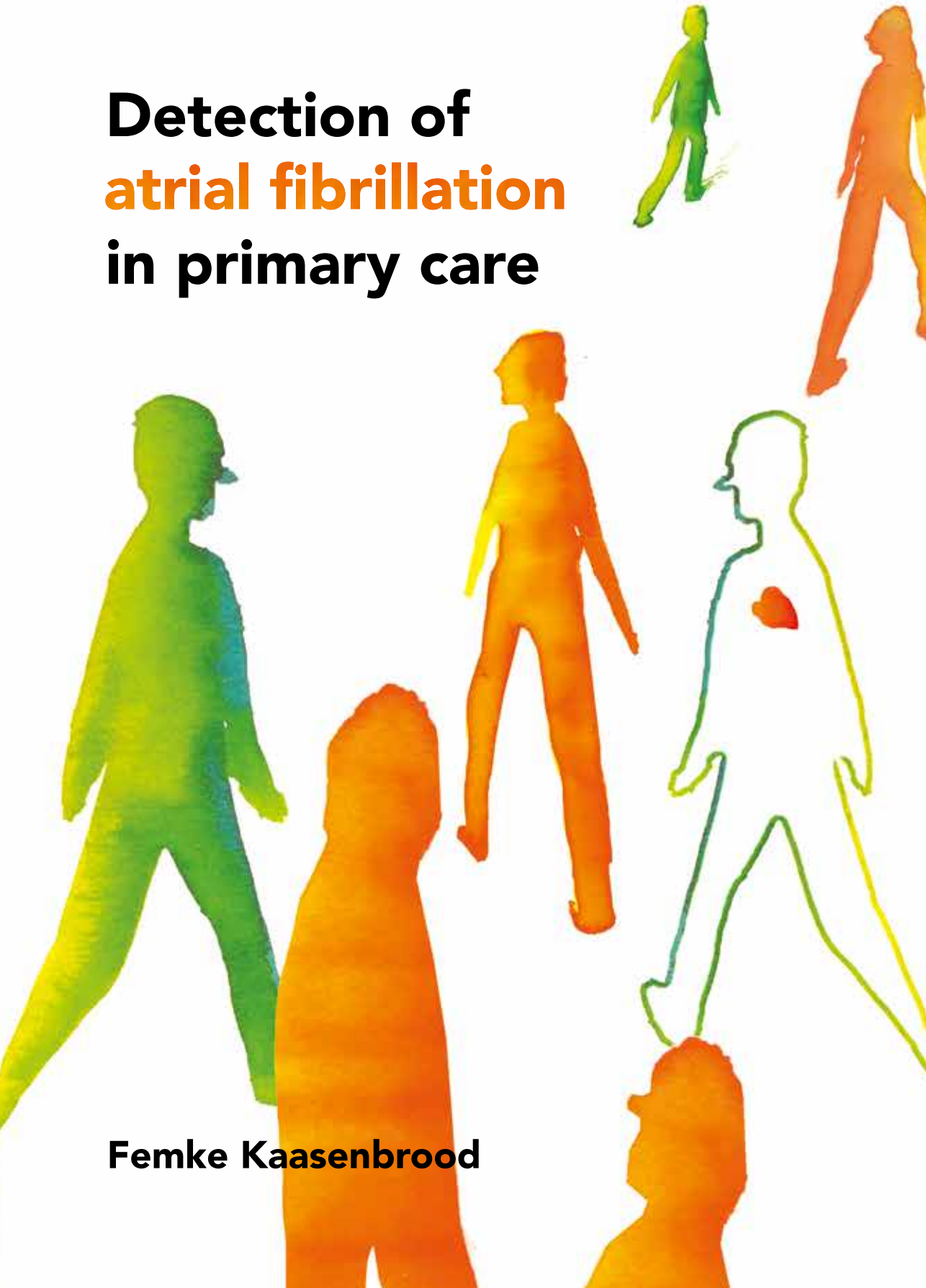
Detection of atrial fibrillation in primary care



Femke Kaasenbrood

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Colofon

Detection of atrial fibrillation in primary care
Femke Kaasenbrood
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Detection of atrial fibrillation in primary care

Detectie van atriumfibrilleren in de eerste lijn
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op het gezag van de rector magnificus, prof. dr. H.R.B.M. Kummeling, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op donderdag 10 oktober 2019 des middags te 2.30 uur

door

Femke Kaasenbrood
geboren op 5 maart 1988
te Utrecht

Promotoren:	Prof. dr. F.H. Rutten
	Prof. dr. A.W. Hoes
Copromotoren:	Dr. M. Hollander
	Dr. R.G. Tieleman

Contents

Introduction

Case

Mr. K, a 68-year old man with type 2 diabetes (T2D) has been participating in a primary care disease management program for diabetes in the last five years. He visits the practice nurse for one of his regular control visits. The last three months he did not experience T2D-related symptoms, but with the doorknob in his hand, he mentions "By the way, I had several episodes of palpitations during the last few months, lasting a couple of minutes. In fact, even at this very moment I experience similar complaints. Nothing to worry about I suppose?"

The practice nurse decides to palpate the pulse, and the pulse is irregular. Later that day she discusses her findings with the general practitioner (GP), and it is decided to make a 12-lead ECG two days later. This 12-lead ECG shows a sinus rhythm, without any further abnormalities. The option of event recording or Holter is not considered and they agree upon a 'wait and see' in shared decision with Mr. K.

Two years later Mr. K visits the primary care practice to receive his yearly flu vaccination. The primary practice participated in an initiative to screen for atrial fibrillation (AF) during the influenza vaccination campaign by holding a device for one minute that generates a lead I single lead registration. The device shows 'a red signal' which means the heart rhythm is irregular, and after interpretation of the registration by the cardiologist, he is diagnosed with AF.

His GP explains to him that he has paroxysmal AF. On hindsight, the palpitations he previously experienced were probably caused by AF. Given the paroxysmal character it was missed during the 12-lead ECG recording two years ago. Because Mr. K has a CHA_2DS_2-VASc score of 2, the GP discusses the possibility to start anticoagulation, because this is expected to reduce the risk of ischaemic stroke sufficiently to compensate for the risk of treatment-related bleeding. The patient leaves with a prescription for a non-vitamin K oral anticoagulants (NOAC). At home after talking to his wife, Mr. K becomes unsure about the diagnostic process. "Could the AF not have been detected earlier?"

Importance of diagnosing AF

Atrial fibrillation (AF) is a common cardiac arrhythmia and the prevalence increases with age up to 8% of those aged ≥65 years and 18% of those aged ≥85 years (figure 1).[1] The prevalence is expected to rise in the near future due to ageing of the population and the increase in the prevalence of important risk factors: arterial hypertension and diabetes.[2] AF increases the risk for

stroke around five-fold and the risk for death two-fold.[3] Moreover, ischaemic strokes in patients with AF are more severe than in patients without AF with an increased risk of a fatal outcome and a higher recurrence rate of stroke.[4] AF is also associated with other cardiovascular problems, notably myocardial infarct and heart failure.[5 6] Treatment with anticoagulants, (vitamin K antagonist (VKA) or NOAC) reduces stroke risk with around 60% at the expense of at least 1% major bleedings yearly including 0.3% intracranial bleeds.[7] Upstream treatment of AF, for example with heart rate reducing medication, at an early stage might delay progression from paroxysmal to persistent or permanent AF, and initiation of risk-factor modification, notably blood pressure lowering or treating heart failure, might reduce complications from AF progression.[8 9] Thus, early detection is crucial to facilitate timely interventions to improve prognosis.

About one third of AF patients experience no or only mild symptoms and many of them will not visit a GP. [10-12] Moreover, AF can occur in paroxysms, notably in the beginning of the disease, in which case it is more difficult to establish the diagnosis. These aspects make diagnosing AF a challenge, notably in its early phase.[12] Patients with undiagnosed AF are sometimes referred to as 'silent AF', and unfortunately, its first manifestation may be stroke.[13] In 11.5% of ischaemic strokes, AF is newly diagnosed if patients' heart rhythm is monitored for at least 12 hours.[13] Also, single time-point screening in the population at large identified 1.4% previously unknown AF among those aged ≥65 years.[14] The majority of these screen-detected AF cases is at increased risk for ischaemic stroke and considered eligible for treatment with anticoagulants.[7] These data suggest there is ample room for improvement in early AF detection in primary care, which could be done by early diagnosis if patients have symptoms suggestive of AF, or by screening, that is, irrespective of presence of symptoms.

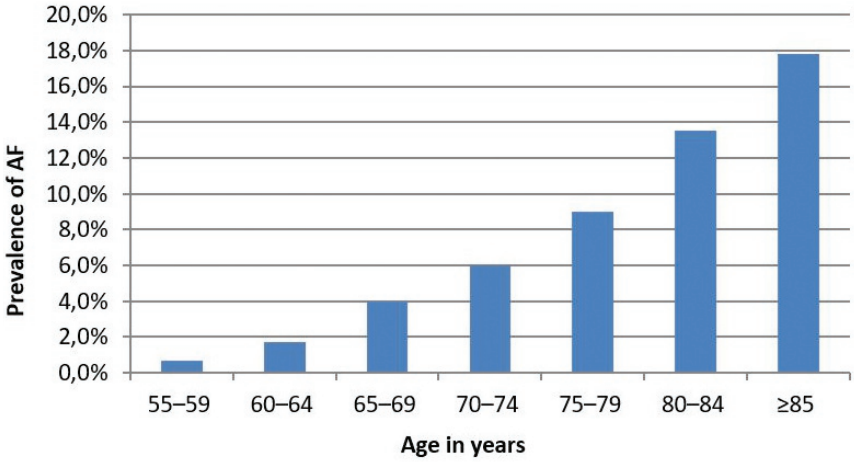

Figure 1. Prevalence of AF detected in usual care in general population aged 55 years or more Data derived from 'the Rotterdam study' by Heeringa et al[1]. This was a population-based prospective cohort study among inhabitants of Rotterdam aged 55 years and above that determined AF prevalence among different age categories.

Approaches to improve AF detection

When a patient visits the doctor with symptoms suspicious for AF, a 12-lead ECG can be made for diagnosis. A typical AF-related symptom is palpitations. Less typical are tiredness, shortness of breath, dizziness, chest pain and (pre) syncope.[15] However, studies on symptomatology are mainly performed in chronic AF cases and symptoms have not been compared to control patients without AF. It remains unknown what symptoms are most relevant to identify AF cases in an early phase.

To improve early detection of AF, current guidelines recommend opportunistic screening for AF in primary care in patients aged ≥65 years by pulse palpation, followed by a 12-lead ECG in case of irregularity.[10 16 17] Some countries explored possibilities of community screening using systematic or opportunistic approaches in cohort studies or by organizing theme events.[18 19] Also pharmacies offer an attractive setting to screen, since patients with chronic diseases visit their pharmacy every 1 to 3 months.[20] When such screening strategies are undertaken, it is necessary to ensure an adequate diagnostic-treatment chain, which includes referral to a physician to confirm AF and to decide on subsequent interventions. An optimal referring policy is necessary to minimalize worrying of patients with false positive results and to start treatment

for AF when necessary. When screening for AF among those aged ≥65 years, the prevalence of AF is around 2%. Consequently, the positive predictive value is relatively low. Moreover, diagnostic devices to screen for AF are mainly developed to ensure a high negative predictive value in order not to miss any AF diagnosis; this results in an increased proportion of false positive results. The burden of handling false positive results (being much higher than true positives) will therefore be a major challenge when formalizing a screening program, especially outside health care settings.

General practice seems an appropriate setting to screen for AF because community dwelling people ≥65 years visit the surgery on average seven times per year.[21] Nowadays, many GP practices have the opportunity to record a 12-lead ECG within their own practice or in a diagnostic center nearby and GPs can either analyze the ECG themselves, if trained, or consult a cardiologist. In addition, practice nurses can support the screening activities. Screening can be performed in an opportunistic or systematic approach. In opportunistic screening, the presence of AF is assessed whenever a patient visits a GP, whereas systematic screening could be performed in a targeted population, e.g. higher risk patients who all are invited for screening. In a cluster randomized trial among 50 primary care centers in the UK, patients aged ≥65 years were randomized to opportunistic screening, systematic screening or routine care. In the opportunistic screening group, all eligible patients were flagged in the electronic GP file and in the systematic screening group all eligible patients were invited by post. After 12 months, new AF was detected in 1.6% in both screening groups as compared to 1.0% in the care as usual group.[22]

An appropriate sustainable screening approach should balance on the one hand the yield of newly detected AF rate and on the other hand the burden on the primary care practice and on those receiving a false positive AF diagnosis. Screening should focus on those aged ≥65 year because of the increased AF prevalence and therapeutic consequences in this age category.

Devices for easy AF detection

With pulse palpation in general practice among those aged 65 or over 8% of those with AF is missed and in 18% of those without AF the pulse palpation will be classified as irregular.[22 23] Importantly, for adequate AF detection employees should be trained to adequately palpate the pulse and in routine primary care the pulse is much less frequently assessed than recommended by guidelines.[16]

[22] In the past decade many diagnostic tools have been developed to improve AF detection, ranging from single-time point measurement devices to devices capable of long-term continuous measurements to characterize brief episodes of AF. Devices to screen patients in primary care should be easy-to-use and capable of single time-point measurements.

Devices that are most often used include oscillometric blood pressure monitors, finger photoplethysmography with smartphone camera and handheld single-lead ECG devices.[23] A meta-analysis combined the results of diagnostic accuracy studies of these devices in different settings, all with a relative high prevalence of AF, and presented only overall sensitivity and specificity. Oscillometric blood pressure monitors with AF detection function offer a high sensitivity of around 0.98 and specificity of 0.92.[23] Finger photoplethysmography with smartphone camera and flash had a sensitivity of 0.97 and specificity of 0.95 and offering the possibility to be built into smart-watches and fitness bands.[23] A range of handheld devices producing single-lead ECGs with automatic algorithms to detect irregularity had a sensitivity of 0.91 and a specificity of 0.95.[23]

In case of suspicion of AF, preferably a 12-lead ECG should follow immediately after a patient has used a screening tool, to confirm AF status. However, in everyday general practice it is not always feasible to perform a 12-lead ECG directly and it is often performed hours to days later, with the risk of missing paroxysmal AF. Single-lead ECG devices are potentially attractive because they record a single-lead ECG for one minute, and this can be transported to a computer for visual interpretation by a trained GP or cardiologist. Guidelines consider a cardiologist's confirmation of AF on a one minute rhythm registration as good as an AF diagnosis based on a 12-lead ECG registration.[10 24] However, single-lead ECGs nearly never show P-waves (or only artificially created ones) in those with sinus rhythm, and therefore the interpretation heavily, if not completely, depends on R-R intervals. These single-lead ECGs are therefore more difficult to interpret than 12-lead ECGs. Although such hand-held single-lead ECG devices are increasingly being used in daily practice, the diagnostic accuracy of a physician's interpretation of these single-lead ECG has not yet been assessed adequately.[10 25 23] Also, the evidence about the value of such devices in primary care is very limited. Importantly, the yield of such devices in daily clinical practice remains unknown, e.g. when tested in conjunction with the yearly influenza vaccination campaign, or when made available on a day-to-day basis in primary care.

Aim and outline of this thesis

This thesis focuses on the role of general practice in detection of AF and aims to i) provide insight in the effectiveness and feasibility of two possible strategies for AF screening in primary care, ii) explore whether patients with screen-detected AF more often experience AF-related signs and symptoms than patients without AF and iii) investigate whether a one minute single-lead ECG recorded by a hand-held ECG device accurately diagnoses AF.

Chapter 1 describes the yield of screening for AF with a hand-held single-lead ECG device (the MyDiagnostick®) during influenza vaccination sessions in ten GP practices. The screening was performed by research nurses.

In **chapter 2** we evaluated the cost-effectiveness of screening for AF during influenza vaccination with this hand-held single-lead ECG device.

Chapter 3 describes a cluster-randomized trial on the yield in terms of AF detection comparing screening with a hand-held single-lead ECG device at the discretion of GP practices to care as usual. In the intervention arm, the GP practices were instructed to screen with the MyDiagnostick® during one year any person aged ≥65 year that visited the surgery.

Chapter 4 describes a case-control study in which patients with newly screen-detected AF are compared with controls without AF to investigate whether they more frequently visited the GP practice with symptoms that may raise suspicion of AF compared to those without AF diagnosis in the two years preceding the AF diagnosis.

In **chapter 5** we describe the results of a survey among patients that were screened for AF in primary care on symptoms that may raise suspicion for AF.

Chapter 6 evaluates the diagnostic accuracy of MyDiagnostick® single-lead ECGs of patients visiting a cardiology outpatient clinic for routine care interpreted by different GPs and cardiologists.

Finally, in **chapter 7** the main findings and conclusions of this thesis are discussed.

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Yield of screening for atrial fibrillation in primary care with a hand-held, single-lead electrocardiogram device during influenza vaccination

Femke Kaasenbrood
Monika Hollander
Frans H. Rutten
Leo J. Gerhards
Arno W. Hoes
Robert G. Tieleman

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2

Abstract

Aims To assess the yield of screening for atrial fibrillation (AF) with a hand-held single-lead electrocardiogram (ECG) device during influenza vaccination in primary care in the Netherlands.

Methods and results We used the MyDiagnostick® to screen for AF in persons who participated in influenza vaccination sessions of ten Dutch primary care practices. In case of suspected AF detection by the stick, the recorded 1-min ECG registrations were analysed by a cardiologist. We scrutinized electronic medical files of the general practitioners to obtain information about the cases screened. Multivariable logistic regression analysis was performed to predict the relation between patient characteristics and a new screen-detected diagnosis of AF. In total, 3,269 persons were screened for AF during the influenza vaccination sessions of 10 general practitioner practices. As a result, 37 (1.1%) new cases of AF were detected. Prior transient ischaemic attack or stroke (OR 6.05; 95%CI 1.93–19.0), and age (OR 1.09 per year; 95% CI 1.05–1.14) were independent predictors for such newly screen-detected AF. Of the 37 screen-detected AF cases, 2.7% had a CHA_2DS_2-VASc of 0, 18.9% a score of 1, and 78.4% a score of 2 or more. The majority needed oral anticoagulant therapy.

