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Detection of atrial fibrillation in primary care with radial pulse palpation, electronic blood pressure measurement and handheld single-lead electrocardiography; a diagnostic accuracy study.

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ABSTRACT

Objective: Establishing diagnostic accuracy of radial pulse palpation and measurements with two devices with an atrial fibrillation (AF) detection algorithm, an electronic blood pressure monitor and a handheld single-lead electrocardiography (ECG) device.

Design: We performed a diagnostic accuracy study in the intention-to-screen arm of a cluster randomized controlled trial aimed at opportunistic screening for AF in general practice. We performed radial pulse palpation, followed by electronic blood pressure measurement (WatchBP Home A) and handheld ECG (MyDiagnostick) in random order. If one or more index tests were positive, we performed a 12 lead ECG at shortest notice. Similarly, to limit verification bias, a random sample of patients with three negative index tests received this reference test. Additionally, we analysed the dataset using multiple imputation. We present pooled diagnostic parameters.

Setting: 47 general practices participated between September 2015 and August 2018.

Participants: In the electronic medical record system of the participating general practices (n=47) we randomly marked 200 patients of ≥65 years without AF. When they visited the practice for any reason, we invited them to participate. Exclusion criteria were terminal illness, inability to give informed consent or visit the practice, or having a pacemaker or an implantable cardioverter-defibrillator.

Outcomes: Diagnostic accuracy of individual tests and test combinations to detect unknown AF.

Results: We included 4339 patients; 0.8% showed new AF. Sensitivity and specificity were 62.8% (range 43.1-69.7%) and 91.8% (91.7-91.8%) for radial pulse palpation, 70.0% (49.0-80.6%) and 96.5% (96.3-96.7%) for electronic blood pressure measurement, and 90.1% (60.8-100%) and 97.9% (97.8-97.9%) for handheld ECG, respectively.

Conclusion: In detecting AF, electronic blood pressure measurement (WatchBP Home A), but especially handheld ECG (MyDiagnostick) showed better diagnostic accuracy than radial pulse palpation.

Key words: atrial fibrillation, diagnostic accuracy, general practice, electrocardiography, blood pressure monitor

Abbreviations:

- AF: atrial fibrillation
- D_2AF study: Detecting and Diagnosing Atrial Fibrillation study
- ECG: electrocardiography
- ICD: implantable cardioverter-defibrillator
- ICPC: International Classification of Primary Care
- IQR: interquartile range
- M: mean
- SD: standard deviation

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The index tests – radial pulse palpation, electronic blood pressure measurement (WatchBP Home A) and handheld ECG (MyDiagnostick) – and reference test were performed in quick succession, with on average only 25 minutes between the first index test and the ECG, minimising the risk of rhythm changes between measurements.
- We minimised verification bias by performing a 12 lead ECG in a random sample of patients with three negative index tests and by performing multiple imputation.
- We excluded patients with known AF, thus increasing the validity of our results for the diagnostic purpose of case-finding.
- Participants were slightly younger and had less comorbidity than non-participants, which may have reduced the yield of AF in our study and decreased positive predictive values.

INTRODUCTION

Patients with atrial fibrillation (AF) often show nonspecific or no symptoms, making it difficult to track them down.[1] When left untreated, AF greatly increases the risk of stroke, heart failure and death.[2] As anticoagulation prevents over 60% of AF related strokes, timely diagnosis of AF is of utmost importance.[3] General practice seems to be a suitable setting for case finding ('opportunistic screening') of AF, as prevention is an important task of primary care and various diagnostic methods seem feasible here.

Timely diagnosis of AF might be established with opportunistic screening.[4] Twelve-lead electrocardiography (ECG) is unsuitable for screening purposes in primary care since it requires extra effort and organization from patients and staff. Palpation of the radial pulse is a simple and inexpensive method with a high reported sensitivity, but low specificity.[5] Devices equipped with an AF detection algorithm, such as various handheld single-lead ECG devices and electronic blood pressure monitors, have shown promising sensitivity and specificity.[6,7] However, these methods have not yet been compared head-to-head in an indicated population without AF.

In the 'Detecting and Diagnosing Atrial Fibrillation' (D_2AF) study, we performed opportunistic screening for AF with three detection methods: radial pulse palpation and measurements with two devices with an AF detection algorithm – an electronic blood pressure monitor and a handheld single-lead electrocardiography device.[8] Here, we present a diagnostic accuracy study nested in the intention-to-screen arm of the D_2AF study. We determine and compare the diagnostic performance of three tests – radial pulse palpation, electronic blood pressure measurement and handheld ECG –for the diagnosis of AF in primary care.

METHODS

Design

We performed a diagnostic accuracy study, nested in the intention-to-screen arm of a cluster randomized controlled trial on opportunistic screening for AF in primary care, the D_2AF study.[8,9] Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Population

The intention-to-screen arm of the D_2AF study included 47 general practices in the Netherlands. General practitioners, practice nurses and assistants performed the study procedures. They received an on-site 1.5-hour training on performing the study.

Patient inclusion ran from September 2015 through August 2018, for one year per practice. Before the start of the study, we preselected 200 patients in each practice, aged 65 years or over without the International Classification of Primary Care (ICPC) code for AF (K78) and marked their electronic medical record.[9] When these patients visited their practice for any reason during the study period, they were invited to participate. At that moment, exclusion criteria were applied: suffering from a terminal illness, being legally incompetent or unable to give informed consent, or having a pacemaker or implantable cardioverter-defibrillator. If AF had already been diagnosed the patient was excluded.

Index tests

Three index tests were performed: radial pulse palpation, electronic blood pressure measurement (WatchBP Home A, Microlife, Widnau, Switzerland) and handheld ECG (MyDiagnostick, MyDiagnostick Medical B.V., Maastricht, The Netherlands), see figure 1.

We gave instructions to perform pulse palpation by feeling the radial artery in the wrist for at least 15 seconds, assessing regularity (regular, one to three extra beats, completely irregular), equality (yes/no), and frequency (beats per minute, bpm). To maximize sensitivity, any irregularity during

pulse palpation – including one to three extra beats and complete irregularity – was considered a positive result.

The upper arm cuff of the WatchBP Home A automatically inflates and deflates three times in the 'usual' mode. The screen displays the average heart rate (bpm) and systolic and diastolic blood pressure (mmHg). It displays an 'AFIB' icon if the built-in algorithm detects AF in two or three measurements. We considered this a positive result.

The MyDiagnostick is a bar of 24cm with metallic electrodes at both ends. When holding it with both hands, it switches on and after one minute a light indicates whether the built-in algorithm detects AF ('red') or not ('green'). When connected to a computer, the associated software stores the rhythm strip and the algorithm-generated automatic interpretation of AF (red indicator light) or no AF (green indicator light). A red indicator light was considered a positive result.

Reference test

We equipped all practices with a 12 lead ECG device (Multichannel Holter ECG recorder model H2, Fysiologic, Amsterdam, The Netherlands). The ECG results were transferred digitally. We defined AF as a completely irregular RR-interval without definable p-peaks.[10] An experienced assessor supervised by a cardiologist checked the 12 lead ECG for AF. A second cardiologist independently assessed all 12 lead ECGs for AF. Al evaluators were blinded for the index test results. In case of disagreement, a third cardiologist decided, blinded for the previous assessments and unaware of being the referee.

Study procedures

Written informed consent was followed by an inquiry of recently experienced symptoms possibly related to AF: palpitations, vertigo, syncope, dyspnoea, chest tightness, and exercise intolerance. These questions were followed by radial pulse palpation, electronic blood pressure measurement and handheld ECG. Ethnic origin was registered as well. To curtail the risk of confirmation bias, the sequence of the last two tests differed per practice; 25 practices were randomly allocated to perform the electronic blood pressure measurement first, followed by the handheld ECG, and 22 practices vice versa. Measurements were not to be repeated, in order to minimize expectancy bias.

All patients with at least one positive index test received a 12 lead ECG at shortest notice. For logistic and financial reasons a 12 lead ECG was not feasible in patients with three negative index tests, due to the expected large number.[11] To limit verification bias, a 12 lead ECG was also performed at shortest notice in a 10% random sample of patients with three negative index tests.

Finally, in the D_2AF screening trial, all patients in whom the 12 lead ECG did not show AF, were offered a two-week Holter registration (Multichannel Holter ECG recorder model H2, Fysiologic, Amsterdam, The Netherlands).

Data collection

Data were collected through an electronic case report form (MEMIC, center for data and information management, Maastricht University, the Netherlands). We downloaded automatic algorithm results of the MyDiagnostick ECG device from the local software, compared them with the manually entered indicator light colours, and corrected them in case of disagreement. After the study period, we extracted ICPC-codes from the electronic medical record system to determine baseline patient characteristics. We manually reviewed all medical records of patients with new AF, to ensure it had not been diagnosed before participation in the study.

Data analysis

We used IBM SPSS Statistics for Windows (version 25.0, Armonk, NY: IBM Corp.). For descriptive statistics, we report numbers and percentages (n, %) for categorical variables and means and standard deviations (M±SD) or medians with interquartile ranges (IQR) for numerical variables. To check for selection bias, we compared characteristics of participants and non-participants, and characteristics of patients with three negative index tests within versus outside of the sample receiving a 12 lead ECG. We used a Chi-square or Fisher's exact test where appropriate for categorical variables and an independent samples T-test for continuous variables. We considered a two-sided p-value ≤ 0.05 statistically significant.

We report our diagnostic accuracy study according to STARD.[12] To limit verification bias, we performed a 12 lead ECG in a 10% random sample of patients with three negative index tests.[9] To

calculate the diagnostic parameters we applied multiple imputation (see text box), which is considered the best method to minimize verification bias.[13] Multiple imputation was based on fully conditional specification, in particular predictive mean matching, creating 100 datasets with 10 iterations per set.[14] Variables used for imputation were gender, age, symptoms, medical history, AF according to the electronic medical record and results of the three index tests, 12 lead ECG and Holter. In all 100 datasets, we computed sensitivity, specificity, predictive values, and likelihood ratios of each index test (or combination of tests). We report pooled diagnostic parameters as a mean plus range of the 100 datasets. With McNemar's test for paired nominal variables, we investigated whether sensitivity and specificity differed significantly between the index tests.

Ethics

The medical research ethics committee of the Amsterdam University Medical Center (Amsterdam UMC), Amsterdam, approved the D_2AF study protocol (14 November 2014, No NL48215.018.14).

RESULTS

Study procedures

Study procedures were performed by a research or practice assistant in 42% (1829/4339) of patients, a practice nurse in 34% (1495/4339), a physician in 12% (520/4339), and by an unspecified practice worker in 11% (495/4339).

The median time between registration of the first index test and the 12 lead ECG was 25 minutes (IQR 18-44). The indicator light of the MyDiagnostick was registered for 4331 patients; for 3607 (83.3%) of them, we obtained the automatic interpretation from the local software. We corrected 17 manually entered handheld ECG results.

Participants

Out of the 9400 patients whose medical file was marked, 4339 patients participated (figure 2), with a mean (±SD) of 92±23 per practice. On average, participants were younger and had less comorbidity than non-participants (appendix 1). Table 1 shows the participant characteristics and a comparison of patients with one or more positive index tests versus patients with three negative index tests. Within the group of patients with three negative tests, a comparison of the random sample who received a 12 lead ECG (n=308) versus patients outside the sample (n=3505) revealed that patient characteristics were not significantly different, except for hypertension (p=0.013; see appendix 2).

