardiologist. Only in eight studies [9,15,17,18,20,25,26,34], in which heart rhythm measurements were being repeated, follow-up was considered long enough for outcome to occur. In one study [23] the proportion of patients eligible for and agreeing to screening who actually were screened did not exceed 80%. In two randomised trials [11,12] risk of bias assessed according to the Cochrane Collaboration’s tool was relatively low and in one [13]–relatively high. The details of risk of bias assessment are presented in the Tables A–D in S2 Appendix.

Effects of interventions

**Newly identified AF.** The incidence of newly detected AF was 1.5% (95% CI 1.1–1.8%) (Fig 2). The hypothesis about the homogeneity of the studies was rejected therefore a random effects model was implemented (Q = 534, p < 0.05, I^2 = 95.13%).

**Age cut-off for screening.** When screening was limited to participants from studies with entry cut-off ≥65 years (mean age 67.2 years), the incidence was 1.5% (95% CI 1.0–2.0%) as compared to 1.4% (95% CI 1.0–1.9%) among participants from studies where entry cut-off was 40–64 years (mean age 52.2 years). This difference was not statistically significant (Table 2).

**Stroke risk.** CHA2DS2-VASc score, which describes the risk of thromboembolic complications, was reported in 11 studies [9,13,14,16–18,24,27,30,31,33], in one study [25] CHADS2 score was calculated. In 9 studies [9,13,14,17,18,24,25,30,33] the stroke risk for previously unknown AF was reported separately. In all 9 studies, median CHA2DS2-VASc score or CHADS2 score was not lower than 2. A vast majority of patients with newly detected AF (90.9–100%) scored ≥2, which made them eligible for OACs.

**Screening setting.** AF incidence was significantly higher in the GP setting than the community setting: 1.9% (95% CI 1.4–2.4%) vs. 1.1% (95% CI 0.7–1.6%), p < 0.05 (Fig 3).

**ECG vs. pulse palpation.** Different screening techniques were compared one to each other and no statistical differences were found whether pulse palpation or ECG was used as a
primary screening modality (1.3% vs. 1.6%, respectively). 12-lead ECG was numerically worse compared to strategies other than 12-lead ECG in identifying new AF cases, but this difference again was not significant: 1.3% vs. 1.9%.

Systematic vs. opportunistic screening. The incidence of newly detected AF was significantly higher in studies in which screening was organized in a systematic way in contrast to studies where it was opportunistic: 1.8% (95% CI 1.4–2.3%) vs. 1.1% (95% CI 0.6–1.6%), p<0.05 (Fig 4).

When studies were subdivided in relation to screening technique and screening organizational process, the differences, though not significant, tended to be greater between systematic screening vs. opportunistic screening groups than between pulse palpation-based vs. ECG-based groups (Table 2).

Single vs. repeated measurements. Studies in which heart rhythm was measured repeatedly within a certain time period as opposed to a single measurement reported significantly higher new AF incidence: 2.1% (95% CI 1.5–2.8%) vs. 1.2% (95% CI 0.8–1.6%), p<0.05 (Fig 5).

Study design. The incidence of newly identified AF was not different in RCTs in comparison with observational studies: 1.8% (95% CI 1.0–2.5%) vs. 1.4% (95% CI 1.0–1.8%), p>0.05.

Fig 2. Meta-analysis of new AF incidence due to screening. Three randomized trials and 22 observational studies were included. The total number of participants was 88,786. Heterogeneity was high at I² = 95.13% (Q = 534, p<0.05). The incidence of newly detected AF was 1.5% (95% CI 1.1–1.8%). AF—atrial fibrillation.
Sensitivity analysis

In sensitivity analysis we excluded studies in which recruited participants had to have either of the following: AF or stroke risk factor, coronary heart disease, congestive heart failure [13,18,21,25,26]. However, the incidence of new AF was grossly unchanged and equalled 1.4% (95% CI 1.0–1.8%).

Meta-regression analysis

Results of the meta-regression analysis are presented in Table 3. Only heart rhythm measurement frequency had statistical significance in the multivariate model (p<0.05).

Publication bias

Asymmetric Begg’s funnel plot of newly identified AF together with the result of Egger’s test (p = 0.002) suggested the presence of publication bias. Using “trim and fill” method, four potentially missing studies were imputed on the left side of the funnel plot, yielding an adjusted risk difference of 1.2% (95% CI 0.8–1.5%) (Fig 6).