Conclusions Screening seems feasible with an easy to use single-lead, hand-held ECG device with automatic AF detection during influenza vaccination in primary care and results in a '1-day' yield of 1.1% new cases of AF.

Trial registration clinicaltrials.gov NCT02006524.

Introduction

Atrial fibrillation (AF) affects 1–2% of the total population, with prevalence increasing with age.[1] If untreated, AF increases the risk of ischaemic stroke, heart failure, and mortality.[2] Anticoagulants are very effective and reduce the stroke risk by 60% and all-cause mortality by 25%.[3] Underdiagnosis of AF is, however, common and may at least partly be related to a lack of symptoms, so-called 'silent AF'.[4] In patients admitted with an ischaemic stroke in the presence of AF, the arrhythmia was unknown in one-fourth to almost half of the patients.[5,6] Early detection of AF followed by adequate anticoagulation can help prevent ischaemic strokes.[1] Older age and co-morbidities such as heart failure, hypertension, diabetes, prior transient ischaemic attack (TIA)/stroke, and vascular disease (CHA_2DS_2-VASc score) drive the risk of thromboembolism.[7] Guidelines recommend prescribing anticoagulation therapy to AF patients with a CHA_2DS_2-VASc score of 1 or more (or 2 or more), independent of whether AF is paroxysmal or persistent, screen detected, or diagnosed in patients with symptoms. [1,4,8,9]

The 2010 European Society of Cardiology (ESC) guidelines recommend screening for AF among those aged 65 years and over in primary care, for instance by pulse palpation during blood pressure measurement, and followed by an electrocardiogram (ECG) in case of irregularity.[1] Practice studies in primary care showed that active pulse feeling is infrequently performed nowadays, and there seems to be room for improvement of (early) detection of AF with devices.[10] Non-invasive devices such as specialized blood pressure monitors that automatically detect AF (MicroLife® RR monitor), and devices that register single-lead ECGs (AliveCor®, MyDiagnostick®) may be considered good alternatives for AF screening.[11,12] The MyDiagnostick® is an easy to apply device that registers and automatically analyses a single-lead I rhythm strip after holding the device with both hands for one minute. It signals a red light in case of rhythm irregularity suspicious for AF, and a green light in case of absence of AF. The rhythm strip can be visualized and analysed by linking the device to a computer. A recent validation study showed that the sensitivity and negative predictive value of a green light signal was very good (both 100%) in a cardiology setting with a prevalence of AF of 28%. In a pilot study, this device seemed feasible as a screening tool during influenza vaccination in primary care.[11] These results need confirmation in a larger study to quantify the yield of selective 'mass screening' during influenza vaccination.

Every autumn, general practitioners (GPs) in the Netherlands invite eligible community-dwelling persons for a 1-day influenza vaccination session. Dutch

indications for influenza vaccination are: (i) age 60 years or over, and (ii) for younger persons, (a history of) diabetes mellitus, COPD, asthma, ischaemic heart disease, or heart failure.[13] This setting provides an ideal opportunity for selective screening of a large population of community-dwelling persons who are at increased risk of AF.

We aim to (i) calculate the proportion of newly detected cases, (ii) assess feasibility of large-scale screening with a single-lead ECG device during influenza vaccination, (iii) evaluate the patient characteristics most predictive for a new screen-detected diagnosis of AF, (iv) determine the CHA_2DS_2-VASc score of novel screen-detected cases and compare these with known cases with AF who received influenza vaccination, and (v) identify enablers and barriers to the implementation of screening with the MyDiagnostick® during influenza vaccination.

Methods

Study population

Ten general practices participated, all located in the northern part of the Netherlands, in the vicinity of Groningen. These practices had 49,190 community-dwelling persons enlisted and in the year 2013, 15,032 (30.6%) persons were eligible and invited for the yearly influenza vaccination. Eventually, 9,450 (62.9%) showed up to receive the influenza vaccination at the 1-day session. We invited a sample of 3,269 persons (34.6% of all participants of the influenza vaccination) to hold the MyDiagnostick®. Patients were invited to participate, irrespective of whether the patient was already known with the arrhythmia. Patients were informed that AF mainly affects elderly, that is, those aged ≥65, and research nurses were instructed to selectively screen people aged over 60, including those already known with AF. All participants signed informed consent. The management of newly detected cases of AF was at the discretion of the participating GP.

The study was approved by the medical ethics committee of the Martini Hospital Groningen.

Study procedure

Most general practices in the Netherlands use two rooms for the mass influenza vaccination. Two GP nurses perform the registration in one room, and in the second room three to four healthcare workers (a mix of nurses and GPs) do the

immunization. During the year of the study, the 10 participating GP practices performed their influenza vaccination each on another evening. Thus, one and the same research team could visit each practice and blend screening for AF with the immunization programme. Two trained research nurses explained the MyDiagnostick® to influenza participants older than 60, and two other nurses took care of the handling of the device by patients, the informed consent, and the registration of the results (green or red signaling). The four research nurses received a training of 30 min on the ins and outs of the MyDiagnostick® device, about asking informed consent, and the filling out of the case record form.

Within the logistics of the influenza vaccination every eligible participant received a short-lasting instruction on how to hold the device during 1 min and information on the consequences of a green and red signal. Our research team used 10 sticks every evening and was able to screen 160 persons per hour. For the purpose of this study, a cardiologist was present during the influenza vaccination session in all 10 locations, and immediately judged the one-channel ECG on the computer with the stick connected to it.

After the screening sessions, the MyDiagnostick® rhythm registrations of all 3,269 participants were analysed. In case of a red light, the ECG recording was analysed by two cardiologists (R.T. and L.J.G.) for the presence or absence of AF. In case of conflicting interpretation, the two cardiologists discussed the case to come to consensus. The ECG recordings of the green MyDiagnostick® results were analysed by one single cardiologist (R.T.). In this article, we refer to a green MyDiagnostick® light in combination with no AF on the single-lead ECG registration as a 'negative MyDiagnostick® result'. A red light in combination with confirmation of AF on the ECG strip is a 'positive MyDiagnostick® result'.

Data collection from the electronic medical files of the participating general practitioners.

Of all participants, age and gender were registered, and from a random sample of 220 persons with a negative MyDiagnostick® result the information on co-morbidities was gathered by scrutinizing the GP's electronic medical files including letters from medical specialists. The same was done in all AF cases with the screening, both new and already known cases.

Table 1. Patient characteristics of attendees of the influenza vaccination, irrespective of AF status.

	Persons attending influenza vaccination N = 9,450	Individuals who did not hold the MyDiagnostick® N = 6,181	Individuals who held the MyDiagnostick® N = 3,269	P-value*
Men (%)	4,375 (46.3)	2,773 (44.9)	1,602 (49.0)	<0.001
Mean age in years (± SD)	64.1 ± 16.5	60.8+18.3	69.4 ± 8.9	<0.001
Age > 60 years (%)	6,795 (71.9)	3,797 (61.4)	2,998 (91.7)	<0.001
Age > 65 years (%)	5,306 (56.1)	2,749 (44.5)	2,557 (78.2)	<0.001
Age > 75 years (%)	2,153 (22.8)	1,325 (21.4)	828 (26.2)	<0.001

*P-value is given for the comparison of individuals who held the MyDiagnostick® (N = 3,269) and those who did not hold this device (N = 6,181).

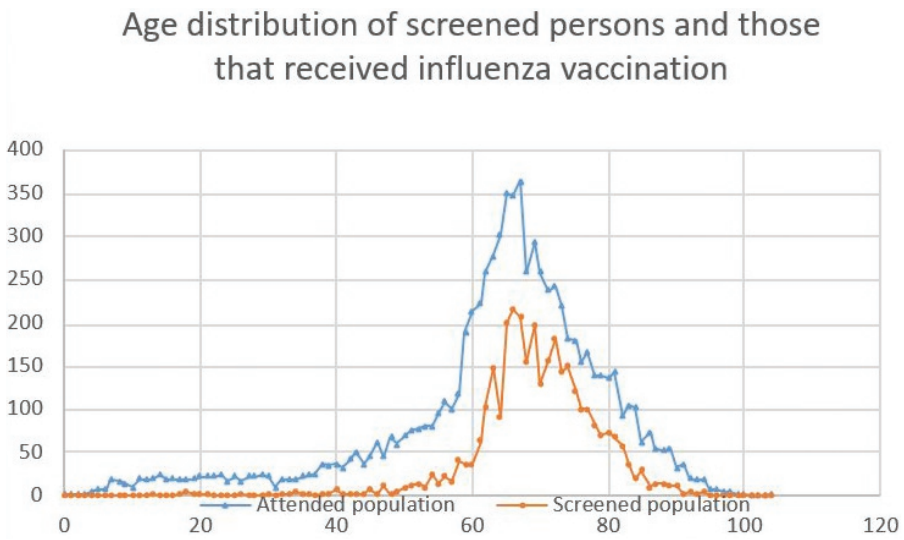

Figure 1. Age distribution of the 9,450 persons attending influenza vaccination compared with 3,269 screened persons. Attended population: all persons who came for influenza vaccination in 2013. Screened population: all persons who held the MyDiagnostick® during this vaccination.

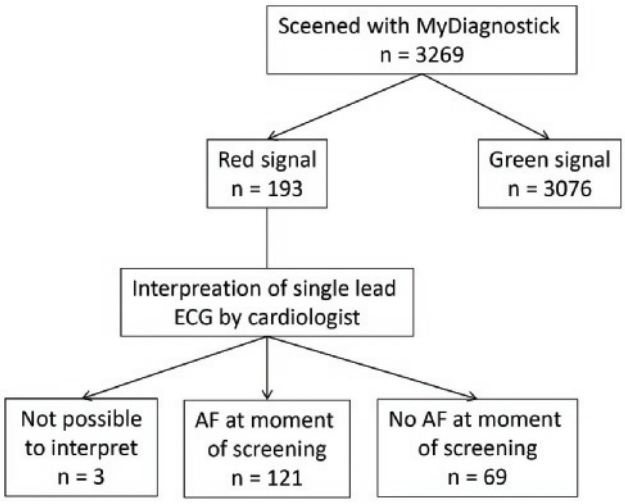

Figure 2. Flow chart of study.

Data analysis

For comparison between groups, we used the $\chi 2$ test or Fisher's exact test for dichotomous variables and Student's t-test for continuous variables. Medical characteristics between sample with no AF at screening (n = 220) and the screen-detected cases (n = 37) were first compared using univariable logistic regression. We included age, male gender, history of stroke or TIA and at least one of remaining CHA_2DS_2-VASc score co-morbidities. We used only four predictors for both univariable and multivariable logistic regression analyses because we had 37 new cases of screen-detected AF. All analyses were performed with R for windows version 3.1 (The R foundation statistical computing, http://cran.r-project.org).

Results

In total, 9,450 persons participated in the influenza vaccination (mean age 64.1, SD 16.5, years). The 3,269 persons (34.6%) who held the MyDiagnostick® were more often men (49.0 vs. 44.9%) and on average 8.6 years older than the 6,181 persons who were not screened (Table 1 and Figure 1). It was logistically not feasible to ask all eligible persons to participate because providing written informed consent took some time.

Table 2. Baseline characteristics of individuals who held the MyDiagnostick® divided in new screen-detected cases of AF, patients already known with AF, and a random sample of patients with no AF

	Newly detected AF with screening N = 37	Already known with AF and a red light with screening N = 84	Sample of patients with no AF[a] N = 220
Men (%)	21 (56.8)	49 (58.3)	101 (45.9)
Mean age (SD)	75.9 (8.6)	75.6 (8.3)	65.9 (12.4)
Medical history			
Hypertension (%)	24 (64.9)	55 (65.5)	95 (43.2)
Diabetes (%)	9 (24.3)	23 (27.4)	52 (23.6)
Heart failure (%)	2 (5.4)	18 (21.4)	2 (0.9)
Stroke (%)[b]	7 (18.9)	9 (10.7)	6 (2.7)
TIA (%)	3 (8.1)	10 (11.9)	1 (0.5)
VTE (%)[c]	2 (5.4)	7 (14.3)	10 (4.5)
Peripheral arterial disease (%)	3 (8.1)	2 (2.4)	7 (3.2)
Prior myocardial infarct (%)	2 (5.4)	10 (14.3)	7 (3.2)
Valvular repair (%)	0 (0)	6 (7.1)	1 (0.5)
CABG/PCI (%)	2 (5.4)	14 (16.7)	19 (8.6)
COPD (%)	4 (10.8)	12 (17.1)	17 (7.7)
Renal disease (%)	3 (8.1)	11 (15.7)	8 (3.6)
Pacemaker (%)	0 (0.0)	4 (4.8)	2 (0.9)
Vitamin K antagonists (%)	2 (5.4)[d]	70 (83.3)	5 (2.3)[d]
NOACs (%)	0 (0.0)	7 (8.3)	0 (0.0)
ASA (%)	4 (10.8)	7 (8.3)	46 (20.9)
ACE inhibitors (%)	10 (27.0)	31 (36.9)	55 (25.0)
Beta-blockers (%)	11 (29.7)	59 (70.2)	58 (26.4)
Calcium channel blockers (%)	13 (35.1)	21 (25.0)	27 (12.3)

[a] Sample of 220 persons unknown with AF and also sinus rhythm on the MyDiagnostick® single-lead ECG with screening during influenza vaccination. [b] Stroke is defined as ischaemic stroke or cryptogenic stroke not being an haemorrhagic stroke. [c] VTE ¼ venous thromboembolism, including history of pulmonary embolism and/or deep vein thrombosis. [d] Indications for VKA in two cases was (1) a history of deep vein thrombosis and lung embolus, and a history of ischaemic stroke. The indications in five cases with a negative MyDiagnostick® result were (1) a history of more than one deep vein thrombosis or lung embolus, (2) heart valve replacement, and (3) secondary prevention after ischaemic stroke. NOAC, non-vitamin K antagonist oral anticoagulant.

In total, 193 participants (5.9% of the screened population) had a red signaling with the MyDiagnostick®. Of them, 121 (3.7% of the screened population) had AF on the single-lead rhythm strip according to the cardiologists (Figure 2). Eighty-four cases were already known with AF and 37 (1.1% of the screened population) were new screen-detected cases. In 3 of the 193 cases with a red signal, the rhythm strip could not be interpreted by either cardiologist and these were considered as 'no AF'. In all 3076 cases with a green light, the cardiologist could confirm sinus rhythm.

The 37 new screen-detected cases of AF were older, had more co-morbidities such as hypertension (64.9% vs. 43.2%), stroke (18.9% vs. 2.7%), TIA (8.1 vs. 0.5%), and COPD (10.8% vs. 3.2%) than a random sample of 220 participants of the influenza vaccination, but without AF (Table 2). The unadjusted odds ratios of a new screen-detected diagnosis of AF were 9.78 (95% CI 3.38–28.33) for a history of stroke or TIA, 0.65 (95% CI 0.32–1.31) for male gender, 1.09 per year for older age (95% CI 1.05–1.14), and 1.83 (95% CI 0.85–3.98) for a history of either diabetes mellitus, hypertension, heart failure, or vascular disease. Multivariable logistic regression showed that age (OR 1.09 per year; 95% CI 1.05–1.14) and a history of ischaemic stroke or TIA (OR 6.05; 95%CI 1.93–19.0) were independent predictors of a screen-detected diagnosis of AF (Table 3).

The prevalence of screen-detected AF cases increased with age, from 0% in those aged, 60 years to 4.9% in those aged 85 years and over (Table 4).

Among screen-detected AF patients, 2.7% had a CHA_2DS_2-VASc of 0, 18.9% a score of 1, and 78.4% a score of 2 or more. The distribution was similar to cases already known with AF (Table 5).

Of the 193 individuals with a red signal, 72 (37.3%) had no AF on the single-lead I ECG analysed by the two cardiologists. Thirty-four (47.2%) had premature atrial or ventricular complexes, 25 (34.7%) had sinus arrhythmia, and 10 (13.9%) had irregularity caused by artefacts. Three cases had un-interpretable results (0.1% of all cases who held the MyDiagnostick®); one because of artefacts, one because of a pacemaker rhythm, and one because of the cardiologists thought that it could be either extra systoles or atrial flutter. With a 12-lead ECG 1 day later, two had sinus rhythm, and one sinus arrhythmia. One of these three cases was known with paroxysmal AF and had DDDR pacemaker for bradycardia, and the pacemaker was active at the time he held the MyDiagnostick® and not during the 12-lead ECG.

Table 3. Multivariable logistic regression analysis relating participants' characteristics to screen-detected AF

	Univariable analysis		Multivariable analysis	
	OR for screen-detected AF	95% Confidence interval	OR for screen-detected AF	95% Confidence interval
Age per year	1.09	1.05-1.14	1.09	1.05-1.14
Male gender	0.65	0.32-1.31	0.56	0.25-1.23
History of stroke/TIA	9.78	3.38-28.33	6.05	1.93-18.98
History of one or more remaining co-morbidities of the CHA_2DS_2-VASc score[a]	1.83	0.85-3.98	0.91	0.38-2.18

[a] Diabetes mellitus, hypertension, heart failure, and/or vascular disease (coronary heart disease, CABG/PCI, myocardial infarction, and/or peripheral arterial disease).

Table 4. Cases with a red signal with the MyDiagnostick® divided in those with no AF and with AF on the rhythm strip, categorized per age category and divided by the number of cases screened

Age	Red light but no AF/screened cases[a]	%	Red light and already known AF/ screened cases[b]	%	Red light and new screen-detected AF/ screened cases[c]	%
<60	5/271	1.8	3/271	1.1	0	0
60-64	10/441	2.3	4/441	0.9	4/441	0.9
65-74	29/1,729[d]	1.7	31/1,729	1.8	14/1,729	0.8
75-84	24/725[e]	3.3	37/725	5.1	14/725	1.9
>85	4/103	3.9	9/103	8.7	5/103	4.9

[a] Red light with MyDiagnostick® suggesting irregular heart rhythm and possibly AF, but without AF after interpretation of the single-lead ECG registration of 1 min by the cardiologist, per number screened individuals per age category. [b] Cases with AF at moment of screening that was already known per number of screened individuals per age category. [c] Screen-detected AF cases per number of screened individuals per age category. [d] From 29 cases, 2 were previously diagnosed with paroxysmal AF but showed no AF at moment of screening. [e] From 24 cases, 7 were previously diagnosed with paroxysmal AF but showed no AF at moment of screening.