Observed cases and multiple imputation

Out of the 4339 screened patients, 793 (18.3%) received a 12 lead ECG; 485 of them had at least one positive index test and 308 were triple-negative (figure 2). The cumulative incidence of AF in the observed cases was 0.7% (30/4339). Figure 3 shows the observed cases with at least one positive index test result (n=526) and their overlap.

Table 2 shows the pooled results after multiple imputation; complete cases (i.e. patients with both an index as a reference test result) can be found in appendix 3 and index test combinations in appendix 4. The mean (±SD) pulse frequency was 71±11 bpm with pulse palpation. In patients with AF this was 76±13 (not shown in table).

Diagnostic accuracy

Table 3 displays the diagnostic test characteristics based on the pooled data. Both sensitivity and specificity of electronic blood pressure measurement (70.0% and 96.5%) and handheld ECG (90.1% and 97.9%) were higher than those of radial pulse palpation (62.8% and 91.8%). The sensitivity and specificity of the MyDiagnostick were significantly higher than those of the other two index tests in all 100 imputed datasets (all p-values were ≤0.039). The negative predictive values of all index tests were ≥99.7%. The positive predictive value of the handheld ECG was the highest (25.2% versus 13.8% and 5.8% for electronic blood pressure measurement and radial pulse palpation, respectively). The positive likelihood ratios of electronic blood pressure measurement (19.9) and handheld ECG (42.0) were high;

the negative likelihood ratio of handheld ECG was 0.1. Additional analysis of five index test combinations did not reveal a superior combination (see appendix 5).

DISCUSSION

Main findings

Our diagnostic accuracy study – performed in 4339 patients of 65 years and older, visiting the general practice for any reason, of whom 0.8% had new AF – showed that all three AF detection methods could exclude AF (negative predictive value ≥99.7%). However, electronic blood pressure measurement using the WatchBP Home A and handheld ECG using the MyDiagnostick had a higher diagnostic accuracy than radial pulse palpation in detecting unknown AF (sensitivity and specificity 70.0% and 96.5%, 90.1% and 97.9%, 62.8% and 91.8%, respectively). The MyDiagnostick showed the highest sensitivity and specificity; its positive predictive value was 25.2% in this population. Combining index tests had no clear advantage.

Strengths and limitations

Our study had several strengths. Firstly, the index and reference tests were performed in quick succession, with on average only 25 minutes between the first index test and the ECG. This short interval minimized the risk of rhythm changes between measurements.

Secondly, we minimised verification bias in the calculated diagnostic parameters. Rather than labelling patients with three negative index tests as 'no AF', we performed a 12 lead ECG in a random sample of these patients. A comparison of patient characteristics within versus outside the sample showed that our sample was representative. In addition, we applied multiple imputation to compute all diagnostic accuracy parameters in a valid way.[13] Inverse probability weighting would have overestimated sensitivity and – to a lesser extent – the negative predictive value for the scenarios with the handheld ECG, due to zero false-negative results.[15]

Thirdly, we excluded patients with known AF, which increased the validity of our results for the diagnostic purpose of case-finding. Clinical features of patients with known AF may differ from those with newly diagnosed and untreated AF, affecting test characteristics.[16] Moreover, including patients with known AF would artificially have raised AF frequency in the study population, affecting predictive values.[17]

A limitation of our study is that participants were slightly younger and had less comorbidity than non-participants. This may have reduced the yield of AF in our study and decreased positive predictive values.

Incidence of atrial fibrillation and positive predictive values

The cumulative incidence of AF in our study (0.8%) is lower than in diagnostic studies that did not exclude known AF. Consequently, positive predictive values for all three methods are lower in our study than in previous studies.[18-20] Nonetheless, the positive predictive values in our study better reflect real-life screening situations, with a low cumulative incidence of AF.

Radial pulse palpation

Despite defining 'any' irregularity as a positive result, the sensitivity of radial pulse palpation was lower in our study (62.8%) than in a previous meta-analysis (92%; 95% CI 85-96%); specificity (91.8%) was higher (82%; 95% CI 76-88%).[21] The heart rate of patients with new AF in our study (76 bpm), was only slightly lower than the mean heart rate in our study population (71-72 bpm) and much lower than the typical AF frequency of 100-160 bpm.[22] This makes it more challenging to discern AF from sinus rhythm and may explain our low sensitivity. The low cumulative incidence of AF in our study could explain the relatively high specificity.[23]

Electronic blood pressure measurement

In a recent study of Chan et al. and in the meta-analysis of Verberk et al., the sensitivity of the WatchBP Home A is markedly higher (80.6% and 98%) than in our study (70.0%).[20,24] However, they did not always apply the reference test in case of a negative index test, nor apply a statistical

computation to limit verification bias. Furthermore, they did not exclude patients with known AF. Test characteristics can also be influenced by variation in setting – not all studies were conducted in primary care – or country.

Handheld electrocardiography

The sensitivity and specificity of the MyDiagnostick in our study are comparable to those in previous studies.[7] Predictive values in two other studies (56.3%, 45%) were higher than in ours (25.2%), probably because patients with known AF were not excluded.[18,19] In our head-to-head comparison, we showed that diagnostic characteristics of electronic blood pressure measurement and handheld ECG exceed those of pulse palpation. This is in accordance with the results of the systematic review of Taggar et al.[21]

Implications for practice

This study showed that all three index tests could exclude AF in a case finding setting in primary care. Both devices outperformed radial pulse palpation. The diagnostic parameters of the handheld ECG device – in particular its sensitivity and positive predictive value - were the most favourable.

The use of ambulatory devices or technologies in healthcare – Mobile Health (mHealth) – rapidly increases, resulting in the development of many new devices.[25] Results for WatchBP Home A and MyDiagnostick cannot simply be extended to other blood pressure monitors and handheld single-lead ECG devices with AF detection function. Other devices recording pulse irregularities or single-lead ECGs should be investigated in further research, preferably again in 'indicated' populations without known AF. Such studies should address the establishment or rejection of a new diagnosis of AF, either induced by physicians (case finding in high-risk patients) or by patients presenting with signs or symptoms suggestive of AF.

Conclusion

This study showed that radial pulse palpation, and measurements with two devices with AF detection algorithm – electronic blood pressure measurement (WatchBP Home A) and handheld ECG

(MyDiagnostick) – are suitable for excluding AF in a case finding situation. Diagnostic accuracy of the WatchBP Home A and especially the MyDiagnostick exceeded that of radial pulse palpation.

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CONFLICT OF INTEREST

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

SBU and NV-vG contributed equally to this work. SBU, NV-vG, WAML, PMGE, JAK, HCPMvW, and HEJHS conceived and designed the study. JAK and HCPMvW supervised the study. WAML, PMGE, JAK, HCPMvW, and HEJHS obtained funding. SBU, NV-vG, WAML, BW, and HEJHS acquired, analysed, and interpreted the data. NV-vG wrote the first draft of the manuscript, and all authors revised the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

DATA SHARING

Relevant anonymised patient level data are available on reasonable request.

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Table 1 Characteristics of the total study population, including patients with at least one positive index test versus patients with three negative index tests.

Characteristic	All (n=4339)	≥1 positive index test[a] (n=526)	Three index tests negative (n=3813)	p-value
Female, n (%)	2336 (53.8)	248 (47.1)	2088 (54.8)	0.001
Age in years, M (SD)	73.5 (5.5)	74.8 (5.9)	73.4 (5.4)	<0.001
Ethnic origin[b]				0.052
White, n (%)	4173 (96.2)	513 (97.5)	3660 (96.0)	
Black, n (%)	77 (1.8)	10 (1.9)	67 (1.8)	
Other, n (%)[c]	84 (1.9)	3 (0.6)	81 (2.1)	
History[d]				
Hypertension, n (%)	2212 (51.1)	280 (53.2)	1932 (50.7)	0.251
Stroke/TIA, n (%)	329 (7.6)	37 (7.0)	292 (7.7)	0.621
Diabetes, n (%)	783 (18.1)	110 (20.9)	673 (17.7)	0.065
Heart failure, n (%)	80 (1.8)	18 (3.4)	62 (1.6)	0.004
Thromboembolism, n (%)	200 (4.6)	19 (3.6)	181 (4.7)	0.248
Vascular disease, n (%)	644 (14.8)	102 (19.4)	542 (14.2)	0.002
Symptoms[e]				
Palpitations, n (%)	735 (17.0)	102 (19.4)	633 (16.6)	0.108
Vertigo, n (%)	935 (21.6)	141 (26.8)	794 (20.8)	0.002
Syncope, n (%)	164 (3.8)	25 (4.8)	139 (3.6)	0.213
Dyspnea, n (%)	925 (21.3)	158 (30.0)	767 (20.1)	<0.001
Chest tightness, n (%)	426 (9.8)	64 (12.2)	362 (9.5)	0.054
Exercise intolerance, n (%)	962 (22.2)	153 (29.1)	809 (21.2)	<0.001
Any of the above, n (%)	2228 (51.3)	316 (60.1)	1912 (50.1)	<0.001

Signs				
Unequal pulse, n (%)	125 (4.9)	78 (14.8)	47 (1.2)	<0.001
Heart rate in bpm, M (SD)[f]				
Radial pulse palpation	71.2 (11.2)	68.8 (11.3)	71.5 (11.1)	<0.001
Watch BP Home A	72.1 (12.8)	71.7 (12.9)	72.1 (12.8)	0.512
MyDiagnostick	72.0 (11.9)	72.2 (14.1)	72.0 (11.6)	0.722
Systolic blood pressure[g], M (SD)	143.0 (18.7)	141.9 (18.9)	143.2 (18.8)	0.152
Diastolic blood pressure[g], M (SD)	78.7 (9.8)	78.7 (10.1)	78.7 (9.7)	0.865
AF on Holter[h i], n (%)	4 (0.1)	0	4 (0.1)	0.029

Abbreviations: M (mean), SD (standard deviation), TIA (transient ischemic attack), ECG (electrocardiography), AF (atrial fibrillation).

[a] Index tests were: radial pulse palpation and two devices with AF detection algorithm: an electronic blood pressure monitor (WatchBP Home A) and a handheld ECG device (MyDiagnostick).

[b] For every patient, only one answering option could be filled in (exclusive categories). For five patients, the ethnic origin was missing (n=4334).

[c] Patients in this category were mostly born outside the Netherlands (n=78); the four predominant countries of birth were Indonesia (n=36), Suriname (n=14), Morocco (n=8) and Turkey (n=5).

[d] For nine patients, history was missing (n=4330).

[e] Results were missing in five patients for palpitations (n=4334), four for vertigo (n=4335), three for syncope (n=4336), two for dyspnea (n=4337), one for chest tightness (n=4338) and 13 for exercise intolerance (n=4326).

[f] There were 157 results missing for heart rate on WatchBP Home A (n=4182) and 732 for MyDiagnostick (n=3607).

[g] If the WatchBP Home A failed, blood pressure was measured manually. Blood pressure was still missing for 53 patients (n=4286).

[h] Holter results were available for 270 patients.

[i] Fisher's exact test.

Table 2 Computed results for the three index tests after multiple imputation (pooled data, n=4339) [a].

Index test	Index test result	12 lead ECG[b]		
		AF	*No AF*	*Total*
Radial pulse palpation	*Irregular*	22	353	375
	Regular	13	3951	3964
	Total	35	4304	4339
WatchBP Home A	*'AFIB'*	24	152	176
	No 'AFIB'	11	4152	4163
	Total	35	4304	4339
MyDiagnostick	*Red indicator light*	31	92	123
	Green indicator light	4	4212	4216
	Total	35	4304	4339

Abbreviations: AF (atrial fibrillation)

[a] To limit verification bias, we performed the reference test (12 lead ECG) in a 10% random sample of patients with three negative index tests. In addition, to calculate all relevant diagnostic parameters, we used multiple imputation in the analysis.