Discussion

In this systematic review and meta-analysis of contemporary studies, our principal findings are as follows: (i) active screening for previously undiagnosed AF is more effective than no screening in terms of detection of new cases of AF in various populations of patients above 40 years of age; (ii) the incidence of “silent” AF in the current study was 1.5% which is consistent with the previous report [35]; and (iii), the organisation of screening process may be more important than technical solutions used for heart rhythm assessment.

In the present meta-analysis we analysed results of 25 studies employing different screening modalities and approaches. This allowed for the comparison of various aspects of the screening process. Such assessment was not possible in earlier review by Moran et al.[36] due to strict inclusion criteria resulting in analysis of only one randomized controlled trial. Two recent
systematic reviews differed from our work due to higher age cut-off (≥65 years) for patients included in analysed studies or exclusion of non-randomized studies. Nonetheless, both reviews reported superiority of screening comparing to no screening for detection of previously undiagnosed AF[37,38].

Superiority of the systematic approach in identifying previously undiagnosed AF was shown in the subgroup analysis of the current meta-analysis. Interestingly, higher efficiency of systematic vs. opportunistic screening did not depend on the age-cut off in meta-regression analysis. It suggests that systematic screening programmes may also be effective when addressed towards individuals younger than septuagenarians and octogenarians.

When comparing systematic and opportunistic approach it should be noted that the results of SAFE trial questioned the cost-effectiveness of the systematic screening [11,39] performed in broad group of patients age ≥65 years. However, the analysis of STROKESTOP study showed that if carried out in precisely targeted population (75 to 76-years-old) the systematic approach may well be cost-effective[40].

In our analysis, we also divided analysed studies into two groups based on the age cut-off: (1) below 65 years and (2) equal or above 65 years. This particular cut-off was chosen in accordance to ESC guidelines[8]—recommendation based on the entry criteria and the results of
SAFE study[11,39]. We found no difference in terms of the effectiveness of screening aimed at patients ≥65 in comparison to screening employing lower cut-offs of age. However, it must be noted that actual mean age of participants in these two groups of studies while undoubtedly different (52.2 vs. 67.2 years) was still relatively low. Furthermore, while shifting down the cut-off age for the participation in screening programmes to values between 40 and 65 years might result in a similar detection rate of new AF (and thus higher absolute number of new cases), it might not necessarily be a cost-effective approach as significant proportion of patients below 65 years will not require oral anticoagulation due to low CHA$_2$DS$_2$-VASc scores[8]. This aspect was not assessed in our analysis.

Of interest, we showed that GP-led screening (carried out in local practices by primary care physicians) was more effective than screening performed in the community. This observation was proven to be valid also in meta-regression analysis which suggests its independence from other aspects of screening. Similar findings were reported in previous systematic review by Lowres et al.[35] It remains to be found which characteristics of GP-led screening give this strategy an edge over community based screening. Among them the specific features of individuals attending GP surgeries (e.g. concomitant diseases) might increase the detection rate of previously unknown AF[41]. Regardless of the potential explanation, our results clearly

![Fig 4. Subgroup meta-analysis of new AF incidence according to systematic vs. opportunistic screening.](https://doi.org/10.1371/journal.pone.0213198.g004)
suggest that the GP-led approach might be a preferable method for further screening programmes when compared to the community based initiatives.

Importantly, the majority of patients (90.9% to 100%) with previously unknown AF qualified for the anticoagulation treatment because of high thromboembolic risk[8]. Introduction of such therapy might be of particular clinical [4,5] and economic benefit [40] for these individuals and thus further reinforces the practice of active screening.

Also, the current meta-analysis shows a similar effectiveness of screening modalities based on ECG comparing to pulse palpation when used as initial assessment of the cardiac rhythm.

![Figure 5](https://doi.org/10.1371/journal.pone.0213198.g005)

**Fig 5. Subgroup meta-analysis of new AF incidence according to single vs. repeated screening.** New AF incidence was significantly higher in studies (n = 10) in which heart rhythm was measured repeatedly as opposed to studies with a single measurement performed (n = 17): 2.1% (95% CI 1.5–2.8%) vs. 1.2% (95% CI 0.8–1.6%), p<0.05. AF—atrial fibrillation.