Table 5. CHA_2DS_2-VASc[a] scores for individuals with AF, screen-detected cases vs. previously known AF cases

	Screen-detected AF N = 37	Already known AF N = 84	P-value
Mean CHA_2DS_2VASc score	3.4 (1.9)	3.6 (1.7)	0.49
CHA_2DS_2VASc score 0	1 (2.7)	1 (1.2)	0.55
CHA_2DS_2VASc score 1	7 (18.9)	10 (11.9)	0.31
CHA_2DS_2VASc score ≥2	29 (78.4)	73 (86.9)	0.23

[a] CHA2DS2-VASc score is a clinical decision rule used to predict the risk of stroke in patients with AF. A higher score indicates a greater risk of stroke. Scores range from 0 to 9, categories include heart failure (1), hypertension (1), age ≥65 years (1), age ≥75 years (1), diabetes mellitus (1), prior ischaemic stroke and/or TIA and/ or arterial thromboembolism (2), vascular disease[b] (1), and female gender (1). [b] Vascular includes coronary heart disease, CABG/PCI, myocardial infarction, and/ or peripheral arterial disease.

Discussion

By screening community-dwelling persons during influenza vaccination in primary care AF was detected in 3.7% (2.6% already known cases of AF, and 1.1% new cases). The screen-detected cases of AF had a similar CHA_2DS_2-VASc score as those already known with AF, and the large majority would need anticoagulation. Age (OR 1.09 per year, 95%CI 1.05–1.14) and a history of TIA or stroke (OR 6.05 95%CI 1.93–18.98) were independent predictors for screen-detected AF.

In a previous study in the UK, community-dwelling person aged 65 years or over from primary care were investigated by systematically taking the pulse followed by a 12-lead ECG if irregular. With this method, 1.6% new cases were detected during 1 year, while 1.0% a year was detected with care as usual.[10] A systematic review including 16 screening studies in persons aged 65 years or over from the community, primary care, or cardiology outpatients clinics showed that screening with pulse palpation resulted in 1.4% new screen-detected cases of AF.[14] This is in line with our results achieved by a single screening session during influenza vaccination.

Guidelines consider screen-detected AF cases to be at increased risk for stroke and eligible for stroke prevention based on the CHA_2DS_2-VASc score.[15] In a substudy of the AFFIRM study, including 481 asymptomatic and 3,576 symptomatic AF patients, the absence of symptoms (silent AF) did not result

in a significant difference in mortality after correction for baseline differences (adjusted hazard ratio 1.07, 95% CI 0.79–1.46) or major events (death, disabling stroke, major central nervous system haemorrhage, or cardiac arrest) (adjusted HR 1.14, 95% CI 0.87–1.50) compared with AF with symptoms.[4] Another study compared the prognosis of 148 asymptomatic and 952 symptomatic AF patients during a mean follow-up of 10 years. After adjustment for differences in baseline characteristics a borderline-significant increased risk for ischaemic stroke was seen in asymptomatic patients (hazard ratio 1.8, 95% CI 1.0–3.8) compared with symptomatic AF, whereas asymptomatic patients were more often treated with anticoagulants (40 vs. 21%).[16] The fact that in the present study 27% of patients with screen-detected AF already had a history of TIA or stroke underlines the importance of detecting silent AF.

Two previous studies validated the accuracy of the light signal of the MyDiagnostick® against an immediately followed 12-lead ECG as the reference test. In a case–control design with an AF prevalence of 28 and 53%, respectively, the negative predictive values were 100 and 93%, and the sensitivities 100 and 94%, respectively.[11] In a screening setting with a low prevalence of (unknown) AF, a green light signal with the MyDiagnostick® will result in a very small number of missing cases (low false negatives). A red signal, however, should be followed by an adequate interpretation of electrocardiographic data, either the 1-min lead I registration recorded by the MyDiagnostick® or a 12-lead ECG taken immediately after holding the device. Current guidelines on AF recommend diagnosing AF with either a 12-lead ECG, or a single-lead ECG lasting for 30 s or more.[1 8] Ambulatory ECG monitors that record two leads of an ECG showed high sensitivity to detect a variety of cardiac arrhythmias,[17] and such devices are widely used nowadays for detecting AF in high-risk patients (e.g. after ischaemic stroke).[18] Interpretation of a lead-I ECG by an experienced physician has a high correlation with a 12-lead ECG, with a sensitivity and specificity of 95–96 and 90–95%, respectively.[19]

Feasibility

We could not detect a single novel case of AF among 271 persons aged 60 years, which underlines that screening of community dwelling persons should focus on older individuals, i.e. aged 60 or 65 years or over.

Screening during influenza vaccination is a single time-point screening, and thus, paroxysmal AF may be missed. The Stroke Stop study has demonstrated that repeated measurements during 2 weeks in patients aged 75–76 years increases the yield of screening compared with single time-point screening.[20] However, this

approach requires an extensive and expensive programme. Our study blended single-point screening with the existing programme of influenza vaccination. This is feasible at limited costs and generating a considerable yield. It may therefore have a large impact on general health of those aged over 60 years.

Screening with the MyDiagnostick® is easily performed; it takes only 1 min and can be done without supervision. In our study, 160 persons per hour were screened with 10 MyDiagnostick® by four research nurses. In general, the participants of influenza vaccination were very willing to participate. The main barriers are the need for more personnel and the informed consent procedure.

In the present study, silent AF was present in 1.3% of all patients ≥65 years (derived from Table 4; 33/2,557 patients). Seventeen per cent of the in total 17 million inhabitants in the Netherlands is aged at least 65 years, and influenza vaccination rate in this age category is around 80%.[13] Blending screening with a handheld device with such vaccination could potentially result in screening of 2.3 million people (0.80×0.17×17 million) with as a result up to 30,000 (1.3%) new cases of AF that could receive adequate stroke prevention. Therefore, such a screening approach is scalable to make a significant nationwide impact on stroke reduction.

A previous study described that screening of community-dwelling people aged over 65 years with 12-lead electrocardiography was cost effective with a participating rate of 50%.[9] Our approach, to screen for AF with an easy to use handheld device during an existing influenza vaccination programme, is potentially even more cost effective to reduce ischaemic strokes.

For the purpose of the study, the cardiologist was present on the location of screening and immediately judged the ECG from the stick. When implemented on a large scale, this may not always be possible or desirable. In that case, the MyDiagnostick® ECG rhythm strips can be sent to a cardiologist to confirm the presence of AF. In our study, in only 3 cases (0.1%), the rhythm strip was not adequately interpretable.

Limitations

We did not screen all participants of the influenza vaccination, but selectively aimed at those aged 60 years or over. This selection was applied because under the age of 60 years AF is very uncommon. Secondly, we missed some eligible persons because of time commitment for informed consent, and this could have resulted in more selectively inclusion of more healthy and literate patients. We considered it unlikely that this had substantial impact on our point estimate of screen-detected AF, the more because when such a screening is institutionalized a selection towards more healthy and literate persons would also occur.

We had information of a random sample of 220 persons with a negative MyDiagnostick® result. We decided to only assess a random selection of all persons with a negative lightning result for practical and logistic reasons. Higher age in the screened population than in the controls may have resulted in bias towards detecting age as an independent factor.

The lead I registrations of the MyDiagnostick® were interpreted by the cardiologists while having knowledge of the lightning results. Cardiologists were not blinded to the red/green signaling. Importantly, our aim was the yield of screening, not evaluation of the accuracy of the MyDiagnostick®.

Conclusions

Screening with a single-lead ECG device during influenza vaccination in primary care resulted in 1.1% new cases of AF and is a feasible option for large-scale screening.

Authors' contribution

F.K. designed the project and did the data collection and statistical analysis, and drafted the first version of the paper. R.G.T. initiated the project, co-designed the project, analysed single-lead ECG registrations, and revised the paper. L.J.G. analysed single-lead ECG registrations, and revised the paper. F.H.R. co-designed data collection and analysis plan and revised the paper. M.H. co-designed data collection and analysis plan and revised the paper. A.W.H. revised the paper. F.K. is guarantor of the study.

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Conflict of interest

All authors have completed the ICMJE uniform disclosure form and declare: no support from any organization for the submitted work; R.G.T. is co-inventor of the MyDiagnostick® and receives royalties from Applied Biomedical Systems (ABS) BV. None of the other authors have a financial relationship with any organization that might have an interest in the submitted work in 36 months prior to this study. There are no other relationships or activities that could appear to have influenced the submitted work.

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Cost-effectiveness of screening for atrial fibrillation in primary care with a hand-held, single-lead electrocardiogram device in the Netherlands

Maartje S. Jacobs
Femke Kaasenbrood
Maarten J. Postma
Marinus van Hulst
Robert G. Tieleman

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3

Abstract

Aims Atrial fibrillation (AF) is the most common arrhythmia and prevalence increases with age. Patients with AF have a high risk of stroke, and screening for AF is recommended in all people aged 65 years or older to identify patients eligible for stroke prevention. A hand-held, single-lead electrocardiogram (ECG) device can be used for systematic screening in the population at risk. The objective of this study is to estimate the cost-effectiveness of screening for AF in primary care with the MyDiagnostick® during seasonal influenza vaccination in the Netherlands.

Methods and results Lifetime costs and effects of a single screening session for AF detection were assessed from a societal perspective with a decision analytic model consisting of a straightforward decision tree and a joining Markov model. The decision model simulated all patients aged 65 years and over attending the seasonal influenza vaccination in the Netherlands. Event probabilities were derived from clinical trials. Sensitivity analyses were performed to assess the impact of important model assumptions as well as determining the relative effect of individual parameters. Screening for AF with the MyDiagnostick® in all patients older than 65 years that attend seasonal influenza vaccination in the Netherlands would decrease the overall costs by E764 and increase the quality-adjusted life-years (QALYs) by 0.27 years per patient. Early detection of AF would prevent strokes and leads to beneficial health effects with subsequent cost savings. This screening method would have an estimated probability of 99.8% for being cost-effective at a conservative willingness-to-pay of E20,000/QALY.

Conclusion Screening for AF in primary care with a hand-held, single-lead ECG device during seasonal influenza vaccination is very likely to be cost saving for identifying new cases of AF in the Dutch population aged 65 years and over. Active screening for AF with a single-lead, hand-held ECG device during seasonal influenza vaccination could be implemented in primary care.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia with a prevalence of 1.5–2.0% in the general population, increasing with age up to 5.9% above 65 and 8.8% in those aged 80 years or older.[1 2] Patients with AF have a five-fold higher risk for stroke.[3] A prevailing arrhythmia is unknown in almost 30–50% of the patients who are admitted with an ischaemic stroke (IS).[4 5] Screening for AF, as recommended by the European Society of Cardiology (ESC), in combination with the CHA_2DS_2-VASc score can help to identify patients who are eligible for stroke prevention irrespective of the occurrence of symptoms.[6-8] Anticoagulation prevents IS by at least 60% and mortality by at least 25%, with non-vitamin K antagonist oral anticoagulants (NOACs) having non-inferior efficacy compared with vitamin K antagonists (VKAs).[9 10]

The seasonal influenza vaccination session in primary care provides an ideal setting for systematic screening, since participants are at an increased risk for AF because risk factors for AF overlap with indications for seasonal influenza vaccination, e.g. the age group (≥65 years) and co-morbidity such as diabetes, ischaemic heart disease, and heart failure.[11] A recent pilot study demonstrated the feasibility of AF screening with an innovative hand-held, single-lead electrocardiogram (ECG) device called the MyDiagnostick® during seasonal flu vaccination.[12] The MyDiagnostick® is a validated, easy-to-apply device that registers and automatically analyses a single-lead I ECG rhythm strip after holding the device with both hands for 1 min. It signals a red light in case of rhythm irregularity suspicious for AF and a green light in case of absence of AF. The ECG rhythm strip can be visualized and analysed by linking the device to a computer.[13] In this pilot study, silent AF was detected in 1.3% of the screened population aged ≥65 years and anticoagulation was indicated for all of these patients.[12] Screening for AF based on the yield of screening seemed feasible; however, the question remained whether the costs of screening could outweigh the resulting beneficial effects. Cost-effectiveness studies on AF screening so far assumed newly detected cases ranging from 1% (SAFE study) up to 3% (STROKESTOP study). Incremental cost-effectiveness ratios (ICERs) for AF screening in these studies ranged from £337 per additional case detected up to E4,313 per quality-adjusted life-year (QALY) gained.[14-16]

The objective of this study is to estimate the cost-effectiveness of screening for AF in those aged at least 65 years in primary care with the MyDiagnostick® during seasonal influenza vaccination in the Netherlands using a decision analytic model.

Methods

Design and setting

A static, decision analytic model was used to study the economic impact of a single screening session over a lifetime horizon. The patient population in the model was based on the newly detected AF cases of the previous conducted pilot study where patients were screened for AF with the MyDiagnostick® during seasonal influenza vaccination.[12] A short decision tree (Figure 1) described the screening procedure and served as the input for the Markov model (see Supplementary material, Figure S1). The decision tree started with a hypothetical cohort of all people aged ≥65 years in the Netherlands, a total population of 2,919,000 persons in 2014. Subsequently, people attending the seasonal influenza vaccination programme were included in the analyses. The vaccination coverage in the population aged ≥65 years with or without a medical indication was 66.9%. Atrial fibrillation was newly detected in 1.3% of the hypothetical screened population that attended the seasonal influenza vaccination.[12] In the base-case scenario, we assumed that 3% of the undetected AF patients would be detected in routine practice per year. The average age of individuals aged 65 years and older with newly detected AF was 77.4 years with a mean CHA_2DS_2-VASc score of 3.7.

Patients with newly diagnosed AF were followed in 3-month cycles lifelong or until death using a Markov model approach. In the base-case, anticoagulation therapy with an NOAC (apixaban, dabigatran, or rivaroxaban equally distributed) or dose-adjusted VKA with a target international normalized ratio (INR) of 2.0–3.0 was compared with no treatment. The NOAC/VKA ratio was 50%/50% in the base-case. Patient preference for an anticoagulant was 85% in the base-case. A patient preference of 85% was based on unpublished data from the pilot study and anticoagulant persistence after 1 year found in literature. We assumed that the treatment discontinuation rate was 20% in the first year with a 30% decrease annually. The efficacy and adherence were assumed to remain constant over time. The following health states were included in the base-case: stable AF, IS (minor, major, or fatal), intracranial haemorrhage (ICH; minor, major, or fatal), myocardial infarction (MI), systemic embolism (SE), gastrointestinal (GI) haemorrhage, and death-by-age. All major extracranial haemorrhages were assumed to be a GI haemorrhage. All patients who experienced an event moved to a matching post-event phase after one cycle of 3 months. Costs and effects were reflected in a societal perspective, but productivity losses were not taken into account owing to the high age of the patients. The model was

developed in Microsoft Excel 2010 software (Microsoftw Inc.). Health gains were discounted by 1.5%; all unit costs were converted to costs for 2014 by correcting for inflation (factor 1.035) and discounted by 4%. All event probabilities, utilities, costs, and remainder model input including their references are listed in the Supplementary material, Table S1.

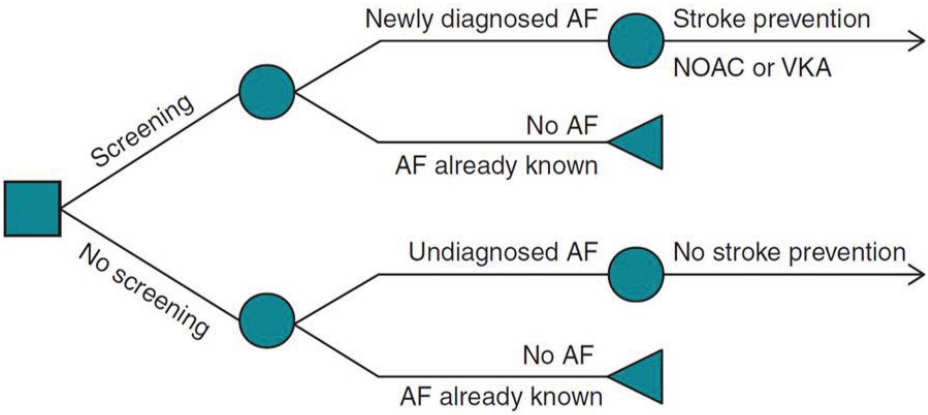

Figure 1 Short decision tree representing AF screening outcome. A total of 1,952,811 patients enter the decision tree, which is 66.9% of the total population of 65 years or older in the Netherlands. In all screened patients, 6.5% has a positive ECG and 1.3% has newly detected AF. The decision tree output was used as input for the Markov model. A schematic representation of the Markov structure can be found in the Supplementary material, Figure S1.

Event probabilities

The risks of clinical events for NOACs and VKA (warfarin) were based on combined clinical trial data from ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation), RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy), and ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation). The combined event rates for VKA and NOACs were calculated as weighted means from the trials. The event rate for SE was based on the event rate percentage/ year and relative risk in ARISTOTLE since the other trials did not report this specific event. Minor IS were all events classified minor or non-disabling (40.6 vs. 50.6% base-case), IS major were all events classified major or disabling (37.1 vs. 39.2% base-case), and IS fatal were all events leading to death

(22.3 vs. 10.2% base-case). For ICH, 17.0% of the events were considered minor, 41.0% major and 42.0% fatal. The severity of ICH was assumed to be equal in the base-case. The clinical events for patients with AF without stroke prevention were based on relative risks compared with warfarin. The mortality rate for the simulated population was adjusted for age by increasing the age-specific mortality rate during a patient's lifetime, starting at 75 years. The mortality rate was 3.7 times higher after an ischaemic event or ICH; after a MI, the age-related mortality was 1.051 times higher.