[b] These are the computed results of 100 datasets with 10 iterations per set, created with multiple imputation (see main text).

Table 3 Diagnostic accuracy of three index tests for atrial fibrillation (AF) detection in a primary care population undergoing opportunistic screening for AF (0.8% AF, 35/4339), pooled results based on multiple imputation.[a]

	Sensitivity (%) M, range	Specificity (%) M, range	PPV (%) M, range	NPV (%) M, range	Positive LR M, range	Negative LR M, range
Radial pulse	62.8	91.8	5.8	99.7	7.7	0.41
palpation	43.1-69.7	91.7-91.8	5.3-6.1	99.3-99.7	5.2-8.5	0.33-0.62
WatchBP	70.0	96.5	13.8	99.7	19.9	0.31
Home A	49.0-80.6	96.3-96.7	12.2-14.8	99.4-99.9	14.1-23.5	0.20-0.53
MyDiagnostick	90.1	97.9	25.2	99.9	42.0	0.10
	60.8-100	97.8-97.9	24.2-25.8	99.5-100	28.3-46.8	0.00-0.40

Abbreviations: M (mean), PPV (positive predictive value), NPV (negative predictive value), ECG (electrocardiography), LR (likelihood ratio).

[a] To limit verification bias, we performed the reference test (12 lead ECG) in a 10% random sample of patients with three negative index tests. In addition, to calculate all relevant diagnostic parameters, we used multiple imputation in the analysis. These are the pooled results (mean plus range) of 100 datasets with 10 iterations per set, created with multiple imputation (see main text).

FIGURE LEGENDS

Fig 1 The three index tests. A) Radial pulse palpation. B) WatchBP Home A, an automatic blood pressure monitor with atrial fibrillation detection algorithm. C) MyDiagnostick, a handheld single-lead electrocardiography device with atrial fibrillation detection algorithm.

Fig 2 Patients receiving index tests and their results.

[a] Terminally ill, unable to give informed consent, unable to visit the practice, pacemaker/ICD, previous diagnosis of atrial fibrillation.

[b] We included 4339 patients in the diagnostic accuracy study and 4106 in the randomized controlled trial.[8] The screening of 233 patients occurred after the end of the study year and therefore they were not eligible for the randomized controlled trial. However, we did include them in the diagnostic accuracy study.

[c] An 'AFIB' icon appears on the screen in case of suspected atrial fibrillation.

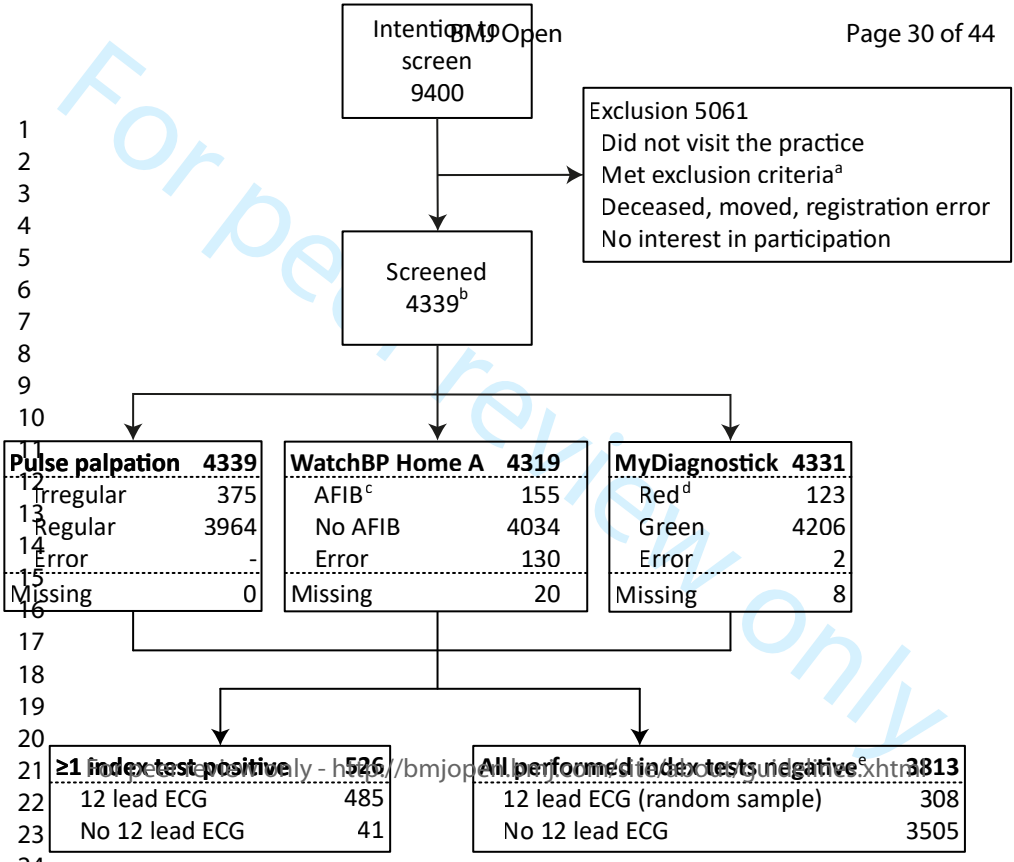
[d] A red light is indicative of atrial fibrillation, whereas a green light is not.

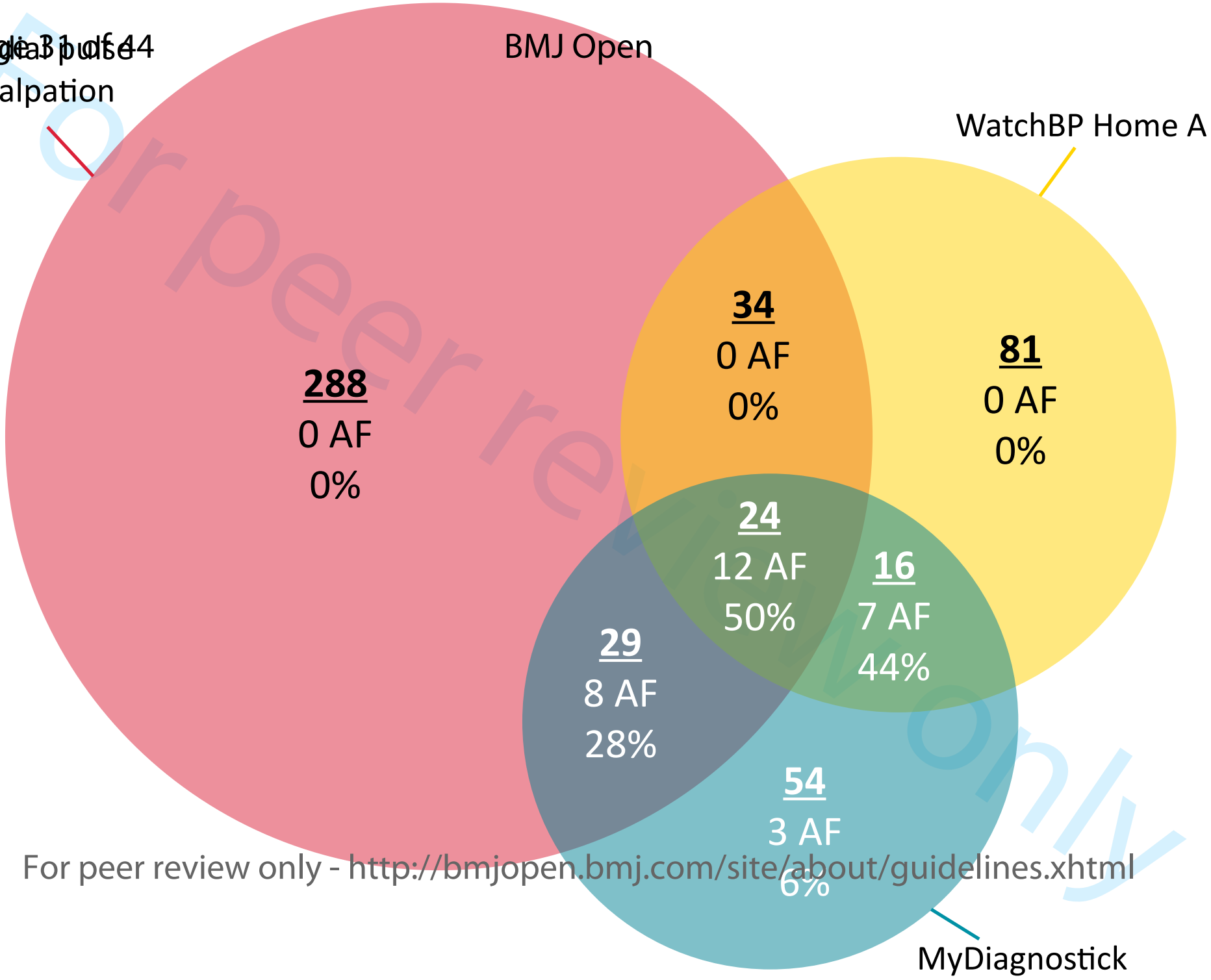
[e] A random sample of patients with all performed tests negative received a 12 lead ECG.

Fig 3 Venn diagram[a] depicting the positive test results of the three index tests (n=526/4339[b]), including the distribution of patients with atrial fibrillation (n=30).

[a] Created with Pacific Northwest National Laboratory (PNNL) software from omics.pnl.gov.

[b] 12 lead ECG results were available for 485 out of 526 patients.





Appendix 1

Comparison of characteristics of participants[a] versus non-participants within the eligible intention-to-screen population of the D2AF study.

Characteristic	Participants (n=4339)	Non-participants (n=5061)	p-value
Female, n (%)	2336 (53.8)	2831 (55.9)	0.041
Age in years, M (SD)	73.5 (5.5)	76.7 (7.4)	<0.001
History[b]			
Hypertension, n (%)	2212 (51.1)	2416 (48.3)	0.008
Stroke/TIA, n (%)	329 (7.6)	603 (12.1)	<0.001
Diabetes, n (%)	783 (18.1)	1029 (20.6)	0.002
Heart failure, n (%)	80 (1.8)	304 (6.1)	<0.001
Thromboembolism, n (%)	200 (4.8)	271 (5.4)	0.077
Vascular disease, n (%)	644 (14.9)	968 (19.4)	<0.001

Abbreviations: M (mean), TIA (transient ischemic attack), SD (standard deviation).

[a] In the current diagnostic accuracy study, we analyse 4339 patients whereas we included 4106 patients in the intention-to-screen arm of the D2AF randomized controlled trial. The screening of 233 patients occurred after the end of the study year, and they were therefore not eligible for the randomized controlled trial. However, we did include them in the diagnostic accuracy study.

[b] For nine participants and 64 non-participants, history was missing.

Appendix 2

Characteristics of patients with three negative index tests, including the sample of patients receiving a 12 lead ECG versus the patients outside the sample, not receiving an ECG.