| Variable                                | Regression coefficient | Standard error | Lower 95% CI | Upper 95% CI | p  |
|-----------------------------------------|------------------------|----------------|--------------|--------------|----|
| Systematic screening (ref. opportunistic) | 0.0064                 | 0.0039         | -0.0013      | 0.0141       | 0.103 |
| ECG (ref. pulse palpation)              | 0.0052                 | 0.0056         | -0.0059      | 0.0162       | 0.360 |
| Age >64 (ref. <65)                      | 0.0013                 | 0.0052         | -0.0089      | 0.0115       | 0.803 |
| Repeated HR measurement (ref. single)   | 0.0089                 | 0.0043         | 0.0005       | 0.0173       | 0.037 |
| GP (ref. community)                     | 0.0062                 | 0.0043         | -0.0022      | 0.0147       | 0.146 |

https://doi.org/10.1371/journal.pone.0213198.t003

Table 3. Results of meta-regression analysis.
While incidence of undiagnosed AF was slightly higher with ECG (1.6% vs. 1.3%), the difference was not statistically meaningful. It is a reassuring finding as pulse palpation, when performed by appropriately trained personnel, is more widely available as a first step of screening for AF than ECG. Additionally, we confirmed non-inferiority of ECG systems using less than 12-leads tracings comparing to standard 12-lead ECG. In fact, the incidence of newly detected AF was numerically greater in studies employing simplified ECG recordings.

Carrying out the repeated testing increased the detection rate of new AF and in fact, heart rhythm measurement frequency was the only variable that showed statistical significance in a multivariate meta-regression model. It is worth to note that the review by Lowres et al. [35] included studies that screened on only one occasion. Interestingly in STROKESTOP study intermittent monitoring diagnosed 4 times as many individuals with new AF compared with the initial ECG [9]. Patients with permanent AF may have already been diagnosed, whereas paroxysmal AF is more problematic to detect with single time-point measurement, as patients may be in sinus rhythm when screened. User-friendly features of less than 12-lead ECG systems make the simplified and repeatable ECG approaches a viable option for further screening programmes for "silent" AF—especially in individuals with low-burden, paroxysmal AF.

Fig 6. Funnel plot of newly identified AF. Begg’s funnel plot of newly identified AF was asymmetric suggesting the presence of publication bias. Open circles represent the imputed studies to adjust the analysis for the effect of potential publication bias. AF—atrial fibrillation.

https://doi.org/10.1371/journal.pone.0213198.g006
In contrast to ESC guidelines the UK National Screening Committee (NSC) does not advocate population screening for AF[42] based on: (1) lack of high-quality evidence coming from randomised controlled trials confirming that screening for silent AF saves lives or reduces morbidity and (2) uncertainty whether risk of stroke in someone with screen-detected AF is the same as in individual with AF detected due to clinical presentation. However, in large UK cohort study[43] it was shown that patents with incidentally detected ambulatory AF are characterized by high risk of stroke which can be significantly reduced (similarly as the risk of death) by introduction of anticoagulation treatment as compared to no therapy. Thus, the British Cardiovascular Society issued a subsequent statement[44], in response to rather conservative recommendation of NSC, suggesting that it would be in the public interest to reconsider their decision. We believe that results of our study (among other recent publications[37,38]) support the concept of wide screening for AF.

Limitations

Our study is not without limitations. First of all, the heterogeneity of analysed studies must be appreciated. Secondly, only three studies[11–13] were performed in a randomized manner and only these included control groups what may question the reliability of the results obtained. In fact, a proportion of new AF diagnoses may be due to incidental findings or development of symptoms within the screening period. Finally, we analysed the effectiveness of different aspects of the screening process only in relation to new cases of AF. Therefore, we were not able to assess the incidence of patients with previously diagnosed AF who were not using adequate anticoagulation. Recognition of such individuals may be clinically as important as finding patients with newly identified AF.

Conclusions

In conclusion, this meta-analysis showed that active screening for undiagnosed AF is efficacious beginning from 40 years of age. Our results suggest that the organisation of screening process (GP-led, systematic and repeated screening) is more important than technical solutions used for the heart rhythm assessment.

Supporting information

S1 Table. PRISMA checklist.
(DOC)

S1 Appendix. Search strategies for EMBASE and MEDLINE.
(DOCX)

S2 Appendix. (Tables A-D). Risk of bias assessment.
(DOCX)

Author Contributions

Conceptualization: Pawel Petryszyn, Piotr Niewinski.

Data curation: Pawel Petryszyn, Piotr Niewinski, Aleksandra Staniak, Patryk Piotrowski, Anna Well, Michal Well, Izabela Jeskowiak.