Utilities

The majority of baseline patient utilities and disutilities were calculated on the basis of EQ-5D scores matching the International Classification of Diseases (ICD) codes of the specific clinical events. Anticoagulant therapy disutility was applied for NOACs and VKAs, assuming that the disutility was comparable for both treatments. The utilities for IS and ICH were based on a non-randomized controlled cluster trial, which explored the medical costs concerning stroke services. Quality of life for IS and ICH was measured at hospital discharge and 6 months after the event occurred, subdivided based on modified Rankin Scales (mRS) of 0–1, 2–3, 4, and 5. The utilities from the trial were recalculated for a pharmaco-economic evaluation of rivaroxaban. For IS, the utilities were based on two categories: mRS 1–2 (minor) and 3–5 (major). For ICH, a weighted average was calculated between the mRS scores based on frequency. A higher disutility was allocated to the first cycle of IS and ICH; after the first cycle all patients moved to the post-event phase with matching utility. The utility of major GI haemorrhage was based on the assumption that a temporary utility of 0.8 applied during 1 week. Minor haemorrhage had no disutility.

Costs

Screening costs for AF consisted of costs for the MyDiagnostick®, primary care costs, and costs for the evaluation of the ECGs of positive MyDiagnostick® results, including false-positive results and newly diagnosed AF patients. The costs for the ECG device were based on one device for every general practitioner (GP) practice in the Netherlands and amortized over a 3-year period. The costs were also calculated if every GP would get their own ECG device. Personnel costs were an estimation based on the hour tariff and the number of hours needed for the total screening programme. In the primary care costs, we assumed that nurses would perform the screening. Costs of a cardiologist were included, meaning cardiologist costs for evaluating all positive MyDiagnostick® readings suspicious for AF (6.5% with red signal).

Drug costs for NOACs and VKAs were based on total costs as presented by the Dutch Care Institute (see Supplementary material, Table S1). The ratio of the NOACs (apixaban 5 mg, dabigatran 150 mg, rivaroxaban 20 mg) was assumed to be equally distributed. International normalized ratio monitoring costs were based on average costs per patient per year with no differentiation for the frequency of INR monitoring. For the NOAC users, we included the costs of an annual GP visit with the measurement of renal function.

The costs for IS and ICH are described in Supplementary material, Table S1. The same underlying calculation based on the severity of the event applied for the costs as mentioned for the utilities of the IS and ICH states. Higher costs were applied to the acute IS and ICH; after the first cycle, all patients moved to the post-event phase with matching costs. Costs for fatal IS and fatal ICH were applied separately; costs of fatal IS were derived from a study evaluating cost-effectiveness of treatment with statins in the prevention of coronary heart disease. The costs for SE are based on the assumption that 50% of the patients do not need intensive treatment; the costs are an average of the lowest and highest costs as defined by the Dutch Health Authority (NZA). The costs for acute MI are the mean treatment costs, non-differentiating for type of MI and type of intervention applied. Costs for minor ECH were based on one emergency room (ER) visit; costs for major ECH were based on treatment costs for a GI haemorrhage. For both minor and major ECH, it was assumed that full recovery occurred within 3 months.

Sensitivity analysis

A series of univariate sensitivity analysis were performed to assess the impact of important model assumptions as well as determining the relative effect of individual parameters. The effect of costs was assessed by taking 50% of the mean value as the lower value and 200% of the mean value as the upper value. The total costs for screening were explored with plausible variations in key assumptions. The event probabilities of IS (minor, major or fatal) and ICH (non-fatal or fatal) were varied in the base and case at the same time, with the calculation of the lower and upper being the same as for the costs. The model was designed to estimate the uncertainty surrounding the cost-effectiveness results by using probabilistic sensitivity analysis (PSA). All model parameters, except for total screening costs, were varied over plausible ranges mainly based on their statistical distribution [95% confidence interval (95% CI)]. Event probabilities and utilities were assumed to have b distributions; costs were assumed to have g distributions. The sensitivity analyses were also used to consider the broader issue of the generalizability of the results.

Results

Base-case

Compared with no screening, screened patients who were newly diagnosed with AF and treated with an NOAC or VKA over lifetime horizon experienced fewer IS (minor, major, or fatal), MI, and SE but more ICH (non-fatal or fatal), GI haemorrhage, and minor haemorrhage. Total events that occurred are summarized in Table 1. Compared with no screening, screening provided an additional 0.27 QALYs with cost savings of E764 per patient. Undiscounted, screening provided an additional 0.32 QALYs with cost savings of E216 per patient (Table 2). Total costs of screening for AF were E8,152,835, with 5,068 participating GP offices receiving one MyDiagnostick® per office. Screening of the 1,952,811 patients will yield 25,387 new cases with screen-detected AF. Total screening costs per newly detected AF patients were E321 and E4.17 per patient screened independent of AF detection.

Table 1. Total number of events in the base-case scenario over lifetime horizon in 25,387 patients

	Total events	
	No screening	**Screening**
Ischaemic stroke minor	1,775	1,172
Ischaemic stroke major	1,605	954
Fatal ischaemic stroke	952	478
Myocardial infarction	3,413	1,945
Systemic embolism	194	149
Intracranial haemorrhage	194	292
Fatal intracranial haemorrhage	141	211
Gastrointestinal haemorrhage (Major)	737	947
Minor haemorrhage	9,751	12,880

Sensitivity analysis

Total costs of screening for AF would be E8,812,458 if every independent GP received a device. Variation in total screening costs was based on variance in costs per single-lead ECG, GP costs, and number of ECGs to be evaluated. General practitioner costs had the largest share in total costs. The screening costs had a lower value of E5,696,955 and a higher value of E20,204,427 with resulting total costs saving of E860 and E289 per patient, respectively, for the base-case scenario.

Univariate sensitivity analyses were conducted for yield of screening, patient preference on anticoagulation, AF detection in general practice, percentage of NOAC vs. VKA users, costs for IS/ ICH/GI haemorrhage, event probabilities of IS/ICH, and costs for NOACs and VKAs to determine the impact on the results of the model (Figure 2). Costs of IS were of particular influence with the upper limit, leading to a more dominant ICER with a reduction in costs of E3,764 per patient over a lifetime horizon compared with mean IS costs. With half of the mean costs for all IS events, the screening was not cost saving anymore, but still cost-effective at a willingness-to-pay (WTP) threshold of E20,000 per QALY gained. Variation in the event probabilities of IS did not influence the probability of AF screening being cost-effective. Higher costs for NOACs and a higher ratio of NOAC users also had a negative influence on the ICER. When costs for NOACs would be E471 instead of E235 per 3 months, this leads to a cost increase of E2,257 per patient over lifetime horizon, making total cost E1,493 per patient compared with no treatment. Assuming all patients would be using NOACs, the costs and effects were dominant. A patient preference of 70% for initiating anticoagulant treatment after AF detection leads to a cost increase of E187 and QALY loss of 0.05 per patient compared with 85% patient preference over lifetime horizon. Atrial fibrillation screening was cost saving with this lower patient preference. The yield of screening was of marginal influence.

Figure 3 presents the results of the PSA comparing the joint distribution of costs and QALYs after 10,000 simulations. The PSA showed that ICERs for screening for AF are below a WTP threshold of E20,000 per QALY gained in 99.8% of the simulations (Figure 3). Screening for AF was cost saving in 61.9% of the simulations. Mean cost savings in the Monte Carlo simulation with 10,000 simulations were E381 (95% CI 2E4,142 to E2,834) per newly detected AF patient, and mean QALYs were 0.27 (95% CI 0.22–0.71) per newly detected AF patient when comparing screening vs. no screening.

Table 2. Model results: total costs per patient, QALYs per patient with AF, and ICER over lifetime horizon in 25,387 patients

	Base-Case		
	Total Costs	**QALYs**	**ICER**
No screening	€ 12,554.08	7.75	Dominant
Screening	€ 11,790.33	8.02	

Discussion

This study evaluated the cost-effectiveness of screening for AF in patients aged 65 years and older during seasonal influenza vaccination, using a hand-held single-lead ECG device. Screening for AF would decrease the overall costs by E764 and increase the QALYs by 0.27 years per patient over lifetime horizon. These results were sensitive to variability in a number of parameters, predominantly the costs associated with IS, the costs for NOACs, and the ratio of patients using an NOAC for stroke prevention. Cost-effectiveness of screening programmes is scarcely shown to be worth the investment relative to the benefits. One of the reasons is the high upfront costs that are associated with systematic, population-based screening. Early detection of AF can help identify patients who are eligible for anticoagulation irrespective of the occurrence of symptoms and thus reduce high future costs associated with stroke. Screening for AF with MyDiagnostick® in all patients of at least 65 years who attend seasonal influenza vaccination in the Netherlands would have a probability of being cost saving in 61.9% of the time (less costly and more efficacious) with a probability of being cost-effective of 99.8% at a conservative WTP of E20,000/QALY.[17] By linking AF screening to the seasonal influenza vaccination and assuming all patients attending the vaccination will be screened for AF, we indirectly assume an uptake rate of 66.9% for AF screening in the 'intention to treat' population. The univariate sensitivity analyses demonstrated the robustness of the outcome and did not identify any parameters with a negative influence on the probability of being cost-effective.

The yield of screening was assumed to be 1.3% based on the previously conducted pilot study.[12] The sensitivity analysis showed that the variation in detection of new AF cases was of minor influence on the cost-effectiveness. Asymptomatic AF detection during routine practice (i.e. without screening) was based on the randomized controlled trial of Fitzmaurice and calculated into a 3-month probability relative to the yield of screening of 1.3% in the pilot study.[14] Detection in general practice was assumed 3% of the asymptomatic AF patients; in the sensitivity analysis, we explored the effect of 1 and 5% detection based on the assumption made in cost-effectiveness analyses of the STROKESTOP study and the SAFE study.[15,16] A higher or lower detection rate of asymptomatic AF in general practice had only minor influence on the costs and benefits and did not influence the probability of cost-effectiveness with AF screening.

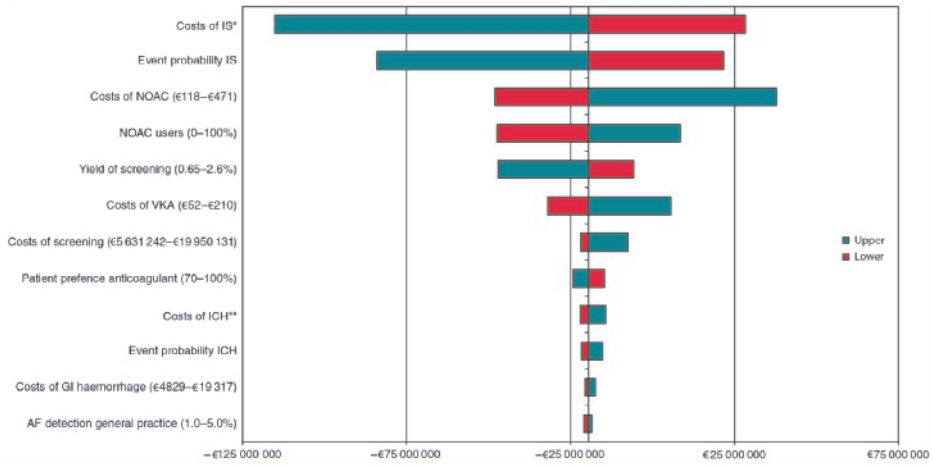

Figure 2 Tornado diagram representing the incremental costs expected from a lower and upper value for each variable in the univariate sensitivity analyses. The incremental effects (QALYs) were .0 within the explored ranges in all scenarios. For IS and ICH, base and case probabilities for minor, major, and fatal events were varied at the same time. The vertical line represents the mean incremental costs of 2E19,388,935. *Acute minor (E9,537–E38,293); post minor (E742–E2,968); acute major (E22,069–E88,275); post major (E1,979–E7,915); fatal (E5,589–E22,356). **Acute (E12,146–E48,585); post (E846–E3,382); fatal (E3,019–E12,074). Lower values of event probabilities were half the mean value; upper values were twice the mean value. The event probabilities used in the sensitivity analysis can be found in the Supplementary material, Table S1.

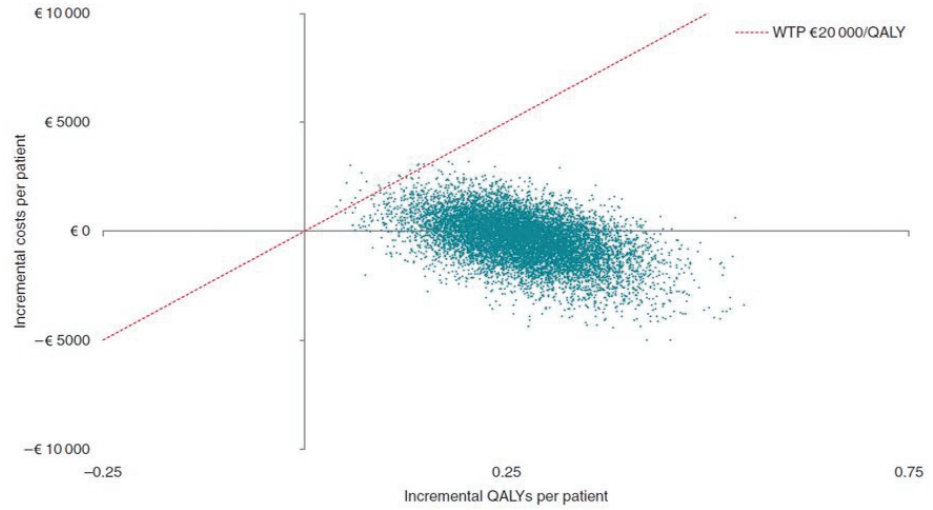

Figure 3 Incremental cost-effectiveness plane showing 10,000 Monte Carlo estimates of incremental costs per patient and benefits per patient of AF screening compared with no screening. Points falling above the dotted line have an ICER .E2,0000 per QALY gained. Atrial fibrillation screening was found to be cost-effective strategy (less costly, more effective) in 99.8% of the simulations. Screening for AF was cost saving in 61.9% of the simulations.

To our knowledge, this health-economic analysis is the first to evaluate preventive AF screening with a single-lead ECG device using a straightforward Markov model approach that includes stroke prevention. Hobbs et al. conducted a discrete event simulation (DES) approach to explore the cost-effectiveness of screening strategies and subsequent treatment decision. They found systematic population screening to result in 27 cases detected at a cost of £48,260; £1,787 per additional case detected were compared with no screening using a 12-lead ECG.[16] Our study found the costs of systematic AF screening to be lower, with E321 per newly detected AF case. One cause of the difference in costs per newly detected AF case presumably lies in the ECG method used; our single-lead ECG device with automated rhythm irregularity detection is less costly than a full 12-lead ECG. Desteghe et al. reported that the costs of screening for AF with the MyDiagnostick® were E134 and E293 per newly detected AF patient at the geriatric ward and cardiology ward, respectively, when using the algorithm. When a physician also reviewed all ECG results regardless of AF detection, the costs were E200 and E681, respectively, per newly detected AF patient.[18] In our scenario, because of a sensitivity of 100%, only the positive MyDiagnostick® readings suspicious for AF were reviewed to confirm the diagnosis. On the basis of a 65-year-old male cohort, Hobbs et al. calculated that opportunistic screening with a single lead had mean costs of £6,719 and 10.4250 QALYs compared with £6,756 and 10.4153 QALYs in the 'no screening' scenario with approximately 12 ISs averted and 2.5 haemorrhagic strokes caused (500,000 patients).[16] This would mean costs savings of E37 per patient with 0.0097 QALYs gained per patient. Non-vitamin K antagonist oral anticoagulants for stroke prevention were not incorporated into the model of Hobbs et al.; incorporation would have additional beneficial effect but also higher costs. Our results found AF screening to be more cost-effective, with more IS events averted but more ICH events caused. Levin et al. estimated the cost-effectiveness of screening for silent AF after IS using a hand-held ECG. This study assessed that the implementation of an AF screening programme on 1,000 patients with recent stroke over a 20-year period resulted in 23 QALYs gained and cost savings of E55,400 compared with no screening.[19]

Limitations of study

The event probabilities for stroke prevention were derived from three studies (ARISTOTLE, RE-LY, and ROCKET AF) with a relatively short follow-up period. One limitation is that we extrapolated these results to a lifetime horizon, assuming the effect would remain constant over time. It is nevertheless possible

that adverse events would be higher with a longer follow-up. The disadvantage of using clinical trial data is that they do not always reflect real-life efficacy and safety, e.g. by superior adherence and a more complete follow-up. A second limitation is the external validity of the patient characteristics of the clinical trials compared with the characteristics of the population to be screened. The clinical trials had an average age somewhat lower than the screen-detected AF population in the pilot study (70–73 years compared with 77.4 years old), and the stroke risk was comparable in the pilot study with an average CHA_2DS_2-VASc of 3.7. We used a straightforward, static Markov model that did not correct for any changes in the $CHADS_2$ score during a patient's lifetime. A limitation of our model is an expected underestimation of the total events occurred, mainly IS, and is thus an underestimation of the event-associated costs. The event probabilities derived from the clinical studies are somewhat conservative for the population being evaluated. In our univariate sensitivity analysis, we explored the effect of the event probability of IS, which indirectly represents the effect of lower and higher $CHADS_2$ scores in the population. A lower or higher stroke risk did not influence the cost-effectiveness. We indirectly explored the effect of higher event probabilities in the PSA and did not find any major influence on the cost-effectiveness. Also, the higher occurrence of events would affect the base as well as the case group and would probably not affect the overall probability of AF screening being cost-effective. We discourse that our conservative approach represents the minimal cost savings with associated benefits and that it is an accurate approximation of the costs and benefits resulting from AF screening.