Characteristic	Patients with three negative index tests[a]			
	Total (n=3813)	ECG (random sample, n=308)	No ECG (n=3505)	p-value
Female, n (%)	2088 (54.8)	168 (54.5)	1920 (54.8)	0.937
Age in years, M (SD)	73.4 (5.4)	73.1 (5.3)	73.4 (5.5)	0.274
Ethnic origin[b]				0.495
White, n (%)	3360 (96.0)	293 (95.1)	3367 (96.2)	
Black, n (%)	67 (1.8)	8 (2.6)	59 (1.7)	
Other, n (%)[c]	81 (2.1)	7 (2.3)	74 (2.1)	
History[d]				
Hypertension, n (%)	1932 (50.7)	135 (44.0)	1797 (51.4)	0.013
Stroke/TIA, n (%)	292 (7.7)	17 (5.5)	275 (7.9)	0.143
Diabetes, n (%)	673 (17.7)	44 (14.3)	629 (18.0)	0.109
Heart failure, n (%)	62 (1.6)	5 (1.6)	57 (1.6)	1.000
Thromboembolism, n (%)	181 (4.7)	9 (2.9)	172 (4.9)	0.117
Vascular disease, n (%)	542 (14.2)	39 (12.7)	503 (14.4)	0.422
Symptoms[e]				
Palpitations, n (%)	633 (16.6)	51 (16.6)	582 (16.6)	0.976
Vertigo, n (%)	794 (20.8)	63 (20.5)	731 (20.9)	0.862
Syncope, n (%)	139 (3.6)	10 (3.2)	129 (3.7)	0.695
Dyspnea, n (%)	767 (20.1)	70 (22.7)	697 (19.9)	0.235
Chest tightness, n (%)	362 (9.5)	20 (6.5)	342 (9.8)	0.061

Exercise intolerance, n (%)	809 (21.2)	62 (20.1)	747 (21.3)	0.604
Any of the above, n (%)	1912 (50.1)	148 (48.1)	1764 (50.3)	0.444
Signs				
Unequal pulse, n (%)	47 (1.2)	2 (0.6)	45 (1.3)	0.585[k]
Heart rate in bpm, M (SD)[f]				
Radial pulse palpation	71.5 (11.1)	72.1 (11.0)	71.5 (11.2)	0.363
WatchBP Home A	72.1 (12.8)	72.1 (13.1)	72.1 (12.7)	0.953
MyDiagnostick	72.0 (11.6)	71.5 (10.5)	72.0 (11.7)	0.466
Systolic blood pressure[g], M (SD)	143.2 (18.8)	142.3 (19.7)	143.3 (18.6)	0.398
Diastolic blood pressure[g], M (SD)	78.7 (9.7)	79.0 (9.8)	78.7 (9.7)	0.671
AF on Holter[h], n (%)	4 (0.1)	4 (1.3)	0	1.000[i]

Abbreviations: M (mean), SD (standard deviation), TIA (transient ischemic attack), ECG (electrocardiography), AF (atrial fibrillation), eBPM-AF (electronic blood pressure monitor with AF detection algorithm), hand-ECG (handheld single-lead ECG device with AF detection algorithm).

[a] Index tests were: radial pulse palpation and two devices with AF detection algorithm: an electronic blood pressure monitor (WatchBP Home A) and a handheld ECG device (MyDiagnostick).

[b] Mutually exclusive categories. For every patient, only one answering option could be filled in (exclusive categories). The ethnic origin did not differ significantly between patients with one or more positive tests and patients with three negative tests (p=0.495).

[c] Patients in this category were mostly born outside the Netherlands (n=76); the four predominant countries of birth were Indonesia (n=35), Suriname (n=14), Morocco (n=8) and Turkey (n=5).

[d] For seven patients, history was missing (n=3806).

[e] Results were missing in four patients for palpitations (n=3809), three for vertigo (n=3810), three for syncope (n=3810), two for dyspnea (n=3811), one for chest tightness (n=3812) and 13 for exercise intolerance (n=3800).

[f] There were 93 results missing for heart rate on WatchBP Home A (n=3720) and 638 for MyDiagnostick (n=3175).

[g] If the WatchBP Home A failed, blood pressure was measured manually. Blood pressure was still missing for 53 patients (n=3781).

[h] Holter results were available for 112 patients.

[i] Fisher's exact test.

Appendix 3

Diagnostic test results for the three index tests in the complete cases receiving a 12 lead ECG as reference test (n=793) [a].

Index test	Index test result	12 lead ECG result		
		AF	*No AF*	*Total*
Radial pulse palpation	*Irregular*	20	332	352
	Regular	10	431	441
	Total	30	763	793
WatchBP Home A	*'AFIB'*	19	124	143
	No 'AFIB'	6	580	586
	Total[b]	25	704	729
MyDiagnostick	*Red indicator light*	30	84	114
	Green indicator light	0	679	679
	Total	30	763	793

Abbreviations: AF (atrial fibrillation).

[a] By protocol, to limit verification bias, we performed the reference test (12 lead ECG) in a 10% random sample of patients with three negative index tests. The complete cases shown here, describe the patients receiving the 12 lead ECG, i.e. the patients with ≥1 positive index test plus the random sample of patients with three negative index tests.

[b] 64 patients who underwent a 12 lead ECG had no conclusive result on the WatchBP Home A (62 errors and two missing) and had to be imputed. Therefore, the total number of patients is 729 instead of 793.

Appendix 4

Diagnostic test results for five different index test combinations in the complete cases receiving a 12 lead ECG as reference test (n=793) and the pooled data after multiple imputation (n=4339) [a].

Index test combinations		Combined test result	12 lead ECG results					
			Complete cases[b]			Pooled data[c]		
			AF	*No AF*	*Total*	*AF*	*No AF*	*Total*
	A	*≥1 index test +*	30	455	485	32	499	531
		All index tests -	0	308	308	3	3805	3808
		Total	30	763	793	35	4304	4339
	B	*Radial pulse and/or MyDiagnostick +*	30	384	414	32	413	445
		Radial pulse and MyDiagnostick -	0	379	379	3	3891	3894
		Total	30	763	793	35	4304	4339
	C	*Radial pulse and/or WatchBP Home A +*	27	412	439	29	448	477
		Radial pulse and WatchBP Home A -	3	343	346	6	3856	3862
		Total	30	755	785	35	4304	4339
	D	*Radial pulse and MyDiagnostick +*	20	32	52	21	32	53
		Radial pulse and/or MyDiagnostick -	10	731	741	14	4272	4286
		Total	30	763	793	35	4304	4339
	E	*Radial pulse and WatchBP Home A +*	12	44	56	17	56	73
		Radial pulse and/or WatchBP Home A -	13	668	681	18	4248	4266
		Total	25	712	737	35	4304	4339

Abbreviations: AF (atrial fibrillation).

[a] By protocol, to limit verification bias, we strived to perform the reference test (12 lead ECG) in a 10% random sample of patients with three negative index tests. In addition, to calculate all relevant diagnostic parameters, we used multiple imputation in the analysis.

[b] The 'complete cases' present the patients actually receiving the 12 lead ECG, i.e. the patients with ≥1 positive index test plus the random sample of patients with three negative index tests.

[c] The 'pooled data' present the computed results (rounded numbers) of 100 datasets with 10 iterations per set, created with multiple imputation (see main text).

Appendix 5

Diagnostic accuracy of five different index test combinations in a primary care population undergoing opportunistic screening for atrial fibrillation (AF; 0.8% AF, 35/4339), pooled results after multiple imputation.[a]

Index test combinations[b]	Sensitivity (%) M, range	Specificity (%) M, range	PPV (%) M, range	NPV (%) M, range	Positive LR M, range	Negative LR M, range
A	92.1	88.4	6.0	99.9	7.9	0.09
	62.7-100	88.3-88.5	5.6-6.2	99.5-100	5.4-8.7	0.00-0.42
B	92.1	90.4	7.1	99.9	9.6	0.09
	62.7-100	90.3-90.4	6.7-7.4	99.5-100	6.5-10.5	0.00-0.41
C	83.1	89.6	6.0	99.8	8.0	0.19
	56.9-90.9	89.5-89.6	5.6-6.3	99.4-99.9	5.4-8.8	0.10-0.48
D	60.8	99.3	39.5	99.7	81.5	0.39
	41.2-67.7	99.2-99.3	37.7-39.6	99.3-99.8	55.2-91.2	0.33-0.59
E	49.7	98.7	23.4	99.6	38.1	0.51
	35.0-58.1	98.4-98.8	20.0-26.5	99.2-99.7	27.3-47.0	0.43-0.66

Abbreviations: M (mean), PPV (positive predictive value), NPV (negative predictive value), ECG (electrocardiography), LR (likelihood ratio).

[a] By protocol, to limit verification bias, we strived to perform the reference test (12 lead ECG) in a 10% random sample of patients with three negative index tests. In addition, to calculate all relevant diagnostic parameters, we used multiple imputation in the analysis (see main text). We report the pooled results (mean plus range) of 100 datasets with 10 iterations per set, created with multiple imputation (see main text).

[b] Description of the index test combinations:

A. All three index tests, positive if at least one was positive.

B. Radial pulse palpation and handheld electrocardiography, positive if either test was positive.

C. Radial pulse palpation and electronic blood pressure measurement, positive if either test was positive.

D. Radial pulse palpation and handheld electrocardiography, positive if both tests were positive.

E. Radial pulse palpation and electronic blood pressure measurement, positive if both tests were positive.

Reporting checklist for diagnostic test accuracy study.

Based on the STARD guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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Reporting Item	Page Number
Title or abstract	

None	#1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	1
Abstract			
None	#2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts https://www.equator-network.org/reporting-guidelines/stard-abstracts/)	3
Introduction			
None	#3	Scientific and clinical background, including the intended use and clinical role of the index test	6
None	#4	Study objectives and hypotheses	6
Methods			
Study design	#5	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	7
Participants	#6	Eligibility criteria	7
Participants	#7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	7
Participants	#8	Where and when potentially eligible participants were identified (setting, location and dates)	7

Participants	#9	Whether participants formed a consecutive, random or convenience series	7
Test methods	#10	Index and reference tests in sufficient detail to allow replication	7-8
Test methods	#11	Rationale for choosing the reference standard (if alternatives exist)	n/a
Test methods	#12	Definition of and rationale for test positivity cut-offs or result categories of the index and reference tests, distinguishing pre-specified from exploratory	7-8
Test methods	#13	Whether clinical information and reference standard results were available to the performers / readers of the index test; Whether clinical information and index test results were available to the assessors of the reference standard	8
Analysis	#14	Methods for estimating or comparing measures of diagnostic accuracy	9
Analysis	#15	How indeterminate index test or reference standard results were handled	9
Analysis	#16	How missing data on the index test and reference standard were handled	9
Analysis	#17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	n/a
Analysis	#18	Intended sample size and how it was determined	7

Results			
Participants	#19	Flow of participants, using a diagram	Figure 1
Participants	#20	Baseline demographic and clinical characteristics of participants	Table 1
Participants	#21	Distribution of severity of disease in those with the target condition, and distribution of alternative diagnoses in those without the target condition	n/a
Participants	#22	Time interval and any clinical interventions between index test and reference standard	10-11
Test results	#23	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	Table 2 Appendix 3
Test results	#24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Table 3
Test results	#25	Any adverse events from performing the index test or the reference standard	n/a
Discussion			
None	#26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	12
None	#27	Implications for practice, including the intended use and clinical role of the index test	14

Other information			
None	#28	Registration number and name of registry	2
None	#29	Where the full study protocol can be accessed	18
None	#30	Sources of funding and other support; role of funders	16

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Detection of atrial fibrillation in primary care with radial pulse palpation, electronic blood pressure measurement and handheld single-lead electrocardiography; a diagnostic accuracy study.

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Appendices: 5

ABSTRACT

Objective: To determine the diagnostic accuracy of three tests – radial pulse palpation, an electronic blood pressure monitor and a handheld single-lead electrocardiography (ECG) device – for opportunistic screening for unknown atrial fibrillation (AF).