Formal analysis: Pawel Petryszyn, Piotr Niewinski, Aleksandra Staniak, Patryk Piotrowski.

Investigation: Pawel Petryszyn, Piotr Niewinski, Aleksandra Staniak, Patryk Piotrowski, Anna Well, Michal Well, Izabela Jeskowiak.
Methodology: Pawel Petryszyn, Piotr Niewinski, Aleksandra Staniak, Patryk Piotrowski, Anna Well, Michal Well, Izabela Jeskowiak.

Project administration: Pawel Petryszyn.

Software: Pawel Petryszyn.

Supervision: Pawel Petryszyn, Gregory Lip, Piotr Ponikowski.

Validation: Pawel Petryszyn, Piotr Niewinski, Aleksandra Staniak, Patryk Piotrowski, Anna Well, Michal Well, Izabela Jeskowiak, Gregory Lip, Piotr Ponikowski.

Visualization: Pawel Petryszyn, Piotr Niewinski, Aleksandra Staniak, Patryk Piotrowski, Anna Well, Michal Well, Izabela Jeskowiak, Gregory Lip, Piotr Ponikowski.

Writing – original draft: Pawel Petryszyn, Piotr Niewinski, Aleksandra Staniak, Patryk Piotrowski.

Writing – review & editing: Pawel Petryszyn, Piotr Niewinski, Gregory Lip.

References
1. Heering a J, van der Kuip DAM, Hofman A, Kors JA, van Herpen G, Stricker BHC, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur Heart J. 2006; 27: 949–53. https://doi.org/10.1093/eurheartj/ehi825 PMID: 16927826
2. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation. 2006; 114: 119–25. https://doi.org/10.1161/CIRCULATIONAHA.105.595140 PMID: 16818816
3. Chugh SS, Blackshear JL, Shen WK, Hammill SC, Gersh BJ. Epidemiology and natural history of atrial fibrillation: clinical implications. J Am Coll Cardiol. 2001; 37: 371–8. PMID: 11216949
4. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007; 146: 857–67. PMID: 17577005
5. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med. 2009; 361: 1139–1151. https://doi.org/10.1056/NEJMoa0905561 PMID: 19717944
6. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomized trials. J Am Coll Cardiol. 2014; 63: 955–62. PMID: 24315724
7. Christensen LM, Krieger DW, Hojberg 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: 884–889. https://doi.org/10.1111/ene.12400 PMID: 24628954
8. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016; 37: 2893–2962. https://doi.org/10.1093/eurheartj/ehw210 PMID: 27567408
9. Svennberg E, Engdahl J, Al-Khalili F, Friberg L, Frykman V, Rosenqvist M. Mass screening for untreated atrial fibrillation the STROKESTOP study. Circulation. 2015; 131: 2176–2184. https://doi.org/10.1161/CIRCULATIONAHA.114.014343 PMID: 25910800
10. Higgins JPT, Green S, Cochrane Collaboration. Cochrane Handbook for Systematic Reviews of Interventions. 2008; 1–262. Available: http://books.google.com/books?id=s11gCx4LS_EC
11. Fitzmaurice DA, Hobbs FDR, Jowett S, Mant J, Murray ET, Holder R, et al. Screening versus routine practice in detection of atrial fibrillation in patients aged 65 or over: cluster randomised controlled trial. Br J Gen Pract. 2002; 52.
12. Morgan S, Mant D. Randomised trial of two approaches to screening for atrial fibrillation in UK general practice. Br J Gen Pract. 2002; 52.
13. Benito L, Coll-Vinent B, Gómez E, Marti D, Mitjavila J, Torres F, et al. EARLY: A pilot study on early diagnosis of atrial fibrillation in a primary healthcare centre. Europace. 2015; 17: 1688–1693. https://doi.org/10.1093/europace/euv146 PMID: 26071233
14. Bury G, Swan D, Cullen W, Keane D, Tobin H, Egan M, et al. Screening for atrial fibrillation in general practice: A national, cross-sectional study of an innovative technology. Int J Cardiol. Elsevier Ireland Ltd; 2015; 178: 247–252. https://doi.org/10.1016/j.ijcard.2014.03.137 PMID: 25464263