Stroke risk and eligibility for stroke prevention in screen-detected AF patients were based on CHA_2DS_2-VASc score according to guidelines nowadays.[6] It is debatable whether it is reasonable to apply this risk assessment on screen-detected AF patients because this method is mainly based on research performed in AF detected in usual care. Two studies showed that asymptomatic AF patients did not significantly differ from symptomatic patients on mortality rate and major events (death, disabling stroke, major haemorrhage) and even have increased risk for IS (hazard ratio 1.8, 95% CI 1.0–3.8).[7 8] The absence of symptoms does not necessarily imply a more favorable prognosis. The thromboembolic risk appears not to be affected by the asymptomatic status of an AF patient, and the clinical status should therefore not determine the stroke prevention approach.[20]

Conclusions

In conclusion, with the use of a decision analytic model, we demonstrated that screening for AF in primary care with a hand-held, single-lead ECG device during seasonal influenza vaccination is very likely to be cost saving for identifying new cases of AF with subsequent introduction of stroke prevention in the Dutch population aged 65 years and over. Active screening for AF with a single-lead, hand-held ECG device during seasonal influenza vaccination could be implemented in primary care.

Conflict of interest

R.G.T. reports grants and personal fees from Boehringer Ingelheim, personal fees from Bayer and Pfizer/Bristol Meyer Squibb, all outside the submitted work. M.J.P. received grants and honoraria from various pharmaceutical companies, inclusive those developing, producing, and marketing new oral anticoagulants (NOACs). None of these grants or honoraria was directly related to this study. M.v.H. reports grants from Bayer and personal fees from Boehringer Ingelheim during the conduct of the study. R.G.T. is co-inventor of the MyDiagnostick® and receives royalties from Applied Biomedical Systems (ABS).

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Supplementary material

Table S1. Markov model inputs: event probabilities, utilities, and costs.

Model input						Reference
Population ≥65 years (The Netherlands, 2014)						[21]
Vaccination coverage (The Netherlands, 2014)						[22]
GP practices (The Netherlands, 2014)						[23]
GPs (The Netherlands, 2014)						[23]
3-month event probability						
		Range in PSA		Range in SA		Reference
	Base-Case	Lower	Upper	Lower	Upper	
IS						
IS minor						
NOAC	0.00140	0.00126	0.00154	0.00070	0.00280	[24-27]
VKA	0.00157	0.00142	0.00172	0.00078	0.00314	[24-27]
No stroke prevention	0.00378	0.00252	0.00567	0.00189	0.00756	[9 28]
IS major						
NOAC	0.00088	0.00079	0.00097	0.00044	0.00176	[24-27]
VKA	0.00099	0.00089	0.00108	0.00049	0.00198	[24-27]
No stroke prevention	0.00345	0.00230	0.00518	0.00173	0.00691	[9 28]
IS fatal						
NOAC	0.00020	0.00018	0.00022	0.00010	0.00040	[24-27]
VKA	0.00023	0.00020	0.00025	0.00011	0.00045	[24-27]
No stroke prevention	0.00208	0.00138	0.00312	0.00104	0.00416	[9 28]
ICH						
Minor + major						
NOAC	0.00051	0.00042	0.00060	0.00026	0.00102	[24-27]
VKA	0.00109	0.00096	0.00121	0.00054	0.00217	[24-27]
No stroke prevention	0.00036	0.00018	0.00054	0.00018	0.00072	[9 28]
Fatal						
NOAC	0.00037	0.00031	0.00044	0.00019	0.00074	[24-27]
VKA	0.00079	0.00069	0.00088	0.00039	0.00157	[24-27]
No stroke prevention	0.00026	0.00013	0.00039	0.00013	0.00052	[9 28]
MI						
NOAC	0.00166	0.00145	0.00186			[24 25 27]
VKA	0.00167	0.00146	0.00187			[24 25 27]
No stroke prevention	0.00737	0.00296	0.01830			[9 28]
SE						
NOAC	0.00022	0.00010	0.00035			[25]

Table S1. Continued.

3-month event probability						
		Range in PSA		Range in SA		Reference
	Base-Case	Lower	Upper	Lower	Upper	
VKA	0.00026	0.00013	0.00039			25
No stroke prevention	0.00041	0.00017	0.00095			9 28
GI haemorrhage						
NOAC	0.00247	0.00216	0.00278			25 27
VKA	0.00232	0.00201	0.00262			25 27
No stroke prevention	0.00141	0.00023	0.00873			9 28
Minor haemorrhage						
NOAC	0.03267	0.03150	0.03384			24 27
VKA	0.03351	0.03232	0.03470			24 27
No stroke prevention	0.01857	0.01287	0.02690			9 28
Mortality rate						
Age specific	Variable					29
After IS	x 3.7					30
After MI	x 1.051					31
QALY estimates						
Atrial Fibrillation	0.8430	0.7587	0.9273			32
Decrement for anticoagulation	-0.0105	-0.0090	-0.0110			33
IS minor acute	0.6550	0.5266	0.6979			34
IS minor post	0.7520	0.6046	0.8086			34
IS major acute	0.1670	0.1343	0.1698			34
IS major post	0.4490	0.3610	0.4692			34
ICH acute	0.4510	0.3626	0.4713			34
ICH post	0.6660	0.5355	0.7104			34
Decrement for MI	-0.0557	-0.0337	-0.0777			35
Decrement for SE	-0.0508	-0.0261	-0.0755			35
GI haemorrhage*	0.8330	0.7497	0.9163			36
Decrement minor haemorrhage	-	-	-			
* Utility of 0.8 is applied during 1 week						
One-time costs						
Screening costs						
Total costs	€ 8,152,835			€ 5,696,955	€ 20,204,427	
MyDiagnostick®	€ 1,180,844					
Primary care	€ 5,068,000					
Cardiologist	€ 1,903,991					

Table S1. Continued.

Costs per 3 month cycle						
		Range in PSA		Range in SA		Reference
	Base-Case	Lower	Upper	Lower	Upper	
Event costs						
IS minor acute	€ 19,146	€ 11,641	€ 26,652	€ 9,573	€ 38,293	34 37
IS minor post	€ 1,484	€ 902	€ 2,066	€ 742	€ 2,968	34 37
IS major acute	€ 44,138	€ 26,836	€ 61,440	€ 22,069	€ 88,275	34 37
IS major post	€ 3,958	€ 2,406	€ 5,509	€ 1,979	€ 7,916	34 37
IS fatal	€ 11,178	€ 6,796	€ 15,560	€ 5,589	€ 22,356	38
ICH acute (minor+major)	€ 24,292	€ 14,770	€ 33,815	€ 12,146	€ 48,585	34 37
ICH post (minor+major)	€ 1,691	€ 1,028	€ 2,354	€ 846	€ 3,382	34 37
ICH fatal	€ 6,037	€ 3,671	€ 8,404	€ 3,019	€ 12,074	38
MI acute	€ 5,021	€ 3,053	€ 6,989			39
MI post	€ 280	€ 171	€ 390			39
SE	€ 1,778	€ 1,081	€ 2,475			37
GI haemorrhage	€ 9,659	€ 5,872	€ 13,445	€ 4,829	€ 19,317	40
Minor haemorrhage	€ 259	€ 157	€ 361			41
Drug costs						
NOAC	€ 235	€ 157	€ 361	€ 118	€ 471	41 42
VKA[a]	€ 105	€ 143	€ 328	€ 52	€ 210	42 43
Anticoagulation use						
Patient preference	85%[b]			70%	100%	44 12
Discontinuation rate	1st year 20%	30% decrease annually				45 46
Discount rates						
Costs	4.0%			0.0%	4.0%	41
QALYs	1.5%			0.0%	1.5%	41

[a] For VKA: drug costs of acenocoumarol (77%) and fenprocoumon (23%).These VKAs are solely used within the Netherlands. [b] Assumption based on anticoagulant initiation in the AF screening pilot study measured after 10 months ([26]; unpublished data) and based on anticoagulant persistence after one year found in literature.[25]

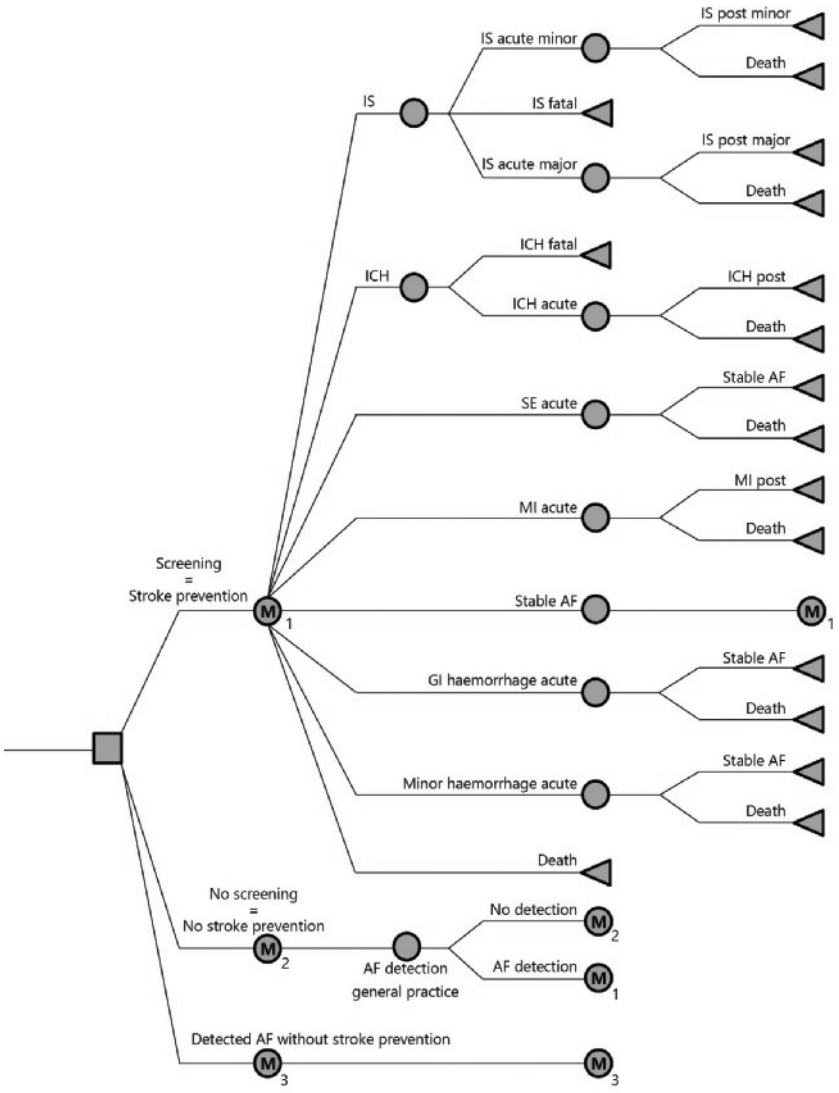

Figure S1. Schematic representation of the Markov model. All patients start with newly diagnosed AF with a mean age of 77 years old. Patients cycle between the different health stated until death occurs or the lifetime horizon is reached. Depicted is the decision node (square), Markov node (circle with 'M'), chance node (circle) and terminal branch (triangle). The Markov branch for 'no screening' (M2) is identical to the 'screening' branch (M1), with the exception of stroke prevention being absent if AF is not yet detected. After the 'Stable AF' state, the branch is identical starting from the Markov node on. The Markov branch 'M3' represents patients not initiating anticoagulation or discontinuing anticoagulation. This branch is identical to the 'no screening branch (M2), with the exception of AF already being known. AF indicated atrial fibrillation; IS, ischemic stroke; ICH, intracranial haemorrhage; SE, systemic embolism; MI, myocardial infarction; GI haemorrhage, gastrointestinal haemorrhage.

Opportunistic screening for atrial fibrillation in general practice: A cluster randomized controlled trial

Femke Kaasenbrood
Monika Hollander
Steven H.M. de Bruijn
Carlijn P.E. Dolmans
Robert G. Tieleman
Arno W. Hoes
Frans H. Rutten

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4

Abstract

Background Atrial fibrillation increases the risk of stroke, heart failure and all-cause mortality. Atrial fibrillation may occur asymptomatically and remain undiagnosed. Devices such as single-lead electrocardiography may help uncovering atrial fibrillation. We aimed to investigate the yield of opportunistic screening for atrial fibrillation in routine primary care using a single-lead device.
Methods We performed a clustered randomized controlled trial among patients aged 65 years or over and unknown with atrial fibrillation. Fifteen intervention general practices used the single-lead device at their discretion, and 16 control practices offered usual care. The follow-up period was one year, and the primary outcome was the proportion of newly diagnosed cases of atrial fibrillation.
Results In total, 17,107 older people unknown with atrial fibrillation were eligible. In the intervention arm on average 10.7% of the eligible people were screened during the study year. The rate of newly diagnosed atrial fibrillation was similar in the intervention and control practices (1.43% vs. 1.37%, p=0.73, respectively). Patients holding the device had more comorbidities, e.g. hypertension, type 2 diabetes and COPD than eligible people not screened in the intervention arm.
Conclusions Opportunistic screening with a single-lead ECG device blended in routine primary care does not result in a higher yield of newly detected cases of atrial fibrillation in elderly than care as usual. More rigorous screening methods may be needed to further improve atrial fibrillation detection in health care systems with a high detection rate in usual care.
Trial registration ClinicalTrials.gov NCT02270151.

Introduction

Atrial fibrillation (AF) is a common heart rhythm disorder, with the prevalence increasing with age; up to 8% in those aged 65 years and over, and 18% in those aged over 85 years.[1] With aging of the Western population the prevalence of AF is expected to duplicate or even triplicate in the coming 50 years. [2] AF is associated with an increased risk of ischaemic stroke, but also heart failure and death.[3 4] Strokes caused by AF are more severe and more often fatal than those of other origin.[5 6] Oral anticoagulants can reduce stroke risk in AF patients with approximately 60% and mortality risk with 25%.[7]

It is speculated that around 30% of the patients with AF is 'asymptomatic'.[8] Current guidelines recommend opportunistic screening for AF in primary care by pulse palpation, followed by a subsequent 12-lead electrocardiogram (ECG) in case of irregularity.[9 10] Several screening devices have been developed to help detecting AF with a single time-point measurement, such as blood pressure monitors with heart rhythm registration, and single-lead ECG devices.[11] Registration of the single-lead ECG can be transported to a computer and analyzed at distance by a cardiologist.

The MyDiagnostick® is such a single-lead ECG device. In an 'artificially created' population of 191 persons with a high prevalence of AF (54%) the diagnostic accuracy of this device was very good (sensitivity 0.94, specificity 0.93, negative and positive predictive values 0.93 and 0.94, respectively).[12] Another study performed among 192 patients who routinely visited a cardiology outpatient clinic with an AF prevalence of 28% showed even better diagnostic accuracy (sensitivity was 1.0, specificity 0.96, negative and positive predictive value 1.0 and 0.90, respectively).[13] Both studies used a simultaneously made 12-lead ECG interpreted by a single cardiologist as the reference test.

Previous studies showed that screening with single-lead devices resulted in an increased detection of AF compared to care as usual,[14-17] but these studies performed a programmatic screening approach, e.g. (i) pro-actively inviting participants to the GP practice, (ii) using pop-ups in the computer of the GP, or (iii) using an additional team of co-workers to screen during the influenza vaccination session.[14 15 17 18] Opportunistic screening programs, leaving screening for AF at the discretion of the primary care practice are scarce. Moreover, one has to realize that the awareness of (unrecognized) AF among GPs increased steeply over recent years and along with that the management of AF in usual primary care. It is therefore unclear whether contemporary opportunistic screening with a single-lead ECG device in everyday general clinical practice is effective if the use of the device was left at the discretion of the health care workers.

We evaluated such an easily to implement strategy by measuring the AF detection yield with a single-lead ECG device used during one year among patients aged at least 65 years who visited the primary care surgery for any reason and compare this with the AF detection yield of general practices providing care as usual.

Methods

Design
We performed a clustered randomized controlled trial in which 15 general practices had the opportunity of screening for AF with a single-lead ECG device, and 16 general practices provided care as usual.

Participants
All patients aged 65 years and over without a history of AF who were enlisted with the participating GP practices were eligible. Practices were located in rural, suburban and urban areas in the Netherlands. The study started October 2014 and lasted until March 2016, with a follow-up period of one year for each of the participating practices.

Intervention and control practices
Intervention practices were given two to eight devices depending on the size of GP practice. The MyDiagnostick® is a handheld single-lead ECG device that registers lead I during one minute. The device is suitable to screen for AF. Patients can hold the device for a minute and then a light will appear; red (indicating irregular RR intervals) or green (indicting mainly regular RR intervals). For a red light more than 75% of the RR intervals should be irregular. These cases are suspected of AF, but frequent premature atrial or ventricular beats and/or sinus arrhythmia may also result in high percentage of RR irregularity. In case of a green signal, in general sinus rhythm will be present. If the device is used to screen in primary care, a low prior probability of AF (around 2-3%) can be expected in those aged ≥65 years and unknown with a history of AF. Such a low prior chance of AF compared to aforementioned diagnostic studies (prior chance 54% and 28%)[12 13] will in general result in higher sensitivity and negative predictive values, but poorer specificity and positive predictive values. In practice, this would mean that a green light may be convincingly considered as sinus rhythm, while a red light needs confirmation with either an additional

12-lead ECG or by visual interpretation by an experienced GP or cardiologist of the recording of the MyDiagnostick® single-lead ECG registration.

Intervention practices were instructed to screen all persons aged 65 years or older without a history of AF and who visited the practice for any reason during the study year. Practices were given examples on how screening with a single-lead device could be organized, but it was left at the discretion of the primary care practice how they implemented the screening in everyday clinical practice.

If the MyDiagnostick® showed a red signal, GPs were instructed to either 1) examine the single lead ECG recording themselves or ask an experienced GP to do it for them, or 2) obtain a 12-lead ECG interpreted by themselves, an experienced colleague or a cardiologist or 3) send the single lead ECG strip or 12-lead ECG to the cardiologist of the research group for interpretation. When AF was diagnosed, AF management was left to the GP. In case of a green light, AF was considered absent, and the result was documented without recommending further action of the GP.

All participants in the intervention arm gave written informed consent and filled out a questionnaire on symptoms possibly related to (yet unrecognized) atrial fibrillation (e.g. palpitations, dizziness, shortness of breath, chest pain, lightheadedness) in the month prior to holding the device. Both informed consent and the questionnaire were filled out directly *before* holding the device.