Design: We performed a diagnostic accuracy study in the intention-to-screen arm of a cluster randomised controlled trial aimed at opportunistic screening for AF in general practice. We performed radial pulse palpation, followed by electronic blood pressure measurement (WatchBP Home A) and handheld ECG (MyDiagnostick) in random order. If one or more index tests were positive, we performed a 12 lead ECG at shortest notice. Similarly, to limit verification bias, a random sample of patients with three negative index tests received this reference test. Additionally, we analysed the dataset using multiple imputation. We present pooled diagnostic parameters.

Setting: 47 general practices participated between September 2015 and August 2018.

Participants: In the electronic medical record system of the participating general practices (n=47) we randomly marked 200 patients of ≥65 years without AF. When they visited the practice for any reason, we invited them to participate. Exclusion criteria were terminal illness, inability to give informed consent or visit the practice, or having a pacemaker or an implantable cardioverter-defibrillator.

Outcomes: Diagnostic accuracy of individual tests and test combinations to detect unknown AF.

Results: We included 4339 patients; 0.8% showed new AF. Sensitivity and specificity were 62.8% (range 43.1-69.7%) and 91.8% (91.7-91.8%) for radial pulse palpation, 70.0% (49.0-80.6%) and 96.5% (96.3-96.7%) for electronic blood pressure measurement, and 90.1% (60.8-100%) and 97.9%

(97.8-97.9%) for handheld ECG, respectively. Positive predictive values were 5.8% (5.3-6.1%), 13.8% (12.2-14.8%) and 25.2% (24.2-25.8%), respectively. All negative predictive values were ≥99.7%.

Conclusion: In detecting AF, electronic blood pressure measurement (WatchBP Home A), but especially handheld ECG (MyDiagnostick) showed better diagnostic accuracy than radial pulse palpation.

Key words: atrial fibrillation, diagnostic accuracy, general practice, electrocardiography, blood pressure monitor

Abbreviations:

- AF: atrial fibrillation
- D_2AF study: Detecting and Diagnosing Atrial Fibrillation study
- ECG: electrocardiography
- ICD: implantable cardioverter-defibrillator
- ICPC: International Classification of Primary Care
- IQR: interquartile range
- M: mean
- SD: standard deviation

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The index tests – radial pulse palpation, electronic blood pressure measurement (WatchBP Home A) and handheld ECG (MyDiagnostick) – and reference test were performed in quick succession, with on average only 25 minutes between the first index test and the ECG, minimising the risk of rhythm changes between measurements.
- We minimised verification bias by performing a 12 lead ECG in a random sample of patients with three negative index tests and by performing multiple imputation.
- We excluded patients with known AF, thus increasing the validity of our results for the diagnostic purpose of case finding.
- Participants were slightly younger and had less comorbidity than non-participants, which may have reduced the yield of AF in our study and decreased positive predictive values.
- We cannot provide the numbers for the individual exclusion reasons, as this was not reported consistently enough to provide a reliable overview.

INTRODUCTION

Patients with atrial fibrillation (AF) often show nonspecific or no symptoms, making it difficult to track them down.[1] When left untreated, AF greatly increases the risk of stroke, heart failure and death.[2] As anticoagulation prevents over 60% of AF related strokes, timely diagnosis of AF is of utmost importance.[3] General practice seems to be a suitable setting for case finding ('opportunistic screening') of AF, as prevention is an important task of primary care and various diagnostic methods seem feasible here.

Timely diagnosis of AF might be established with opportunistic screening, but community screening for AF is still controversial.[4 5] In six randomised controlled trials the effect of screening was studied; three favoured screening, three did not.[6-11] Twelve-lead electrocardiography (ECG) is unsuitable for screening purposes in primary care since it requires extra effort and organization from patients and staff. Palpation of the radial pulse is a simple and inexpensive method with a high reported sensitivity, but low specificity.[12] Devices equipped with an AF detection algorithm, such as various handheld single-lead ECG devices and electronic blood pressure monitors, have shown promising sensitivity and specificity.[13 14] However, these methods have not yet been compared head-to-head in an indicated population without AF.

In the 'Detecting and Diagnosing Atrial Fibrillation' (D_2AF) study, we performed opportunistic screening for AF with three detection methods: radial pulse palpation and measurements with two devices with an AF detection algorithm – an electronic blood pressure monitor and a handheld single-lead electrocardiography device.[10] Here, we present a diagnostic accuracy study nested in the intention-to-screen arm of the D_2AF study. We determine and compare the diagnostic performance of three tests – radial pulse palpation, electronic blood pressure measurement and handheld ECG – for the diagnosis of AF in primary care.

METHODS

Design

We performed a diagnostic accuracy study, nested in the intention-to-screen arm of a cluster randomised controlled trial on opportunistic screening for AF in primary care, the D_2AF study.[10 15] Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Population

The intention-to-screen arm of the D_2AF study included 47 general practices in the Netherlands. General practitioners, practice nurses and assistants performed the study procedures. They received an on-site 1.5-hour training on performing the study.

Patient inclusion ran from September 2015 through August 2018, for one year per practice. Before the start of the study, we preselected 200 patients in each practice, aged 65 years or over without the International Classification of Primary Care (ICPC) code for AF (K78) and marked their electronic medical record.[15] When these patients visited their practice for any reason during the study period, they were invited to participate. At that moment, exclusion criteria were applied: suffering from a terminal illness, being legally incompetent or unable to give informed consent, or having a pacemaker or implantable cardioverter-defibrillator. If AF had already been diagnosed the patient was excluded.

Index tests

Three index tests were performed: radial pulse palpation, and measurements with two devices with an AF detection algorithm, i.e. an electronic blood pressure monitor (WatchBP Home A, Microlife, Widnau, Switzerland) and a handheld ECG device (MyDiagnostick, MyDiagnostick Medical B.V., Maastricht, The Netherlands), see figure 1.

We gave instructions to perform pulse palpation by feeling the radial artery in the wrist for at least 15 seconds, assessing regularity (regular, one to three extra beats, completely irregular), equality

(yes/no), and frequency (beats per minute, bpm). To maximise sensitivity, any irregularity during pulse palpation – including one to three extra beats and complete irregularity – was considered a positive result.

The upper arm cuff of the electronic blood pressure monitor automatically inflates and deflates three times in the 'usual' mode. The screen displays the average heart rate (bpm) and systolic and diastolic blood pressure (mmHg). It displays an 'AFIB' icon if the built-in algorithm detects AF in two or three measurements. We considered this a positive result.

The handheld ECG is a bar of 24cm with metallic electrodes at both ends. When holding it with both hands, it switches on and after one minute a light indicates whether the built-in algorithm detects AF ('red') or not ('green'). When connected to a computer, the associated software stores the rhythm strip and the algorithm-generated automatic interpretation of AF (red indicator light) or no AF (green indicator light). A red indicator light was considered a positive result.

Reference test

We equipped all practices with a 12 lead ECG device (Multichannel Holter ECG recorder model H2, Fysiologic, Amsterdam, The Netherlands), the gold standard for AF detection. The ECG results were transferred digitally. We defined AF as a completely irregular RR-interval without definable p-peaks.[16] An experienced assessor supervised by a cardiologist checked the 12 lead ECG for AF. A second cardiologist independently assessed all 12 lead ECGs for AF. All evaluators were blinded for the index test results. In case of disagreement, a third cardiologist decided, blinded for the previous assessments and unaware of being the referee.

Study procedures

Written informed consent was followed by an inquiry of recently experienced symptoms possibly related to AF: palpitations, vertigo, syncope, dyspnoea, chest tightness, and exercise intolerance. These questions were followed by radial pulse palpation, electronic blood pressure measurement and handheld ECG. Ethnic origin was registered as well. To curtail the risk of confirmation bias, the sequence of the last two tests differed per practice; 25 practices were randomly allocated to perform

the electronic blood pressure measurement first, followed by the handheld ECG, and 22 practices vice versa. Measurements were not to be repeated, in order to minimise expectancy bias.

All patients with at least one positive index test received a 12 lead ECG at shortest notice. For logistic and financial reasons a 12 lead ECG was not feasible in patients with three negative index tests, due to the expected large number.[17] To limit verification bias, a 12 lead ECG was also performed at shortest notice in a 10% random sample of patients; after entering three negative index tests into the electronic case report form, the computer directly performed the randomisation and displayed the result.

Finally, in the D_2AF screening trial, all patients in whom the 12 lead ECG did not show AF, were offered a two-week Holter registration (Multichannel Holter ECG recorder model H2, Fysiologic, Amsterdam, The Netherlands).

Data collection

Data were collected through an electronic case report form (MEMIC, center for data and information management, Maastricht University, the Netherlands). We downloaded automatic algorithm results of the handheld ECG from the local software, compared them with the manually entered indicator light colours, and corrected them in case of disagreement. After the study period, we extracted ICPC-codes from the electronic medical record system to determine baseline patient characteristics. We manually reviewed all medical records of patients with new AF, to ensure it had not been diagnosed before participation in the study.

Data analysis

We used IBM SPSS Statistics for Windows (version 25.0, Armonk, NY: IBM Corp.). For descriptive statistics, we report numbers and percentages (n, %) for categorical variables and means and standard deviations (M±SD) or medians with interquartile ranges (IQR) for numerical variables. To check for selection bias, we compared characteristics of participants and non-participants, and characteristics of patients with three negative index tests within versus outside of the sample receiving a 12 lead ECG. We used a Chi-square or Fisher's exact test where appropriate for categorical variables and an

independent samples T-test for continuous variables. We considered a two-sided p-value ≤0.05 statistically significant.

We report our diagnostic accuracy study according to STARD.[18] To limit verification bias, we performed a 12 lead ECG in a 10% random sample of patients with three negative index tests.[15] To calculate the diagnostic parameters we applied multiple imputation (see text box), which is considered the best method to minimise verification bias.[19] Multiple imputation was based on fully conditional specification, in particular predictive mean matching, creating 100 datasets with 10 iterations per set.[20] Variables used for imputation were gender, age, symptoms, medical history, AF according to the electronic medical record and results of the three index tests, 12 lead ECG and Holter. In all 100 datasets, we computed sensitivity, specificity, predictive values, and likelihood ratios of each index test (or combination of tests). We report pooled diagnostic parameters as a mean plus range of the 100 datasets. With McNemar's test for paired nominal variables, we investigated whether sensitivity and specificity differed significantly between the index tests.

Ethics

The medical research ethics committee of the Amsterdam University Medical Center (Amsterdam UMC), Amsterdam, approved the D_2AF study protocol (14 November 2014, No NL48215.018.14).

RESULTS

Study procedures

Study procedures were performed by a research or practice assistant in 42% (1829/4339) of patients, a practice nurse in 34% (1495/4339), a physician in 12% (520/4339), and by an unspecified practice worker in 11% (495/4339).

The median time between registration of the first index test and the 12 lead ECG was 25 minutes (IQR 18-44). The indicator light of the handheld ECG was registered for 4331 patients; for

3607 (83.3%) of them, we obtained the automatic interpretation from the local software. We corrected 17 manually entered handheld ECG results.

Participants

Out of the 9400 patients whose medical file was marked, 4339 patients participated (figure 2), with a mean (±SD) of 92±23 per practice. On average, participants were younger and had less comorbidity than non-participants (appendix 1). Table 1 shows the participant characteristics and a comparison of patients with one or more positive index tests versus patients with three negative index tests. Within the group of patients with three negative tests, a comparison of the random sample who received a 12 lead ECG (n=308) versus patients outside the sample (n=3505) revealed that patient characteristics were not significantly different, except for hypertension (p=0.013; see appendix 2).

Observed cases and multiple imputation

Out of the 4339 screened patients, 793 (18.3%) received a 12 lead ECG; 485 of them had at least one positive index test and 308 were triple-negative (figure 2). The cumulative incidence of AF in the observed cases was 0.7% (30/4339). Figure 3 shows the observed cases with at least one positive index test result (n=526) and their overlap.