15. Virtanen R, Kryssi V, Vasankari T, Salminen M, Kiivelä SL, Airaksinen KEJ. Self-detection of atrial fibrillation in an aged population: The LietoAF Study. Eur J Prev Cardiol. 2014; 21: 1437–1442. https://doi.10.1177/2047487313494041 PMID: 23780517

16. Clua-Espuny JL, Lechuga-Duran I, Bosco-Princip R, Roso-Llorach A, Panisello-Tafalla A, Lucas-Noll J, et al. Prevalence of Undiagnosed Atrial Fibrillation and of That Not Being Treated With Anticoagulant Drugs: the AFABE Study. Rev Española Cardiol (English Ed. 2013; 66: 545–552. https://doi.org/10.1016/j.rec.2013.03.003 PMID: 24776203

17. Smyth B, Marsden P, Corcoran R, Walsh R, Brennan C, McSharry K, et al. Opportunistic screening for atrial fibrillation in a rural area. QJM. 2016; 109: 539–543. https://doi.org/10.1093/qjmed/hcw011 PMID: 26819299

18. 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: 285–292. https://doi.org/10.1002/clc.22387 PMID: 25873476

19. Minami M, Ishikawa Y, Matsumoto Y, Atarashi H, Atarashi K. Three-Minute ECG Recording and Arrhythmia Detection in the Evaluation and Promotion of Health. Intern Med. 2007; 46: 201–205. https://doi.org/10.2169/internalmedicine.46.1870 PMID: 17329913

20. Scalvini S, Piepoli M, Zanelli E, Volterrani M, Giordano A, Glisenti F. Incidence of atrial fibrillation in an Italian population followed by their GPs through a telecardiology service. Int J Cardiol. 2005; 98: 215–220. https://doi.org/10.1016/j.ijcard.2003.12.005 PMID: 15686770

21. Rockman CB, Jacobowitz GR, Gagne PJ, Adelman MA, Lamparello PJ, Landis R, et al. Focused screening for occult carotid artery disease. Patients with known heart disease are at high risk. J Vasc Surg. 2004; 39: 44–51. https://doi.org/10.1016/j.jvs.2003.07.006 PMID: 14718811

22. Javed W, Fay M, Hashemi M, Lindsay S, Thorpe M, Fitzmaurice D. Using limb-lead ECGs to investigate asymptomatic atrial fibrillation in primary care. Br J Cardiol. 2014; 21: 64–68. https://doi.org/10.5837/bjc.2014.015

23. van Mourik Y, Bertens LCM, Cramer MJM, Lammers J-WJ, Reitsma JB, Moons KGM, et al. Unrecognised Heart Failure and Chronic Obstructive Pulmonary Disease (COPD) in Frail Elderly Detected Through a Near-Home Targeted Screening Strategy. J Am Board Fam Med. 2014; 27: 811–821. https://doi.org/10.3122/jabfm.2014.06.134405 PMID: 25381079

24. Rhys GC, Azhar MF, Foster A. Screening for atrial fibrillation in patients aged 65 years or over attending annual flu vaccination clinics at a single general practice. Qual Prim Care. 2013; 21: 131–140. PMID: 23735694

25. Hendriksen T, Hörnsten R, Rosenqvist M, Sandström H. Screening for atrial fibrillation with baseline and intermittent ECG recording in an out-of-hospital population. BMC Cardiovascular Disord. 2013; 13: 2–9. https://doi.org/10.1186/1471-2261-13-2

26. Wiesel J, Abraham S, Messineo FC. Screening for asymptomatic atrial fibrillation while monitoring the blood pressure at home: Trial of regular versus irregular pulse for prevention of stroke (TRIPPS 2.0). Am J Cardiol. Elsevier Inc.; 2013; 111: 1559–1601. https://doi.org/10.1016/j.amjcard.2013.01.331 PMID: 23499278

27. Frewen J, Finucane C, Cronin H, Rice C, Kearney PM, Harbison J, et al. Factors that influence awareness and treatment of atrial fibrillation in older adults. Qjm. 2013; 106: 415–424. https://doi.org/10.1093/qjmed/hct060 PMID: 23504411

28. Sanmartín M, Fraguela Fraga F, Martín-Santos Á, Moix Blázquez P, García-Ruiz A, Vázquez-Caamaño M, et al. A Campaign for Information and Diagnosis of Atrial Fibrillation: “Pulse Week.” Rev Española Cardiol (English Ed. 2012; 66: 34–38. https://doi.org/10.1016/j.rec.2012.05.009