Control practices provided care as usual, knowing that the 2013 Dutch general practitioners association guidelines on AF recommends pulse taking in everybody when blood pressure is measured.[9] During recruitment for the study we briefly outlined the aim of the study to the interested GPs, without emphasizing information on diagnosing AF as recommended in the guidelines. After notifying them that they were randomized to the control arm, we did not further contact them until the end of the study period.

Main outcome measures

The main outcome of the trial was the number of newly diagnosed cases with atrial fibrillation, either screen-detected or diagnosed otherwise, as a percentage of the total population aged ≥65 years without a known history of atrial fibrillation at baseline. Cases with atrial flutter were excluded because they have regular rhythms. A single occurrence of AF during or directly after cardiac surgery was not considered as AF case as it is most often self-limiting.[19 20]

At the end of the study, we collected data in the participating GP practices. An electronic search was performed to identify all patients ≥65 years with AF. Search terms included International Classification of Primary care (ICPC) codes

(such as K78; atrial fibrillation/flutter) and medication that could be prescribed for treating AF prescribed in the previous year. All search terms are listed in appendix A. An additional search was performed among all patients that died during the year of research. The electronic medical files of all these patients were evaluated to determine whether AF was diagnosed in these patients. In addition, 10% of those aged ≥65 years were randomly selected using a random number generator and their medical files were reviewed for the presence of AF. For patients with newly diagnosed AF, the medical history (notably a history of hypertension, COPD, diabetes mellitus type 2, coronary diseases, heart failure, stroke or TIA) and the use of cardiovascular medication were recorded. From a random sample of patients ≥65 years (around 10%) the same medical history items and information on use of cardiovascular drugs was collected for baseline information of those eligible for screening.

The Medical Ethics Committee (METC) of the University Medical Center Utrecht, the Netherlands confirmed that the Medical Research Involving Human Subjects Act (WMO) does not apply to this trial (METC-protocol number 14-163/C). The study complied with the Data protection law of the Netherlands. All participants who were screened with the MyDiagnostick® device gave written informed consent. All data relating to patients were anonymised before they left the general practice.

Sample size

For the primary outcome we calculated that 10,000 older adult persons (5,000 in each arm) should be included (without a history of AF). The effect sizes used for the power calculation was based on the study of Fitzmaurice et al performed in 2002 in the UK, in which during a year 1.6% new cases of AF was detected in the intervention GP practices (pulse feeling with ECG if irregular or a 12-lead ECG at a random moment during the year of study) and they managed to screen 53% of all eligible persons aged 65 years and over enlisted in these practices.[18] We assumed that we would manage to let the practices screen 80% of all eligible persons during a year given the fact that holding the device by a patient would be more convenient for the practices than pulse feeling or ECG making in eligible people. Based on these assumptions we estimated that 2.0% would be newly diagnosed with AF in the intervention arm and 1.05% in the control arm (similar to the yield in the study of Fitzmaurice). A 5% significance level, 90% power and an inter-cluster correlation coefficient of 0.0027 were used.

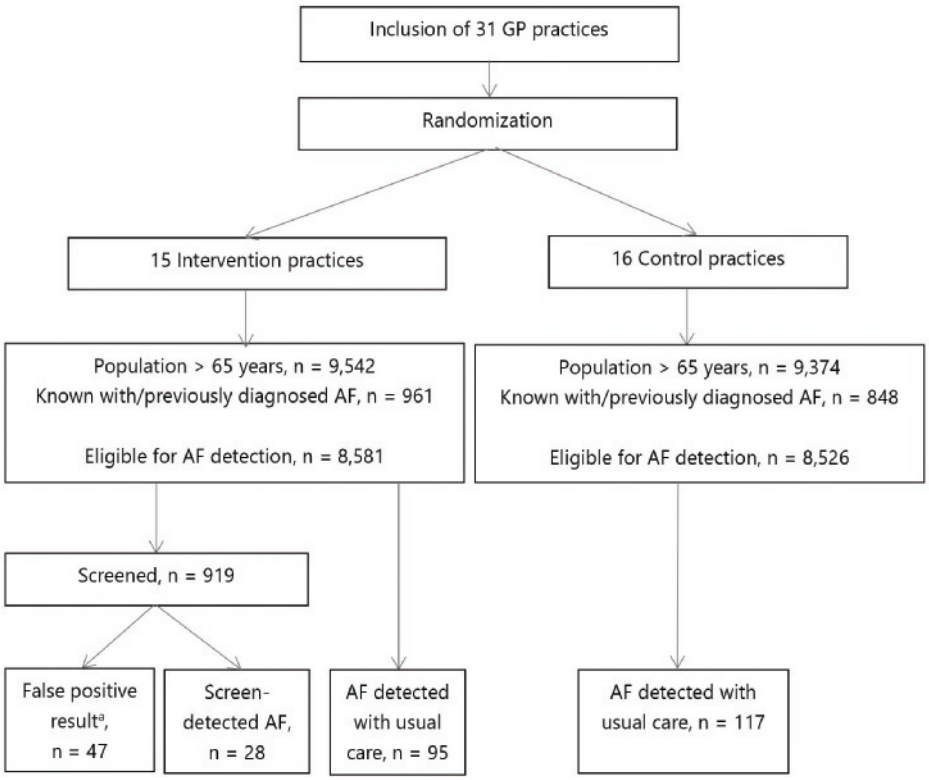

Figure 1. flow-chart of the study
[a]Patient with false positive MyDiagnostick® result with any of screening measurements during study year. Of these false positive results: 41 were measured at fist screening measurement for that person

Randomization

GP practices was randomized in a computerized matter and cluster size was the number of patients enlisted in each practice. All GP practices gave informed consent.

Data analysis

We analyzed the results on an 'intention to treat' basis. We used logistic regression analysis to compare overall 12 months incidence rates between arms. Initially, we incorporated a random intercept in the logistic regression analysis to correct for clustering. The clustering adjustment, however, showed no or very limited impact of clustering (σ^2 close to 0), we therefore applied 'standard' logistic regression without correcting for clustering. For comparison between

screened and non-screened population we used the two-sided χ^2 and Fisher's exact test for dichotomous variables and Student's t-test for continuous variables.

Results

In total, 31 GP practices participated, including 18,916 enlisted persons aged 65 years or over (figure 1). Of these individuals, 1,809 (9.6%) had a history of AF at baseline and were excluded from the trial. Thus, our study population consisted of 17,107 persons; 8,581 enlisted in the intervention arm and 8,526 in the control arm. The mean age was 74.3 in the intervention and 74.5 in the control arm, respectively. Overall, comorbidities were equally distributed over the groups (table 1).

Table 1. Baseline characteristics of the 17,107 adults aged 65 years and over unknown with AF registered in the primary care practices participating in our study, divided in intervention and control arm.

	15 Intervention practices	**16 Control practices**
Number of patients	8,581	8,526
Mean age in years (SD)	74.3 (7.3)	74.5 (7.3)
Females	4,680 (54.5)	4,610 (54.1)
Medical history as collected in a random sample of 10% of both intervention and control group		
Sample-size of random samples	867	848
Comorbidities		
Hypertension	441 (50.8)	427 (50.4)
Type 2 Diabetes	172 (19.8)	145 (17.1)
COPD[a]	70 (8.1)	68 (8.0)
Prior myocardial infarction	59 (6.8)	57 (6.7)
Ischaemic stroke[b]	34 (3.9)	54 (6.4)
TIA[c]	40 (4.6)	40 (4.7)

Absolute numbers (%) are presented unless stated otherwise
[a] COPD = Chronic Obstructive Pulmonary Disease, [b] Strokes were defined as (i) ischaemic or (ii) stroke of undefined origin, [c] TIA = Transient Ischaemic Attack

Table 2. CHA_2DS_2-VASc score and initiated anticoagulant treatment in cases with newly diagnosed AF, separately documented for screen-detected cases and those diagnosed with AF during regular care consultation.

	Intervention arm		Control arm
	Screen-detected AF, n = 28	**Regularly detected, n = 95**	**Regularly detected AF, n = 117**
Mean CHA_2DS_2-VASc score (SD)[a]	3.6 (1.6)	4.0 (1.5)	3.9 (1.5)
CHA_2DS_2-VASc score 1; in men	3 (10.7)	6 (6.3)	3 (2.6)
Female	15 (53.6)	51 (53.7)	71 (60.7)
CHA_2DS_2-VASc score 2 in women	0 (0.0)	4 (7.8)	8 (11.3)
Initiation of anticoagulant treatment[b]			
VKA[c]	18 (64.3)	45 (47.4)	68 (58.1)
NOAC[d]	5 (17.9)	41 (43.2)	34 (29.1)
Antiplatelet	0 (0.0)	1 (1.1)	4[e] (3.4)
Details about anticoagulant treatment			
According to guidelines[f]	26 (92.9)	89 (93.7)	106 (90.6)
On purpose deviation from guidelines[g]	1 (3.6)	4 (4.2)	5 (4.3)
Unintended deviation from guidelines[h]	1 (3.6)	2 (2.1)	6 (5.1)

Absolute numbers (%) are presented unless stated otherwise
[a]CHA_2DS_2-VASc = Congestive heart failure (1 point), Hypertension (1 point), Age >75 years (2 points), Diabetes mellitus (1 point), Stroke including ischaemic stroke or TIA (2 points), Vascular disease including myocardial infarction, angina pectoris, coronary intervention, peripheral artery disease, arterial or venous thrombosis (1 point), Age 65-75 years (1 point), [b] This is initiation of OAC treatment, some patients used OAC before diagnoses for mechanic heart valve or VTE (either lifelong prescription due to multiple VTE or temporary for recent first VTE), this was 2 for AF detection by screening, 4 for detection in usual care of intervention arm and 4 for detection in usual care of control arm, [c] VKA = vitamin-K antagonists, [d] NOAC = Novel Oral Anticoagulants, [e] Including 2 cases in whom either fragmin or clopidogrel was initiated, [f] Treatment according own guideline: NHG guideline for patients treated in primary care and ESC guideline for patients treated in hospital, [g] Documented reason for deviation, [h] No documented reason for deviation from guidelines

We did not observe more newly diagnosed AF in the intervention groups compared to control practices; 123 (1.43%) vs. 117 (1.37%); OR 1.05 (95% CI 0.81 – 1.35). Mean CHA_2DS_2-VASc score was 3.9 for newly detected AF cases in intervention practices and 3.9 also in control practices (table 2). Mean CHA_2DS_2-VASc score was somewhat lower (3.6) for the 28 screen-detected AF cases in the

intervention arm. Among new AF cases in control practices 42 had paroxysmal AF (35.9%), 51 persistent AF (43.6%) and 24 cases had missing data (20.5%). Among new AF cases in screening practices 54 had paroxysmal AF (43.9%), 35 had persistent AF (28.5%) and 34 had missing data (27.6%). Among screen-detected AF cases 10 had paroxysmal AF (35.7%), 7 had persistent AF (25%) and 11 had missing data (39.3%).

The intervention practices screened 10.7% of the eligible population (919 patients of in total 8,581 older people) and found newly detected AF in 28 cases, which is 3.0% of the screened population (table 3). In total 47 (5.1%) patients had a false positive MyDiagnostick® result during the study year (figure 1). Forty-one were measured at the first screening moment of that patient and four of these patients had two times a false positive result. The screened population had approximately the same age as non-screened population (74.8 vs. 74.3 years), but more comorbidity, including hypertension (60.0% vs. 48.7%, $p < 0.001$), type 2 diabetes (24.4% vs. 18.6%, $p = 0.002$) and COPD (11.3% vs. 7.4%, $p = 0.003$). For most screen-detected AF cases, the GP performed an additional 12-lead ECG to decide on AF status instead of interpreting the single-lead ECG derived from the MyDiagnostick® device (in 82.1%; 23 of 28 cases (data not shown)).

Approximately half of all new AF cases were diagnosed during contacts in primary care in both intervention and control practices (49.6% and 53.8%, respectively (figure 2)). The remainder was diagnosed either in the hospital, or outpatient clinic.

Figure 3 shows for each intervention practice the total rate of newly detected AF and the rate of screen-detected AF as a function of the screened percentage in that practice.

Table 3. Overview of the medical history of patients in the 16 intervention GP practices, divided in the screened population versus the non-screened population in domain aged at least 65 years.

	Non-screened population[a] N = 7,662	Screened population[b] N = 919	P-value[c]	Screen-detected AF cases N = 28
Mean age (SD)	74.3 (7.4)	74.8 (6.5)	0.057	76.4 (7.2)
Female	4186 (54.6)	494 (53.8)	0.61	15 (53.6)
	Sample N = 770[d]			
Hypertension	375 (48.7)	551 (60.0)	<0.001	17 (60.7)
Type 2 Diabetes	143 (18.6)	223 (24.3)	0.001	7 (25.0)
COPD[e]	57 (7.4)	104 (11.3)	0.003	4 (14.3)
Prior myocardial infarction	48 (6.2)	78 (8.5)	0.025	2 (7.1)
Ischaemic stroke[f]	30 (3.9)	36 (3.9)	0.98	2 (7.1)
TIA[g]	32 (4.2)	50 (5.4)	0.22	3 (10.7)

Absolute numbers (%) are presented unless stated otherwise
[a] All patients that were not screened within intervention GP practices, [b] all patients that were screened within intervention GP practices, [c] P-value on difference in non-screened and screened population; [d] Comorbidity is collected for a random 10% sample of total population, N = 770, [e] COPD = Chronic Obstructive Pulmonary Disease, [f] Strokes were defined as (i) ischaemic or (ii) stroke of undefined origin, [g] TIA = Transient Ischaemic Attack

Discussion

In our pragmatic cluster randomized controlled trial there was no clear difference in the overall rate of newly detected AF if a single-lead ECG device was used for opportunistic screening at the convenience of the general practice compared to care as usual (1.43% vs. 1.37%, p = 0.73). In total, 919 (10.7%) patients were screened in intervention practices and these patients more often had comorbidities, e.g. hypertension, type 2 diabetes and COPD compared to those not screened. In the intervention arm, 28 (3.0% of screened population) new cases of AF were found by holding the single-lead device, and another 95 new cases with AF were detected during regular medical care by general practitioner or hospital specialist.

There are some issues to consider when interpreting our results. The intervention practices managed to screen only 10.7% (range 0.0% to 39.0% across GP practices) of all eligible older persons. A previously performed

primary care study in the UK in 2002 had much higher 1–year AF screening rates of 53% (systematic arm) and 69% (opportunistic arm). However, they either sent letters to invite eligible persons to make a 12-lead ECG (systematic arm) or they flagged the file of patients to encourage GPs to palpate their pulse (followed by an ECG if irregular) when visiting the GP office (opportunistic arm).[18] In another primary care study in the UK comparing systematic pulse taking by a nurse to opportunistic pulse taking by a doctor or nurse, all eligible persons in the intervention arm received an explanatory leaflet and an invitation letter to attend a specific appointment at the GP office. The screening rates for pulse palpation were 73% in the systematic and 29% in the opportunistic screening arm, clearly demonstrating that 'promotion' is effective for increasing participation rate.[17] Another way to increase participation rate is blending the screening to the influenza vaccination program in primary care; in a previous study of our group we managed to screen 35% of all persons that visited the influenza vaccination session with a single-lead device.[15] The rather low rates of screening in our study might reflect the situation when leaving it at the discretion of the GP. Another reason for our low rate of screening may be the necessity to sign informed consent. Possibly higher rates can be achieved when blending screening with control visits for primary care disease management programs that exist for high-risk people, e.g. cardiovascular risk management, type 2 diabetes or COPD. Or by initiating a financial fee for screening, so GP practices can spend extra time on screening.

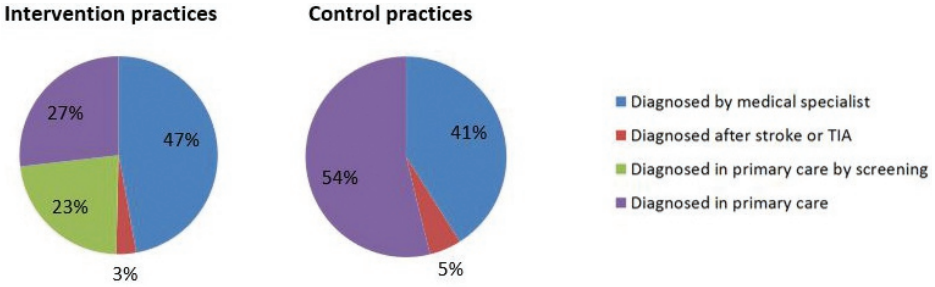

Figure 2. Proportions of cases with atrial fibrillation diagnosed 'regularly' in primary or secondary care, and the proportion by screening in the intervention practices.

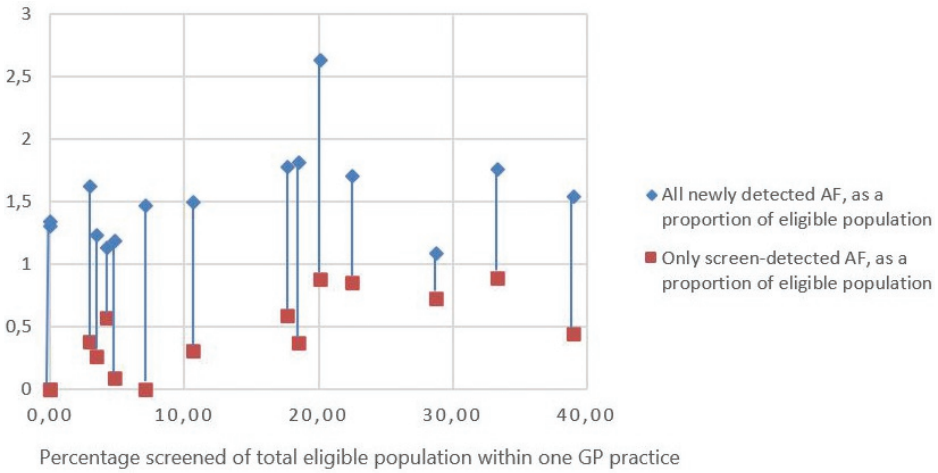

Figure 3. This shows per GP practice the proportion of persons screened (x-as) versus (i) rate of 'all newly diagnosed AF' (blue dots) and (ii) rate of 'only screen-detected AF' (red dots). Each GP practice of intervention arm is represented by two dots (blue and red), which are connected with a line.