Table 2 shows the pooled results after multiple imputation; complete cases (i.e. patients with both an index and a reference test result) can be found in appendix 3 and index test combinations in appendix 4. The mean (±SD) pulse frequency was 71±11 bpm with pulse palpation. In patients with AF this was 76±13 (not shown in table).

Diagnostic accuracy

Table 3 displays the diagnostic test characteristics based on the pooled data. Both sensitivity and specificity of electronic blood pressure measurement (70.0% and 96.5%) and handheld ECG (90.1% and 97.9%) were higher than those of radial pulse palpation (62.8% and 91.8%). The sensitivity and specificity of the handheld ECG were significantly higher than those of the other two index tests in all 100 imputed datasets (all p-values were ≤0.039). The negative predictive values of all index tests were

≥99.7%. The positive predictive value of the handheld ECG was the highest (25.2% versus 13.8% and 5.8% for electronic blood pressure measurement and radial pulse palpation, respectively). The positive likelihood ratios of electronic blood pressure measurement (19.9) and handheld ECG (42.0) were high; the negative likelihood ratio of handheld ECG was 0.1. Additional analysis of five index test combinations did not reveal a superior combination (see appendix 5).

DISCUSSION

Main findings

Our diagnostic accuracy study – performed in 4339 patients of 65 years and older, visiting the general practice for any reason, of whom 0.8% had new AF – showed that all three AF detection methods could exclude AF (negative predictive value ≥99.7%). However, electronic blood pressure measurement and handheld ECG had a higher diagnostic accuracy than radial pulse palpation in detecting unknown AF (sensitivity and specificity 70.0% and 96.5%, 90.1% and 97.9%, 62.8% and 91.8%, respectively). The handheld ECG showed the highest sensitivity and specificity; its positive predictive value was 25.2% in this population. Combining index tests had no clear advantage.

Strengths and limitations

Our study had several strengths. Firstly, the index and reference tests were performed in quick succession, with on average only 25 minutes between the first index test and the ECG. This short interval minimised the risk of rhythm changes between measurements.

Secondly, we minimised verification bias in the calculated diagnostic parameters. Rather than labelling patients with three negative index tests as 'no AF', we performed a 12 lead ECG in a random sample of these patients. A comparison of patient characteristics within versus outside the sample showed that our sample was representative. In addition, we applied multiple imputation to compute all diagnostic accuracy parameters in a valid way.[19] Inverse probability weighting would have

overestimated sensitivity and – to a lesser extent – the negative predictive value for the scenarios with the handheld ECG, due to zero false-negative results.[21]

Thirdly, we excluded patients with known AF, which increased the validity of our results for the diagnostic purpose of case finding. Clinical features of patients with known AF may differ from those with newly diagnosed and untreated AF, affecting test characteristics.[22] Moreover, including patients with known AF would artificially have raised AF frequency in the study population, affecting predictive values.[23]

A limitation of our study is that participants were slightly younger and had less comorbidity than non-participants. This may have reduced the yield of AF in our study and decreased positive predictive values. A second limitation is that we cannot provide the numbers for the individual exclusion reasons, as this was not reported consistently.

Incidence of atrial fibrillation and positive predictive values

The cumulative incidence of AF in our study (0.8%) is lower than in diagnostic studies that did not exclude known AF. Consequently, positive predictive values for all three methods are lower in our study than in previous studies.[24-26] Nonetheless, the positive predictive values in our study better reflect real-life screening situations, with a low cumulative incidence of AF.

Radial pulse palpation

Despite defining 'any' irregularity as a positive result, the sensitivity of radial pulse palpation was lower in our study (62.8%) than in a previous meta-analysis (92%; 95% CI 85-96%); specificity (91.8%) was higher (82%; 95% CI 76-88%).[27] The heart rate of patients with new AF in our study (76 bpm), was only slightly higher than the mean heart rate in our study population (71-72 bpm) and much lower than the typical AF frequency of 100-160 bpm.[28] This makes it more challenging to discern AF from sinus rhythm and may explain our low sensitivity. The low cumulative incidence of AF in our study could explain the relatively high specificity.[29]

Electronic blood pressure measurement

In a study of Chan et al. and in the meta-analysis of Verberk et al., the sensitivity of the WatchBP Home A is markedly higher (80.6% and 98%) than in our study (70.0%).[26 30] However, they did not always apply the reference test in case of a negative index test, nor apply a statistical computation to limit verification bias. Furthermore, they did not exclude patients with known AF. Test characteristics can also be influenced by variation in setting – not all studies were conducted in primary care – or country. In the Screen AF-study, elderly hypertensive patients used the WatchBP Home A twice daily at home to screen for AF.[11] All diagnostic parameters were lower than ours, possibly the quality of the measurements was lower in unsupervised performance at home than in performance by a health care worker.

Handheld electrocardiography

The sensitivity and specificity of the handheld ECG in our study are comparable to those in previous studies.[14] Predictive values in two other studies (56.3%, 45%) were higher than in ours (25.2%), probably because patients with known AF were not excluded.[24 25] In our head-to-head comparison, we showed that diagnostic characteristics of electronic blood pressure measurement and handheld ECG exceed those of pulse palpation. This is in accordance with the results of the systematic review of Taggar et al.[27]

Implications for practice

This study showed that all three index tests could exclude AF in a case finding setting in primary care.[31] Both devices outperformed radial pulse palpation. The diagnostic parameters of the handheld ECG device – in particular its sensitivity and positive predictive value – were the most favourable.

The use of ambulatory devices or technologies in healthcare – Mobile Health (mHealth) – rapidly increases, resulting in the development of many new devices.[32] Results for WatchBP Home A and MyDiagnostick cannot simply be extended to other blood pressure monitors and handheld single-lead ECG devices with AF detection function. Other devices recording pulse irregularities or single-lead ECGs should be investigated in further research, preferably again in 'indicated' populations without known AF. Such studies should address the establishment or rejection of a new diagnosis of

AF, either induced by physicians (case finding in high-risk patients) or by patients presenting with signs or symptoms suggestive of AF.

Conclusion

This study showed that radial pulse palpation, and measurements with two devices with AF detection algorithm – electronic blood pressure monitor (WatchBP Home A) and handheld ECG (MyDiagnostick) – are suitable for excluding AF in a case finding situation. Diagnostic accuracy of the electronic blood pressure monitor and especially the handheld ECG exceeded that of radial pulse palpation.

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CONFLICT OF INTEREST

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

SBU and NV-vG contributed equally to this work. SBU, NV-vG, WAML, PMGE, JAK, HCPMvW, and HEJHS conceived and designed the study. JAK and HCPMvW supervised the study. WAML, PMGE, JAK, HCPMvW, and HEJHS obtained funding. SBU, NV-vG, WAML, BW, and HEJHS acquired, analysed, and interpreted the data. NV-vG wrote the first draft of the manuscript, and all authors revised the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

DATA SHARING

Relevant anonymised patient level data are available on reasonable request.

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Table 1 Characteristics of the total study population, including patients with at least one positive index test versus patients with three negative index tests.

Characteristic	All (n=4339)	≥1 positive index test[a] (n=526)	Three index tests negative (n=3813)	p-value
Female, n (%)	2336 (53.8)	248 (47.1)	2088 (54.8)	0.001
Age in years, M (SD)	73.5 (5.5)	74.8 (5.9)	73.4 (5.4)	<0.001
Ethnic origin[b]				0.052
White, n (%)	4173 (96.2)	513 (97.5)	3660 (96.0)	
Black, n (%)	77 (1.8)	10 (1.9)	67 (1.8)	
Other, n (%)[c]	84 (1.9)	3 (0.6)	81 (2.1)	
History[d]				
Hypertension, n (%)	2212 (51.1)	280 (53.2)	1932 (50.7)	0.251
Stroke/TIA, n (%)	329 (7.6)	37 (7.0)	292 (7.7)	0.621
Diabetes, n (%)	783 (18.1)	110 (20.9)	673 (17.7)	0.065
Heart failure, n (%)	80 (1.8)	18 (3.4)	62 (1.6)	0.004
Thromboembolism, n (%)	200 (4.6)	19 (3.6)	181 (4.7)	0.248
Vascular disease, n (%)	644 (14.8)	102 (19.4)	542 (14.2)	0.002
Symptoms[e]				
Palpitations, n (%)	735 (17.0)	102 (19.4)	633 (16.6)	0.108
Vertigo, n (%)	935 (21.6)	141 (26.8)	794 (20.8)	0.002
Syncope, n (%)	164 (3.8)	25 (4.8)	139 (3.6)	0.213
Dyspnea, n (%)	925 (21.3)	158 (30.0)	767 (20.1)	<0.001
Chest tightness, n (%)	426 (9.8)	64 (12.2)	362 (9.5)	0.054
Exercise intolerance, n (%)	962 (22.2)	153 (29.1)	809 (21.2)	<0.001
Any of the above, n (%)	2228 (51.3)	316 (60.1)	1912 (50.1)	<0.001

Signs				
Unequal pulse, n (%)	125 (4.9)	78 (14.8)	47 (1.2)	<0.001
Heart rate in bpm, M (SD)[f]				
Radial pulse palpation	71.2 (11.2)	68.8 (11.3)	71.5 (11.1)	<0.001
Watch BP Home A	72.1 (12.8)	71.7 (12.9)	72.1 (12.8)	0.512
MyDiagnostick	72.0 (11.9)	72.2 (14.1)	72.0 (11.6)	0.722
Systolic blood pressure[g], M (SD)	143.0 (18.7)	141.9 (18.9)	143.2 (18.8)	0.152
Diastolic blood pressure[g], M (SD)	78.7 (9.8)	78.7 (10.1)	78.7 (9.7)	0.865
AF on Holter[h] [i], n (%)	4 (0.1)	0	4 (0.1)	0.029

Abbreviations: M (mean), SD (standard deviation), TIA (transient ischemic attack), ECG (electrocardiography), AF (atrial fibrillation).

[a] Index tests were: radial pulse palpation and two devices with AF detection algorithm: an electronic blood pressure monitor (WatchBP Home A) and a handheld ECG device (MyDiagnostick).

[b] For every patient, only one answering option could be filled in (exclusive categories). For five patients, the ethnic origin was missing (n=4334).

[c] Patients in this category were mostly born outside the Netherlands (n=78); the four predominant countries of birth were Indonesia (n=36), Suriname (n=14), Morocco (n=8) and Turkey (n=5).

[d] For nine patients, history was missing (n=4330).

[e] Results were missing in five patients for palpitations (n=4334), four for vertigo (n=4335), three for syncope (n=4336), two for dyspnea (n=4337), one for chest tightness (n=4338) and 13 for exercise intolerance (n=4326).

[f] There were 157 results missing for heart rate on WatchBP Home A (n=4182) and 732 for MyDiagnostick (n=3607).

[g] If the WatchBP Home A failed, blood pressure was measured manually. Blood pressure was still missing for 53 patients (n=4286).

[h] Holter results were available for 270 patients.

[i] Fisher's exact test.

Table 2 Computed results for the three index tests after multiple imputation (pooled data, n=4339) [a].

Index test	**Index test result**	**12 lead ECG**[b]		
		AF	*No AF*	*Total*
Radial pulse palpation	*Irregular*	22	353	375
	Regular	13	3951	3964
	Total	35	4304	4339
WatchBP Home A	*'AFIB'*	24	152	176
	No 'AFIB'	11	4152	4163
	Total	35	4304	4339
MyDiagnostick	*Red indicator light*	31	92	123
	Green indicator light	4	4212	4216
	Total	35	4304	4339

Abbreviations: AF (atrial fibrillation)

[a] To limit verification bias, we performed the reference test (12 lead ECG) in a 10% random sample of patients with three negative index tests. In addition, to calculate all relevant diagnostic parameters, we used multiple imputation in the analysis.