29. Yap KB, Ng TP, Ong HY. Low prevalence of atrial fibrillation in community-dwelling Chinese aged 55 years or older in Singapore: a population-based study. J Electrocardiol. 2008; 41: 94–98. https://doi.org/10.1016/j.jelectrocard.2007.03.012 PMID: 17531253

30. Lowres N, Neubek L, Sankeld G, Krass I, McLachian 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; 111: 1167–1176. https://doi.org/10.1160/TH14-03-0231 PMID: 24687081

31. Claes N, van Laethem C, Goethals M, Goethals P, Mairesse G, Schwagten B, et al. Prevalence of atrial fibrillation in adults participating in a large-scale voluntary screening programme in Belgium. Acta Cardiol. 2012; 67: 273–278. https://doi.org/10.2143/AC.67.3.2160714 PMID: 22870733
32. Doliwa PS, Frykman V, Rosenqvist M. Short-term ECG for out of hospital detection of silent atrial fibrillation episodes. Scand Cardiovasc J. 2009; 43: 163–168. https://doi.org/10.1080/14017430802593435 PMID: 19096977

33. Schnabel RB, Wilde S, Wild PS, Munzel T, Blankenberg S. Vorhofflimmern: Prävalenz und Risikofaktorenprofil in der Allgemeinbevölkerung. Dtsch Arztebl Int. 2012; 109: 293–299. https://doi.org/10.3238/arztebl.2012.0293 PMID: 22577476

34. Kim HJ, On YK, Sung J, Kim JH, Song Y Bin, Lee W-S, et al. Risk Factors for Predicting New-Onset Atrial Fibrillation in Persons Who Received Health Screening Tests. Korean Circ J. 2007; 37: 609–915.

35. Lowres N, Neubeck L, Redfern J, Ben Freedman S. Screening to identify unknown atrial fibrillation: A systematic review. Thromb Haemost. 2013; 110: 213–222. https://doi.org/10.1160/TH13-02-0165 PMID: 23595785

36. Moran PS, Teljeur C, Ryan M, Smith SM. Systematic screening for the detection of atrial fibrillation. In: Moran PS, editor. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2016. p. CD009586. https://doi.org/10.1002/14651858.CD009586.pub3 PMID: 27258214

37. Jonas Daniel E., MD, MPH; Kahwati Leila C., MD, MPH; Yun Jonathan D. Y., MD; Middleton Jennifer Cook, PhD; Coker-Schwimmer Manny, MPH; Asher Gary N., MD M. Screening for Atrial FibrillationWith Electrocardiography Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA—J Am Med Assoc. 2018; 320: 485–498. https://doi.org/10.1001/jama.2018.4190 PMID: 30088015

38. Welton NJ, McAleenan A, Thom HHZ, Davies P, Hollingworth W, Higgins JPT, et al. Screening strategies for atrial fibrillation: A systematic review and cost-effectiveness analysis. Health Technology Assess. 2017. https://doi.org/10.3310/hta12290 PMID: 28629510

39. Hobs FDR, Fitzmaurice DA, Mant J, Murray E, Jowett S, Bryan S, et al. A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study. Health Technol Assess. 2005; 9: iii–iv, ix–x, 1–74. https://doi.org/10.3310/hta9400

40. Aronsson M, Svennberg E, Rosenqvist M, Engdahl J, Al-Khalili F, Friberg L, et al. Cost-effectiveness of mass screening for untreated atrial fibrillation using intermittent ECG recording. Europace. 2015; 17: 1023–1029. https://doi.org/10.1093/europace/euv083 PMID: 25868469

41. Brunner KJ, Bunch TJ, Mullin CM, May HT, Bair TL, Elliot DW, et al. Clinical Predictors of Risk for Atrial Fibrillation. Mayo Clin Proc. 2014; 89: 1498–1505. https://doi.org/10.1016/j.mayocp.2014.08.016 PMID: 25444486

42. The UK NSC recommendation on Atrial Fibrillation screening in adults. 2014; Available: https://legacyscreening.phe.org.uk/atrialfibrillation

43. Martinez C, Katholing A, Freedman SB. Adverse prognosis of incidentally detected ambulatory atrial fibrillation. Thromb Haemost. 2014; https://doi.org/10.1160/TH14-04-0383 PMID: 24953051

44. BCS Statement on Screening for Atrial Fibrillation to Prevent Stroke. 2014; Available: https://www.bcs.com/pages/news_full.asp?NewsID=19792297