Another reason for finding rather few newly detected AF and no difference between intervention and control GP practices is the high prevalence of already known AF in the populations of both screening and control GP practices. Already 9.6% of those aged 65 years and over were known with AF at the start of our study. As a comparison, this was 7.2% in the same age category in the study of Fitzmaurice et al.[18] Also; in our study the detection rate of new AF in the control practices was 40% higher than in the control practices in the study of Fitzmaurice et al (1.4% vs. 1.0%).[18] Both findings indicate that AF is currently already more often detected by usual care in general practices. The increased attention for silent AF over last years might have increased awareness in GP practices along with recommendations to screen for AF in elderly in current AF guidelines.

Patients selected for screening more often had comorbidities compared to those not screened within the intervention practices. This 'selection' might be caused by higher awareness of the GP or because practice nurses considered using the device if such patients visited the practice for primary care disease management programs for, e.g. type 2 diabetes or COPD. Selectivity of screening to those more at risk is in line with the somewhat higher screen-detected rate (3.0%) in our study compared to previous primary care screening studies (on average 1.4%).[15 17 18 21] Possibly these patients would also have been

detected with usual care because GPs in the Netherlands often take the pulse in older people with these comorbidities.

Strengths and limitations
Due to the pragmatic design of this trial we could illustrate how opportunistic screening would be executed in current primary care nowadays when left at discretion of the GP practice. We believe this is more relevant information than studies that artificially created higher screening yield, which cannot be achieved in usual practice.

Since this approach resulted in a low participation rate of only 10.7%, and not 80% as we had expected, we cannot exclude that higher screening rates would result in more newly detected AF than contemporary care as usual. However, we assumed a low detection rate of 1.0% in control GP practices for our power calculation based on existing studies. Even with higher screening rates, it is unsure whether you would reach a clinical relevant effect when usual care already detects many AF cases.

The number of screened patients might be an underestimation because some patients did not fill out the questionnaire before holding the MyDiagnostick®, and these persons were not counted. However, this number was far too small to affect our main conclusions.

In our study protocol we mentioned as secondary outcome the incidence of cardiovascular events. Because, there was no difference in rates of newly detected AF cases between the arms, we decided not to report on cardiovascular event rates during the study year.

Conclusion

Screening with a single-lead ECG device during routine primary care does not result in a higher yield of newly detected cases of AF in elderly. More rigorous screening methods are needed to further improve detection of AF.

Acknowledgements

We thank all participating patients and GP practices for their contribution to this study.

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Contributors

FR, MH, AH and FK designed the study. FK performed the statistical analysis and prepared the first draft of the manuscript. FK, SB and CD acquired the data. All authors critically revised the manuscript, approved the final manuscript and met all authorship criteria.

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Competing Interests
All authors have completed the Unified Competing Interest form. Prof. Rutten, dr. Hollander and mrs Kaasenbrood report an institutional unrestricted grant from Boehringer Ingelheim, during the conduct of the study. Dr. Tieleman reports grants and personal fees from Boehringer Ingelheim and personal fees from Pfizer/ BMS and Daiichi Sankyo, outside the submitted work. In addition, Dr. Tieleman has a patent filled by Applied Biomedical Systems with royalties paid. Arno Hoes chairs a large (around 500 employees) research and teaching institute within our University Medical Center. We perform both investigator- and industry-driven research projects with a number of pharmaceutical and diagnostic companies. In addition, some of his members of staff receive unrestricted grants for research projects from a number of companies. It is our explicit policy to work with several companies and not to focus on one or two industrial partners. He receives no personal payment from any industrial partner. Other authors have nothing to disclose.

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Supplementary material

Appendix A: Search terms used to identify patients with atrial fibrillation within general practices.

ICPC Code

K04 Palpitations / 'aware of the heart'
K05 Irregular heartbeat (other)
K78 Atrial fibrillation/flutter
K79 Paroxysmal tachycardia
K80 Ectopic beats / extrasystoles
K89 Transient cerebral ischaemia
K90 Stroke / cerebrovascular accident Code

Medication

(Vaughan Williams[22]) Class I	(Vaughan Williams[22]) Class III
C01BA01 Kinidine	C01BD01 Amiodaron
C01BA02 Procainamide	C07AA07 Sotalol
C01BA03 Disopyramide	
C01BC03 Propafenon	(Vaughan Williams[22]) Class IV
C01BC04 Flecainide	C08DA01 Verapamil
	C08DB01 Diltiazem
(Vaughan Williams[22]) Class II	
C07AB04 Acebutolol	Other
C07AB03 Atenolol	C01AA05 Digoxine
C07AB07 Bisoprolol	B01AC08 Ascal B01AC06 Acetysalicyl acid
C07AG02 Carvedilol	B01AA07 Acenocoumarol
C07AB08 Celiprolol	B01AA04 Fenprocoumon
C07AB09 Esmolol	B01AF02 Apixaban
C07AG01 Labetalol	B01AE07 Dabigatran
C07AB02 Metoprolol	B01AF01 Rivaroxaban
C07AB12 Nebivolol	
C07AA03 Pindolol	
C07AA05 Propranolol	

Signs and symptoms reported to the GP prior to screen-detected atrial fibrillation: A case control study

Femke Kaasenbrood
Monika Hollander
Claire Bausch
Robert G. Tieleman
Frans H. Rutten
Arno W. Hoes

Submitted

5

Abstract

Background Many patients with atrial fibrillation (AF) remain undetected, partly because symptoms are atypical and because in about 30% of patients AF is not diagnosed. Identification of signs and symptoms that are indicative of AF might improve timely detection. We aimed to examine which AF-suggestive symptoms were presented to the general practitioner prior to screen-detected AF.

Methods A case-control study in general practice consisting of 61 screen-detected AF cases and 244 controls without AF, matched on age and sex. The main outcome measure was documentation of signs and symptoms in the medical files of the general practitioner (GP) in the two years prior to the diagnosis. We considered palpitations, shortness of breath, fatigue, dizziness, chest pain, (near)syncope, symptoms suspicious for TIA/minor stroke, and palpation of an irregular pulse as signs and symptoms suggestive for AF.

Results In almost half of screen-detected AF patients, there was at least one sign or symptom reported, which was similar to controls (44.3% vs. 34.0%, p=0.14). Palpitations and an irregular pulse were reported more often in screen-detected AF cases than in controls: 9.8% vs. 3.7% (OR 3.2, 95% CI 1.1 to 9.7) and 9.8% vs. 0.4% (OR 26.5, 95% CI 3.1-224.7), respectively. There were no statistically significant differences in other symptoms between cases and controls.

Conclusion A minority of screen-detected AF patients report AF-suggestive signs or symptoms to the GP in the two years preceding the diagnosis, indicating the importance of screening programs to timely detect AF. However, if patients present with palpitations or have an irregular pulse, the GP should perform additional investigations to diagnose or exclude AF.

Introduction

Atrial Fibrillation (AF) is the most common heart rhythm disorder with a prevalence of 8% in those aged ≥65 years.[1] It increases the risk of stroke, but also of heart failure and death.[2 3-5] Treatment with anticoagulants (VKA or NOACs) reduces the risk of stroke for patients with AF by 60% and the risk of death by 25% compared with no treatment.[6]

Guidelines consider palpitations, shortness of breath, fatigue, dizziness, syncope/near syncope, chest pain and a presentation with CVA/TIA all as symptoms suggestive of (underlying) AF.[7-9] In general practice, these symptoms are very common among persons over 65 of age and may be caused by multiple disorders, e.g. ischaemic heart disease (IHD), heart failure, chronic obstructive pulmonary disease (COPD) and vestibular or neurological problems.[10 11] Only palpitations are more specific for heart rhythm disorders, although these also occur in patients with IHD and heart failure. Most studies on AF symptomatology used questionnaires and only included patients with chronic AF.[12 13] It is unknown whether symptoms in undetected AF cases are similar or different to those with chronic AF. Also, none of the previous studies included comparison group of patients without AF and such a comparison is crucial to assess which symptoms can distinguish between patients with and without AF.[12 13]

About 30 percent of patients with AF seem to be asymptomatic; so called "silent AF".[14 15 16 17] Screening studies showed considerable underdiagnoses of AF.[18 19] To prevent AF-related stroke or other thrombo-embolic events, guidelines recommend case-finding of AF, for example by pulse palpation in the elderly.[2 7]

To optimize detection, it is worthwhile to know whether patients with screen-detected AF presented symptoms suggestive of AF in the period prior to the AF diagnosis. This may identify symptoms or signs that should alert general practitioners (GPs), and prompt them to perform additional investigations to diagnose or exclude AF. We examined whether the aforementioned AF-related signs and symptoms were more often reported in the GP's medical files in the two years prior to diagnosis of patients with screen-detected AF than in age- and sex-matched subjects.

Methods

Design and participants

We performed a retrospective case control study. Cases were screen-detected AF patients from two screening studies applying a single-lead ECG device; the MyDiagnostick®. The first screening study was a screening study among subjects receiving influenza vaccination in primary care in 2013 with 37 screen-detected AF patients.[20] The other study was a cluster RCT in primary care with the MyDiagnostick executed between 2014 and 2016 in which the intervention group used the MyDiagnostick® at the discretion of the practice. That study revealed 28 screen-detected AF patients.

The Medical Ethics Committee (METC) of the University Utrecht and Groningen, the Netherlands confirmed that the Medical Research Involving Human Subjects Act (WMO) in the Netherlands did not apply to these two studies (METC-protocol numbers 2013-85 and 14-163/C, respectively). The study complied with the Data protection law of the Netherlands. All participants who were screened with the MyDiagnostick® device gave written informed consent. All data relating to patients were anonymized before they left the general practice.

MyDiagnostick®

The MyDiagnostick® is a device that can be used to screen for AF. When you hold the device for 1 minute in both hands it registers a single ECG lead (lead I) and if the R-R distances are irregular in length for more than 75% of the time, it gives a red light signal. A red light is suspicious for AF but can also be caused by sinus arrhythmia or frequent premature beats. Therefore, the MyDiagnostick produces a rhythm ECG strip for confirmation of the diagnosis. A green light indicates sinus rhythm.

Controls

For each case, four control patients without AF were selected from the same primary care practices. They were matched for age (+/- 3 years) and sex. Controls were selected using a computerized random number generator.

Data collection

Data was collected at the 25 participating general practices from August to September 2017. FK and CB scrutinized the medical files of all participants for signs and symptoms registered in the two years prior to the start of the

screening year. The following signs and symptoms were collected: palpitations, chest pain/discomfort, shortness of breath, dizziness/lightheadedness, loss of consciousness or (near) fainting, fatigue, possibly TIA/minor stroke and palpation of an irregular pulse.[7]

We further registered whether patients had a medical history of: (i) hypertension, (ii) type 2 diabetes, (iii) heart failure, (iv) ischaemic stroke or transient ischaemic attack (TIA), or (v) chronic obstructive pulmonary disease (COPD). Finally, we collected cardiovascular medication use at the start of screening.

Data analyses

Univariable analysis was performed to identify differences between cases and controls. Statistical significance was defined as $p<0.05$. Relative risk estimates are reported as odds ratios and accompanying 95% confidence intervals (Cis). Analyses were performed in SPSS Statistics 25.

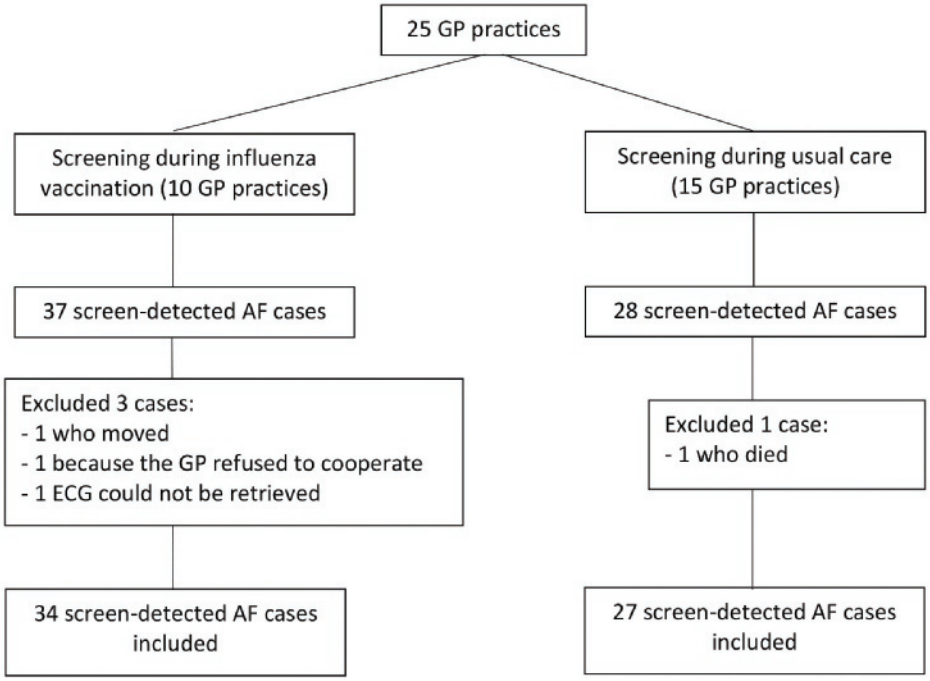

Figure 1. Flow chart of the study

Results

In total, 305 patients were included; 61 screen-detected AF patients and 244 controls without AF (table 1). Mean age was 75.8 years and 49% were women. Cases contacted the GP practice more often than controls in the previous two years (15.0 versus 12.8) and more often had a history of cardio-metabolic problems, notably stroke/TIA (18.0% versus 9.8%). Furthermore, they more often used calcium channel blockers than controls (31.1% versus 15.2%).

Signs and symptoms registered in the GP's electronic medical file (EMF) are shown in table 2. In almost half of the cases (44.3%) at least one sign or symptom as mentioned in table 2 was reported, being similar to 34.0% in the controls (OR 1.5, 95% CI 0.9 to 2.7). Palpitations were 3 times more often reported in cases than in controls (9.8% vs. 3.7%, OR 3.2, 95%CI 1.1 to 9.7). Although not statistically significant, shortness of breath and fatigue were also reported more often in cases than in controls.

In 6 (9.8%) of the AF cases an irregular pulse was documented, and in 0.4% of the controls (OR 26.5, 95% CI 3.1 to 224.7). In four of the six cases an irregular pulse was registered (three times by the practice nurse and one time by the GP), which was not followed by any further action. In a fifth case the practice nurse made an appointment for the patient with the GP later that week, where AF was diagnosed. In the sixth case, a practice nurse registered the irregular pulse and the following 12-lead ECG showed sinus rhythm with right bundle branch block and some premature ventricular contractions, but no AF.

Table 1. Baseline characteristics of screen-detected AF cases and age and gender matched controls from the general population

Characteristics	Cases, n = 61 (%)	Controls, n = 244 (%)
Female sex	30 (49.2)	120 (49.2)
Mean age in years (SD)	75.9 (8.0)	75.7 (8.0)
Mean number of GP consultations[a] (median)	15.0 (14)	12.8 (10)
Medical history		
Diabetes Mellitus[b]	15 (24.6)	49 (20.1)
Hypertension	40 (65.6)	154 (63.1)
Heart failure	3 (4.9)	10 (4.1)
Stroke/TIA[c]	11 (18.0)	24 (9.8)
COPD	6 (9.8)	25 (10.2)

Table 1. Continued.

Medication at start screening		
VKA or NOAC	1 (1.6)	4 (1.6)
Platelet aggregation inhibitors	16 (26.2)	65 (26.6)
Beta-blockers	15 (24.6)	67 (27.5)
ACE inhibitors or ARBs	20 (32.8)	65 (26.6)
Diuretics	24 (39.3)	83 (34.0)
Calcium channel blockers	19 (31.1)	37 (15.2)

COPD, Chronic Obstructive Pulmonary Disease. VKA, Vitamin K Antagonists. NOAC, Non-VKA Oral Anticoagulants. patients used OAC for mechanic heart valve or VTE (either lifelong prescription due to multiple VTE or temporary for recent first VTE). [a] Consultations include practice visits and telephone consultations. [b] Including Diabetes Mellitus type 1 and 2. [c] Either ischaemic or hemorrhagic stroke or Transient Ischaemic Attack.

Table 2. Signs and symptoms for which patients consulted the GP in the two years previous to the screen-detected AF diagnosis and for controls two years back from the moment of AF diagnosis in the matched case

Signs and symptoms	**Cases n = 61 (%)**	**Controls n = 244 (%)**	**Odds Ratio (95% CI)**
Palpitations	6 (9.8)	8 (3.3)	3.2 (1.1-9.7)
Chest pain/discomfort	3 (4.9)	16 (6.6)	0.7 (0.2-2.6)
Shortness of breath	8 (13.1)	26 (10.7)	1.3 (0.5-3.0)
Dizziness/lightheadedness	5 (8.2)	30 (12.3)	0.6 (0.2-1.7)
Syncope/(near) syncope	1 (1.6)	10 (4.1)	0.4 (0.05-3.1)
Fatigue	5 (8.2)	8 (3.3)	2.6 (0.8-8.4)
Suspicious for TIA/minor stroke	2 (3.3)	8 (3.3)	1.0 (0.2-4.8)
Irregular pulse	6 (9.8)	1 (0.4)	26.5 (3.1-225)
At least one of aforementioned signs or symptoms	27 (44.3)	83 (34.0)	1.5 (0.9-2.7)

Discussion

To the best of our knowledge we are the first to compare signs and symptoms reported to primary care in the period preceding screen-detected AF diagnosis with age- and sex matched controls without screen-detected AF. In almost half of the cases (44.3%) at least one sign or symptom suggestive for AF was

reported, being similar to 34.0% in the controls. Only palpitations and an irregular pulse were more often reported in screen-detected AF patients than in controls (OR 3.2 and 26.5 respectively), but both occurred in only 10% of the patients with screen detected AF, indicating the importance of screening programs to timely diagnose AF.