[b] These are the computed results of 100 datasets with 10 iterations per set, created with multiple imputation (see main text).

Table 3 Diagnostic accuracy of three index tests for atrial fibrillation (AF) detection in a primary care population undergoing opportunistic screening for AF (0.8% AF, 35/4339), pooled results based on multiple imputation.[a]

	Sensitivity (%) M, range	**Specificity (%) M, range**	**PPV (%) M, range**	**NPV (%) M, range**	**Positive LR M, range**	**Negative LR M, range**
Radial pulse	62.8	91.8	5.8	99.7	7.7	0.41
palpation	43.1-69.7	91.7-91.8	5.3-6.1	99.3-99.7	5.2-8.5	0.33-0.62
WatchBP	70.0	96.5	13.8	99.7	19.9	0.31
Home A	49.0-80.6	96.3-96.7	12.2-14.8	99.4-99.9	14.1-23.5	0.20-0.53
MyDiagnostick	90.1	97.9	25.2	99.9	42.0	0.10
	60.8-100	97.8-97.9	24.2-25.8	99.5-100	28.3-46.8	0.00-0.40

Abbreviations: M (mean), PPV (positive predictive value), NPV (negative predictive value), ECG (electrocardiography), LR (likelihood ratio).

[a] To limit verification bias, we performed the reference test (12 lead ECG) in a 10% random sample of patients with three negative index tests. In addition, to calculate all relevant diagnostic parameters, we used multiple imputation in the analysis. These are the pooled results (mean plus range) of 100 datasets with 10 iterations per set, created with multiple imputation (see main text).

LEGENDS

Fig 1 The three index tests. A) Radial pulse palpation. B) WatchBP Home A, an automatic blood pressure monitor with atrial fibrillation detection algorithm. C) MyDiagnostick, a handheld single-lead electrocardiography device with atrial fibrillation detection algorithm.

Fig 2 Patients receiving index tests and their results.

[a] Terminally ill, unable to give informed consent, unable to visit the practice, pacemaker/ICD, previous diagnosis of atrial fibrillation.

[b] We included 4339 patients in the diagnostic accuracy study and 4106 in the randomised controlled trial.[10] The screening of 233 patients occurred after the end of the study year and therefore they were not eligible for the randomised controlled trial. However, we did include them in the diagnostic accuracy study.

[c] An 'AFIB' icon appears on the screen in case of suspected atrial fibrillation.

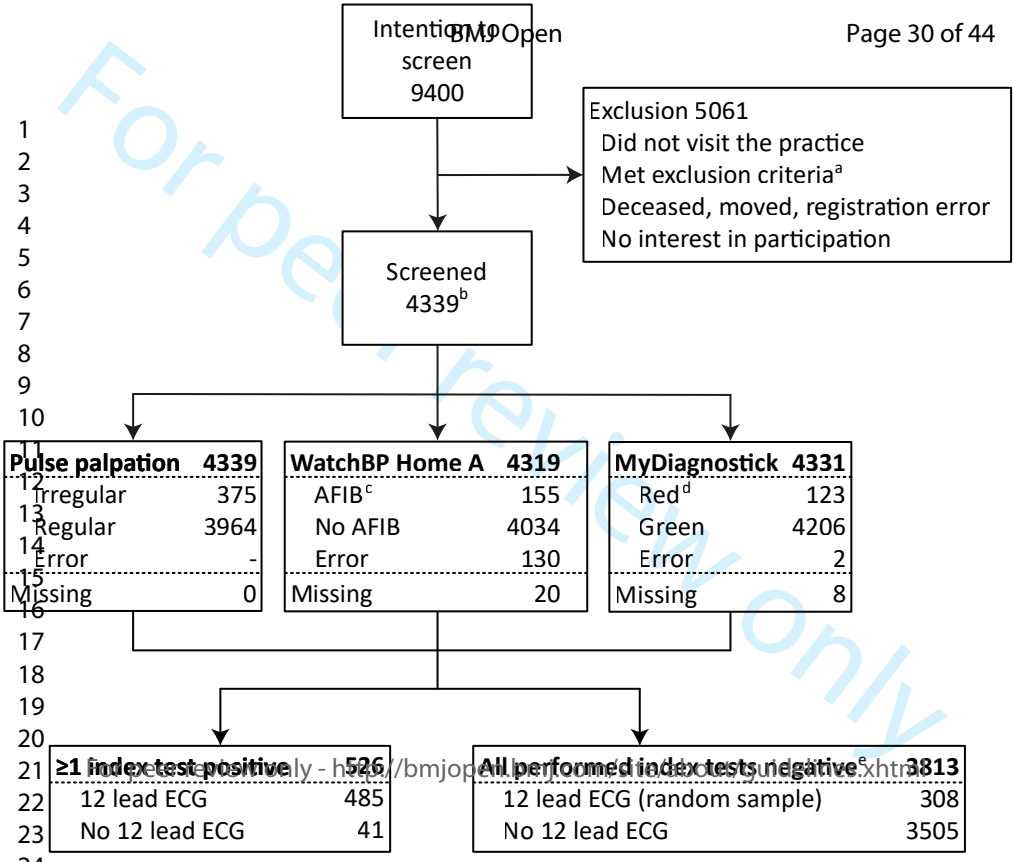
[d] A red light is indicative of atrial fibrillation, whereas a green light is not.

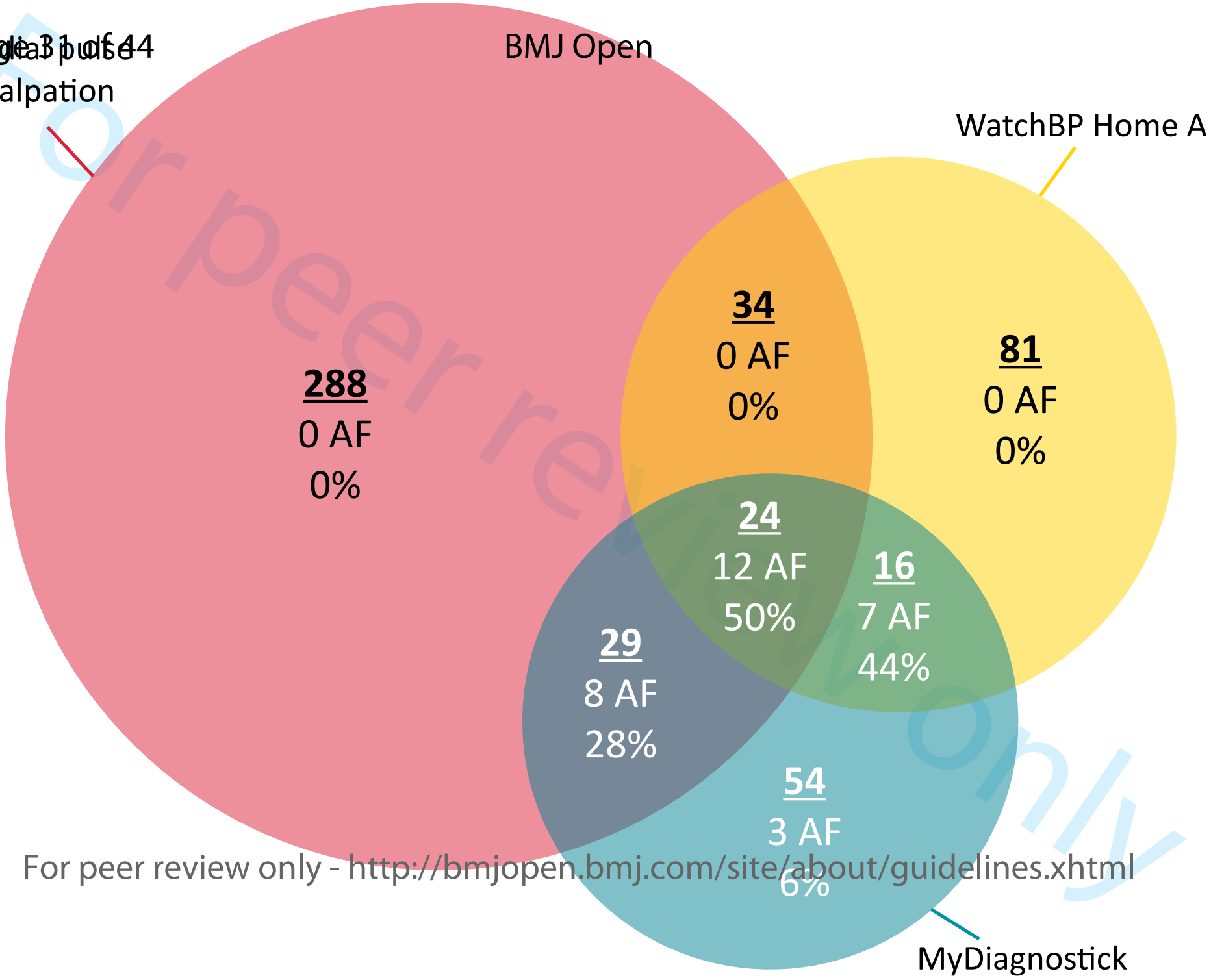
[e] A random sample of patients with all performed tests negative received a 12 lead ECG.

Fig 3 Venn diagram[a] depicting the positive test results of the three index tests (n=526/4339[b]), including the distribution of patients with atrial fibrillation (n=30).

[a] Created with Pacific Northwest National Laboratory (PNNL) software from omics.pnl.gov.

[b] 12 lead ECG results were available for 485 out of 526 patients.





Appendix 1

Comparison of characteristics of participants[a] versus non-participants within the eligible intention-to-screen population of the D2AF study.

Characteristic	Participants (n=4339)	Non-participants (n=5061)	p-value
Female, n (%)	2336 (53.8)	2831 (55.9)	0.041
Age in years, M (SD)	73.5 (5.5)	76.7 (7.4)	<0.001
History[b]			
Hypertension, n (%)	2212 (51.1)	2416 (48.3)	0.008
Stroke/TIA, n (%)	329 (7.6)	603 (12.1)	<0.001
Diabetes, n (%)	783 (18.1)	1029 (20.6)	0.002
Heart failure, n (%)	80 (1.8)	304 (6.1)	<0.001
Thromboembolism, n (%)	200 (4.8)	271 (5.4)	0.077
Vascular disease, n (%)	644 (14.9)	968 (19.4)	<0.001

Abbreviations: M (mean), TIA (transient ischemic attack), SD (standard deviation).

[a] In the current diagnostic accuracy study, we analyse 4339 patients whereas we included 4106 patients in the intention-to-screen arm of the D2AF randomized controlled trial. The screening of 233 patients occurred after the end of the study year, and they were therefore not eligible for the randomized controlled trial. However, we did include them in the diagnostic accuracy study.

[b] For nine participants and 64 non-participants, history was missing.

Appendix 2

Characteristics of patients with three negative index tests, including the sample of patients receiving a 12 lead ECG versus the patients outside the sample, not receiving an ECG.

Characteristic	Patients with three negative index tests[a]			
	Total (n=3813)	ECG (random sample, n=308)	No ECG (n=3505)	p-value
Female, n (%)	2088 (54.8)	168 (54.5)	1920 (54.8)	0.937
Age in years, M (SD)	73.4 (5.4)	73.1 (5.3)	73.4 (5.5)	0.274
Ethnic origin[b]				0.495
White, n (%)	3360 (96.0)	293 (95.1)	3367 (96.2)	
Black, n (%)	67 (1.8)	8 (2.6)	59 (1.7)	
Other, n (%)[c]	81 (2.1)	7 (2.3)	74 (2.1)	
History[d]				
Hypertension, n (%)	1932 (50.7)	135 (44.0)	1797 (51.4)	0.013
Stroke/TIA, n (%)	292 (7.7)	17 (5.5)	275 (7.9)	0.143
Diabetes, n (%)	673 (17.7)	44 (14.3)	629 (18.0)	0.109
Heart failure, n (%)	62 (1.6)	5 (1.6)	57 (1.6)	1.000
Thromboembolism, n (%)	181 (4.7)	9 (2.9)	172 (4.9)	0.117
Vascular disease, n (%)	542 (14.2)	39 (12.7)	503 (14.4)	0.422
Symptoms[e]				
Palpitations, n (%)	633 (16.6)	51 (16.6)	582 (16.6)	0.976
Vertigo, n (%)	794 (20.8)	63 (20.5)	731 (20.9)	0.862
Syncope, n (%)	139 (3.6)	10 (3.2)	129 (3.7)	0.695
Dyspnea, n (%)	767 (20.1)	70 (22.7)	697 (19.9)	0.235
Chest tightness, n (%)	362 (9.5)	20 (6.5)	342 (9.8)	0.061

Exercise intolerance, n (%)	809 (21.2)	62 (20.1)	747 (21.3)	0.604
Any of the above, n (%)	1912 (50.1)	148 (48.1)	1764 (50.3)	0.444
Signs				
Unequal pulse, n (%)	47 (1.2)	2 (0.6)	45 (1.3)	0.585[k]
Heart rate in bpm, M (SD)[f]				
Radial pulse palpation	71.5 (11.1)	72.1 (11.0)	71.5 (11.2)	0.363
WatchBP Home A	72.1 (12.8)	72.1 (13.1)	72.1 (12.7)	0.953
MyDiagnostick	72.0 (11.6)	71.5 (10.5)	72.0 (11.7)	0.466
Systolic blood pressure[g], M (SD)	143.2 (18.8)	142.3 (19.7)	143.3 (18.6)	0.398
Diastolic blood pressure[g], M (SD)	78.7 (9.7)	79.0 (9.8)	78.7 (9.7)	0.671
AF on Holter[h], n (%)	4 (0.1)	4 (1.3)	0	1.000[i]

Abbreviations: M (mean), SD (standard deviation), TIA (transient ischemic attack), ECG (electrocardiography), AF (atrial fibrillation), eBPM-AF (electronic blood pressure monitor with AF detection algorithm), hand-ECG (handheld single-lead ECG device with AF detection algorithm).

[a] Index tests were: radial pulse palpation and two devices with AF detection algorithm: an electronic blood pressure monitor (WatchBP Home A) and a handheld ECG device (MyDiagnostick).

[b] Mutually exclusive categories. For every patient, only one answering option could be filled in (exclusive categories). The ethnic origin did not differ significantly between patients with one or more positive tests and patients with three negative tests (p=0.495).

[c] Patients in this category were mostly born outside the Netherlands (n=76); the four predominant countries of birth were Indonesia (n=35), Suriname (n=14), Morocco (n=8) and Turkey (n=5).

[d] For seven patients, history was missing (n=3806).

[e] Results were missing in four patients for palpitations (n=3809), three for vertigo (n=3810), three for syncope (n=3810), two for dyspnea (n=3811), one for chest tightness (n=3812) and 13 for exercise intolerance (n=3800).

[f] There were 93 results missing for heart rate on WatchBP Home A (n=3720) and 638 for MyDiagnostick (n=3175).

[g] If the WatchBP Home A failed, blood pressure was measured manually. Blood pressure was still missing for 53 patients (n=3781).

[h] Holter results were available for 112 patients.

[i] Fisher's exact test.

Appendix 3

Diagnostic test results for the three index tests in the complete cases receiving a 12 lead ECG as reference test (n=793) [a].

Index test	Index test result	12 lead ECG result		
		AF	*No AF*	*Total*
Radial pulse palpation	*Irregular*	20	332	352
	Regular	10	431	441
	Total	30	763	793
WatchBP Home A	*'AFIB'*	19	124	143
	No 'AFIB'	6	580	586
	Total[b]	25	704	729
MyDiagnostick	*Red indicator light*	30	84	114
	Green indicator light	0	679	679
	Total	30	763	793

Abbreviations: AF (atrial fibrillation).

[a] By protocol, to limit verification bias, we performed the reference test (12 lead ECG) in a 10% random sample of patients with three negative index tests. The complete cases shown here, describe the patients receiving the 12 lead ECG, i.e. the patients with ≥1 positive index test plus the random sample of patients with three negative index tests.

[b] 64 patients who underwent a 12 lead ECG had no conclusive result on the WatchBP Home A (62 errors and two missing) and had to be imputed. Therefore, the total number of patients is 729 instead of 793.

Appendix 4

Diagnostic test results for five different index test combinations in the complete cases receiving a 12 lead ECG as reference test (n=793) and the pooled data after multiple imputation (n=4339) [a].

Index test combinations		Combined test result	12 lead ECG results					
			Complete cases[b]			Pooled data[c]		
			AF	*No AF*	*Total*	*AF*	*No AF*	*Total*
	A	*≥1 index test +*	30	455	485	32	499	531
		All index tests -	0	308	308	3	3805	3808
		Total	30	763	793	35	4304	4339
	B	*Radial pulse and/or MyDiagnostick +*	30	384	414	32	413	445
		Radial pulse and MyDiagnostick -	0	379	379	3	3891	3894
		Total	30	763	793	35	4304	4339
	C	*Radial pulse and/or WatchBP Home A +*	27	412	439	29	448	477
		Radial pulse and WatchBP Home A -	3	343	346	6	3856	3862
		Total	30	755	785	35	4304	4339
	D	*Radial pulse and MyDiagnostick +*	20	32	52	21	32	53
		Radial pulse and/or MyDiagnostick -	10	731	741	14	4272	4286
		Total	30	763	793	35	4304	4339
	E	*Radial pulse and WatchBP Home A +*	12	44	56	17	56	73
		Radial pulse and/or WatchBP Home A -	13	668	681	18	4248	4266
		Total	25	712	737	35	4304	4339

Abbreviations: AF (atrial fibrillation).

[a] By protocol, to limit verification bias, we strived to perform the reference test (12 lead ECG) in a 10% random sample of patients with three negative index tests. In addition, to calculate all relevant diagnostic parameters, we used multiple imputation in the analysis.

[b] The 'complete cases' present the patients actually receiving the 12 lead ECG, i.e. the patients with ≥1 positive index test plus the random sample of patients with three negative index tests.

[c] The 'pooled data' present the computed results (rounded numbers) of 100 datasets with 10 iterations per set, created with multiple imputation (see main text).

Appendix 5

Diagnostic accuracy of five different index test combinations in a primary care population undergoing opportunistic screening for atrial fibrillation (AF; 0.8% AF, 35/4339), pooled results after multiple imputation.[a]

Index test combinations[b]	Sensitivity (%) M, range	Specificity (%) M, range	PPV (%) M, range	NPV (%) M, range	Positive LR M, range	Negative LR M, range
A	92.1	88.4	6.0	99.9	7.9	0.09
	62.7-100	88.3-88.5	5.6-6.2	99.5-100	5.4-8.7	0.00-0.42
B	92.1	90.4	7.1	99.9	9.6	0.09
	62.7-100	90.3-90.4	6.7-7.4	99.5-100	6.5-10.5	0.00-0.41
C	83.1	89.6	6.0	99.8	8.0	0.19
	56.9-90.9	89.5-89.6	5.6-6.3	99.4-99.9	5.4-8.8	0.10-0.48
D	60.8	99.3	39.5	99.7	81.5	0.39
	41.2-67.7	99.2-99.3	37.7-39.6	99.3-99.8	55.2-91.2	0.33-0.59
E	49.7	98.7	23.4	99.6	38.1	0.51
	35.0-58.1	98.4-98.8	20.0-26.5	99.2-99.7	27.3-47.0	0.43-0.66

Abbreviations: M (mean), PPV (positive predictive value), NPV (negative predictive value), ECG (electrocardiography), LR (likelihood ratio).

[a] By protocol, to limit verification bias, we strived to perform the reference test (12 lead ECG) in a 10% random sample of patients with three negative index tests. In addition, to calculate all relevant diagnostic parameters, we used multiple imputation in the analysis (see main text). We report the pooled results (mean plus range) of 100 datasets with 10 iterations per set, created with multiple imputation (see main text).

[b] Description of the index test combinations:

A. All three index tests, positive if at least one was positive.

B. Radial pulse palpation and handheld electrocardiography, positive if either test was positive.

C. Radial pulse palpation and electronic blood pressure measurement, positive if either test was positive.

D. Radial pulse palpation and handheld electrocardiography, positive if both tests were positive.

E. Radial pulse palpation and electronic blood pressure measurement, positive if both tests were positive.

Reporting checklist for diagnostic test accuracy study.

Based on the STARD guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STARDreporting guidelines, and cite them as:

Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L, LijmerJG Moher D, Rennie D, de Vet HCW, Kressel HY, Rifai N, Golub RM, Altman DG, Hooft L, Korevaar DA, Cohen JF, For the STARD Group. STARD 2015: An Updated List of Essential Items for Reporting Diagnostic Accuracy Studies.

Reporting Item	Page Number
Title or abstract	

None	#1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	1
Abstract			
None	#2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts https://www.equator-network.org/reporting-guidelines/stard-abstracts/)	3
Introduction			
None	#3	Scientific and clinical background, including the intended use and clinical role of the index test	6
None	#4	Study objectives and hypotheses	6
Methods			
Study design	#5	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	7
Participants	#6	Eligibility criteria	7
Participants	#7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	7
Participants	#8	Where and when potentially eligible participants were identified (setting, location and dates)	7

Participants	#9	Whether participants formed a consecutive, random or convenience series	7
Test methods	#10	Index and reference tests in sufficient detail to allow replication	7-8
Test methods	#11	Rationale for choosing the reference standard (if alternatives exist)	n/a
Test methods	#12	Definition of and rationale for test positivity cut-offs or result categories of the index and reference tests, distinguishing pre-specified from exploratory	7-8
Test methods	#13	Whether clinical information and reference standard results were available to the performers / readers of the index test; Whether clinical information and index test results were available to the assessors of the reference standard	8
Analysis	#14	Methods for estimating or comparing measures of diagnostic accuracy	9
Analysis	#15	How indeterminate index test or reference standard results were handled	9
Analysis	#16	How missing data on the index test and reference standard were handled	9
Analysis	#17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	n/a
Analysis	#18	Intended sample size and how it was determined	7

Results			
Participants	#19	Flow of participants, using a diagram	Figure 1
Participants	#20	Baseline demographic and clinical characteristics of participants	Table 1
Participants	#21	Distribution of severity of disease in those with the target condition, and distribution of alternative diagnoses in those without the target condition	n/a
Participants	#22	Time interval and any clinical interventions between index test and reference standard	10-11
Test results	#23	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	Table 2 Appendix 3
Test results	#24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Table 3
Test results	#25	Any adverse events from performing the index test or the reference standard	n/a
Discussion			
None	#26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	12
None	#27	Implications for practice, including the intended use and clinical role of the index test	14

Other information			
None	#28	Registration number and name of registry	2
None	#29	Where the full study protocol can be accessed	18
None	#30	Sources of funding and other support; role of funders	16