Six cases (9.8%) with screen-detected AF had an irregular pulse in the two years prior to diagnosis and in four of these cases no further action was undertaken to verify AF status. In two cases an ECG was made some time later showing sinus rhythm. This illustrates the importance of immediately initiating additional diagnostic tests to diagnose or excluded AF in primary care in patients with an irregular pulse. A primary care study evaluated 244 patients who consulted their GP for a new episode of palpitations and/or lightheadedness, and sinus rhythm on an instantly made 12-lead ECG. These patients were randomized in two groups; (i) additional screening with an external loop recorder or (ii) usual care, and followed for six months. With an external loop recorder in 9% new AF was detected, and this was 2% in the usual care group. This suggests that intensive follow-up of patients with symptoms suspicious for AF should be closely monitored, e.g. by (extra) ECG measurements at GP practice or with an event recorder at home, which is in line with our conclusions.[24]

Palpitations, and less typical symptoms such as shortness of breath and fatigue were more often reported to the GP in the 2-year period preceding the screening in screen-detected AF patients than in controls without AF, while dizziness and syncope/near syncope were less often reported. A previous questionnaire study investigated how many of 335 community-dwelling adults with chronic AF experienced current or recent similar symptoms as in our study. Most frequently reported were shortness of breath (56%), palpitations (51%), fatigue (50%), chest pain (41%), syncope/dizziness (36%), and weakness (36%). In total 17% of these chronic AF patients were "self-reported" asymptomatic.[12] Another study scrutinized the hospital medical files of 476 patients with newly diagnosed AF and in 40% palpitations were registered in the medical file, while 34% was asymptomatic.[22] Both studies, however, did not compare the results with a control group without AF. As in our study, most common symptoms in AF patients were palpitations, shortness of breath and fatigue. However, both studies show higher prevalence of symptoms than our study, probably because we evaluated cases with screen-detected AF instead of chronic AF. The first study shows the lowest proportion of asymptomatic patients, probably because they used questionnaires instead of documented symptoms and it is well-known

that many symptoms (reported in the questionnaire) will not be presented to the GP.[23]

Screen-detected cases more often had a history of stroke/TIA than control patients (18.0% vs. 9.8%), and possibly undiscovered (paroxysmal) AF was a cause for these stroke/TIAs. We also observed that patients with screen-detected AF more often used calcium channel blockers than controls without AF. Although this was a remarkable finding, it could be subject to chance, and we do not have a good explanation for it.

Strengths and limitations
A strength is the comparison of screen-detected AF cases with age- and sex-matched controls, thus being able better to evaluate the AF-related signs and symptoms. A limitation is that the researchers were not blinded for AF status during data collection.

Conclusions

Almost half of screen-detected AF patients visit their GP at least once for a sign or symptom suggestive of AF in the prior two years. Especially palpitations and an irregular pulse should urge GPs to (let) make an ECG.

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We thank all participating patients and GP practices for their contribution to this study.

Contributors

FR, MH, AH and FK designed the study. FK and CB acquired the data and performed the statistical analysis. FK prepared the first draft of the manuscript. All authors critically revised the manuscript, approved the final manuscript and met all authorship criteria.

Competing Interests

All authors have completed the Unified Competing Interest form. Prof dr. Rutten, dr. Hollander and mrs Kaasenbrood report an institutional unrestricted grant from Boehringer Ingelheim, during the conduct of the study. Dr. Tieleman reports grants and personal fees from Boehringer Ingelheim and personal fees from Pfizer/ BMS and Daiichi Sankyo, outside the submitted work. In addition, Dr. Tieleman has a patent filled by Applied Biomedical Systems with royalties paid. Prof. dr. Hoes chairs a large (around 500 employees) research and teaching institute within our University Medical Center performing both investigator- and industry-driven research projects with a number of pharmaceutical and diagnostic companies. In addition, some of his members of staff receive unrestricted grants for research projects from a number of companies. It is their explicit policy to work with several companies and not to focus on one or two industrial partners. He receives no personal payment from any industrial partner. Other authors have nothing to disclose.

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Symptoms in patients with screen-detected atrial fibrillation

Femke Kaasenbrood
Monika Hollander
Robert G. Tieleman
Arno W. Hoes
Frans H. Rutten

Submitted

Abstract

Background Atrial fibrillation (AF) is common in older people, but symptoms may be unclear or absent which delays detection of AF. We aimed to investigate to what extent screen-detected AF patients from primary care experience symptoms.

Methods Fifteen GP practices were provided with hand-held ECG devices to screen all patients aged ≥65 years that visited the practice during one year at their own discretion. Participants filled out a questionnaire just before screening about presence of AF-related symptoms during the past month; (i) palpitations, (ii) skipped heart beats, (iii) shortness of breath, (iv) chest discomfort, (v) dizziness and/or (vi) lightheadedness.

Results In total 919 patients were screened for AF and 28 (3.0%) had newly detected AF. Patients with screen-detected AF reported significantly more often AF-related symptoms than those without AF (64.0% vs. 44.2%, RR 1.4; 95% CI 1.1-2.0). Most frequently reported were palpitations (32.0% vs. 11.7%, RR 2.7; 95% CI 1.5-5.0) and shortness of breath (36.0% vs. 15.8%, RR 2.3; 95% CI 1.3-3.9), while dizziness occurred more often among patients without AF (4.0% vs. 13.2%, RR 0.3; 95% CI 0.04-2.1).

Conclusion Older community-dwelling people who experience palpitations and shortness of breath should receive special attention to uncover AF in primary care. To a lesser extent this applies to those with skipped heartbeats, lightheadedness and chest discomfort, while dizziness on the other hand seems not to be related to AF.

Introduction

Atrial Fibrillation (AF) is the most common heart rhythm disorder with a prevalence of 8% in those aged ≥65 years, and the prevalence increases with age.[1] AF increases the risk of stroke, heart failure and death.[2 3-5] Treatment with a vitamin-K antagonists (VKA) or non-vitamin-K oral anticoagulants (NOAC) reduces the risk of stroke by 66% and the risk of death by 25%.[6]

Most common symptoms of AF include palpitations, shortness of breath, fatigue, chest pain, dizziness and (near) syncope.[7-10] But some patients don't experience AF-related symptoms ('silent AF') in which case detection is likely to be delayed and an ischaemic stroke can be first manifestation of the disease.[11] Studies in patients with newly diagnosed AF showed that the prevalence of 'typical' symptoms such as palpitations is around 40%, but also that around 35% of the patients are asymptomatic.[12 13] These studies used symptoms as mentioned in medical files and therefore underestimate the real prevalence of these symptoms. One study compared symptoms reported on a questionnaire with symptoms mentioned in medical files. Of the 558 patients AF, 92% reported AF-related symptoms, while in 56% this was mentioned in the medical files.[14] Although, this study concerns patients with established chronic AF, it suggests that with questionnaires are the best option to assess symptoms in patients.

AF symptomatology has mainly been studied in subjects referred for AF evaluation and not analyzed in comparison to patients without AF as a reference group. [8 15] A reference group is important to determine whether symptoms are truly related to AF, since community persons aged ≥65 years without AF may also experience such symptoms.[16 17] It is still unclear whether silent AF cases are truly asymptomatic or whether they actually experience mild symptoms that are not reported to or notified by the physician. This knowledge is important because it may help clinicians to early detect AF in every-day clinical practice.

We aimed to investigate i) whether older community-dwelling patients with screen-detected AF more often reported AF-related experience symptoms than patients without AF, and ii) what proportion of AF patients is truly asymptomatic.

Methods

Design and participants

A cross-sectional analysis was done within the framework of the IDEAL-MD trial. For IDEAL-MD trial 15 GP practices were provided with MyDiagnostick® devices,

handheld single-lead ECG devices that register lead I ECG during one minute and provide an instant light result based on irregularity of the heartbeat. GP practices were instructed to screen all persons aged ≥65 years without a history of AF, when they visited the practice during the study year. Practices were given examples on how screening with a single-lead device could be organized, but implementation was left at their discretion. In case of a positive MyDiagnostick® result, occurrence of atrial fibrillation was checked with the one minute single-lead ECG registration interpreted by a consulted cardiologist or by a 12-lead ECG interpreted by a treating GP or consulted cardiologist. When AF was diagnosed, further management was left at the discretion of the GP. In case of a green light, AF was considered absent, and there was no further action.

The Medical Ethics Committee (METC) Utrecht, the Netherlands confirmed that the Medical Research Involving Human Subjects Act (WMO) does not apply to this trial (METC-protocol number 14-163/C). All patients gave written informed consent to participate in this study.

MyDiagnostick®

The MyDiagnostick® is a device that can be used to screen for AF. When you hold the device for 1 minute in both hands it registers a single ECG lead and if the heart rate is irregular for more than 75% of the time, it gives a red light which means 'suspicious for AF'. Alternatively, however, a red signal may be caused by sinus arrhythmia or frequent premature beats. A green light indicates sinus rhythm.

In a previous study the sensitivity and specificity of the MyDiagnostick® compared to a 12-lead ECG was 94% and 93%, respectively. Based on an expected prevalence of 6% in community people aged 65 or older, a positive and negative predictive value of 45% and 99% were estimated.[18] Therefore a red light result of the MyDiagnostick® was confirmed by ECG data; the one-minute single lead registration or a 12-lead ECG. A green light was considered as absence of AF.

Data collection

Prior to screening, all participants filled out a questionnaire on symptoms possibly related to (yet unrecognized) AF in the previous month (appendix A). The questionnaire included six symptoms that are suggested to be associated with AF in literature and which are included in guidelines.[2 7-10] We were interested in symptoms that occurred intermittent and therefore did not include fatigue. Because the questionnaires were filled out before the screening moment, both patient and health care professionals were blinded for screen-detected AF status. After the study was conducted, we scrutinized medical files for comorbidities,

including: hypertension, type 2 diabetes, heart failure, ischaemic stroke or transient ischemic attack (TIA) and chronic obstructive pulmonary disease (COPD).

Data analyses

We performed univariate analyses to compare the questionnaire results of screen-detected AF patients with those without AF. Relative risk ratios are reported with accompanying 95% confidence intervals.

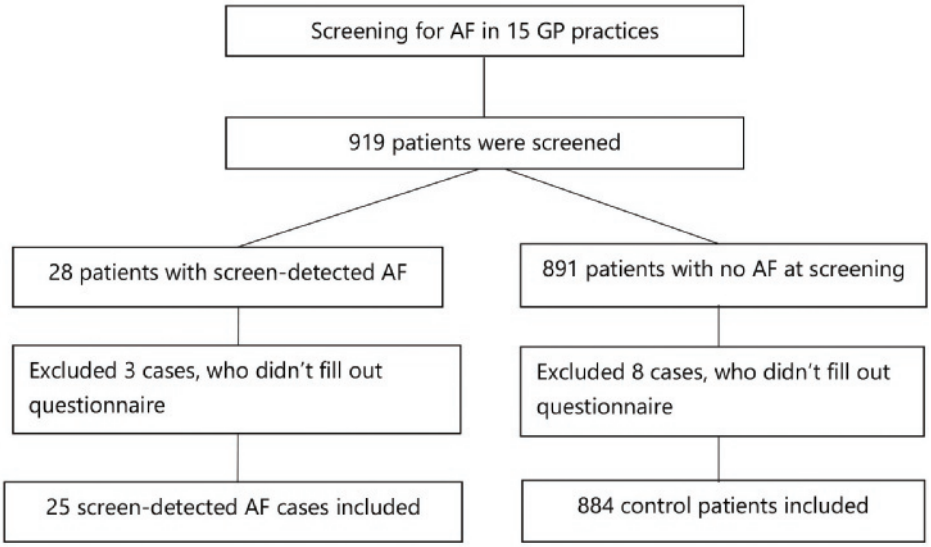

Figure 1. Flow chart of the study

Table 1. Baseline characteristics of 909 adults aged ≥65 years unknown with AF who were screened for AF; divided in newly screen-detect AF patients and controls without AF at screening.

Characteristics	**Screen-detected AF n = 25 (%)**	**Subjects without screen-detected AF, n = 884 (%)**
Mean age in years (SD)	75.1 (6.6)	74.0 (6.9)
Female sex	13 (52.0)	474 (53.6)
Medical history		
Hypertension	16 (64.0)	531 (60.1)
Heart failure	4 (16.0)	23 (2.6)
Type 1 or type 2 diabetes	6 (24.0)	221 (25.0)
COPD	3 (12.0)	100 (11.3)
Angina pectoris	3 (12.0)	89 (10.1)

Results

In total 3.0% had screen-detected AF, and they were slightly older than those without AF (75.1 versus 74.0 years) and more often had a history of heart failure (16.0% vs, 2.6%) (table 1). Three patients with screen-detected AF and eight patients without AF did not fill out a questionnaire at screening (figure 1).

Patients with screen-detected AF reported more often any of the AF-related symptoms in the month before screening than those without AF (64.0% versus 44.2%, RR 1.4; 95% CI 1.1-2.0) (table 2). Most frequently reported symptoms in screen-detected AF patients were palpitations (32.0%; RR 2.7, 95% CI 1.5-5.0) and shortness of breath (36.0%; RR 2.3, 95% CI 1.3-3.9). Dizziness was less often reported (4.0% vs. 13.2%; RR 0.3, 95% CI 0.04-2.1). Skipped heartbeats, chest discomfort and lightheadedness occurred more often in patients with screen-detected AF, although not statistically significant with RRs 2.0 (95%CI 0.9-4.5), 1.5 (95%CI 0.5-4.5) and 1.6 (95%CI 0.8-3.2), respectively.

In total, 36.0% of the screen-detected AF patients reported no AF-related symptoms at all. The corresponding proportion in patients without AF was 55.8% (RR 0.6 95% CI 0.4-1.1) (table 2).

Of the patients with palpitations, 7.2% had AF at screening, and this was 6.0% of patients with shortness of breath (SOB), as compared to 2.1% of those without palpitations or SOB, RR 3.4 (95%CI 1.5-7.7) and 2.9 (95%CI 1.3-6.4), respectively (table 3). Of patients with dizziness 0.9% had screen-detected AF, whereas 3.0% of patients without dizziness had screen-detected AF, RR 0.3 (95%CI 0.04-2.0). Prevalences of screen-detected AF in patients with presence or absence of remaining symptoms are listed in table 3.

Table 2. AF-like symptoms mentioned on a questionnaire before screening. Divided in newly screen-detect AF patients and controls without AF at screening.

Presence of AF-related symptoms	Screen-detected AF cases, n = 25 (%)	Subjects without screen-detected AF, n = 884 (%)	Relative Risk (95% CI)
Any AF-related symptom	16 (64.0)	391 (44.2)	1.4 (1.1-2.0)
Palpitations	8 (32.0)	103 (11.7)	2.7 (1.5-5.0)
Shortness of breath	9 (36.0)	140 (15.8)	2.3 (1.3-3.9)
Skipped heartbeats	5 (20.0)	89 (10.1)	2.0 (0.9-4.5)
Lightheadedness	6 (24.0)	135 (15.3)	1.6 (0.8-3.2)
Chest discomfort	3 (12.0)	70 (7.9)	1.5 (0.5-4.5)
Dizziness	1 (4.0)	117 (13.2)	0.3 (0.04-2.1)

Table 3. Prevalence of screen-detected AF in patients aged ≥65 years screened for AF in patients with and without AF-like symptoms mentioned on a questionnaire before screening.

AF-related symptom	AF in patients with presence of symptom; %	AF in patients with absence of symptom; %	Relative risk (95% CI)
Any AF-related Symptom	3.9	1.8	2.2 (1.0-4.9)
Palpitations	7.2	2.1	3.4 (1.5-7.7)
Shortness of breath	6.0	2.1	2.9 (1.3-6.4)
Skipped heartbeats	5.3	2.5	2.2 (0.8-5.6)
Lightheadedness	4.3	2.5	1.7 (0.7-4.2)
Chest discomfort	4.1	2.6	1.6 (0.5-5.1)
Dizziness	0.9	3.0	0.3 (0.04-2.0)

Discussion

AF was detected with screening in 3.0% of older community people visiting the general practice. Of these, 64.0% experienced AF-related complaints in the month prior to the diagnosis and 36.0% was truly asymptomatic. Palpitations (32.0%) and shortness of breath (36.0%) were most frequently reported complaints on the questionnaire, and in those mentioning these symptoms, the risk of AF discovered with screening was at least doubled; 7.2% and 6.0%, respectively.

In a previous study among 335 patients with chronic AF who filled out a questionnaire, palpitations (55.5%) and shortness of breath (50.5%) were most often reported, while dizziness was less often mentioned (35.5%).[9] Another study using a questionnaire showed similar results; of 558 patients with permanent AF 53.7% experienced palpitations, 82.4% shortness of breath, and 45.2% dizziness.[14] This is in line with our results. Importantly, these studies did not include a comparison with a group of subjects without AF. Such a comparison group is important because the aforementioned symptoms are not specific for AF, but may be caused by multiple other disorders, notably in older people. Moreover, these studies did not measure the presence of lightheadedness and only reported on dizziness.[9 14]

Even though many chronic AF patients report dizziness, it is a less common symptom than palpitations or SOB. Dutch AF guidelines, however, recommend paying special attention to uncover AF in patients with dizziness or lightheadedness.[19] The ESC guidelines on AF do not include this recommendation.[2] In our study dizziness is less often reported by patients with AF than by controls, whereas lightheadedness is reported more often. Dizziness seems not to be caused by AF and occurs mainly due to other diseases that are prevalent in elderly. However, awareness of lightheadedness might be relevant in detection of AF.[16 17]

Overall, our results underline the importance of acting on AF-like symptoms if mentioned by patients. This is also concluded by a Spanish study in which 161 GPs actively searched for AF in patients aged ≥65 years presenting with AF-related symptoms.[20] They included in total 1525 patients and achieved an AF detection yield of 6.8%. Acting on AF-related symptoms seems efficient, but might be time-consuming when adding it to a doctor's consulting-hours in usual care. Sending out questionnaires to high risk patients asking for AF-like symptoms could be part of a more effective selective screening strategy.

Importantly, 36.0% of screen-detected AF patients did not report any AF-related symptom on the questionnaire. Two previous studies among patients with chronic AF, reported lower rates of completely asymptomatic patients when using questionnaires; 8% and 17%.[9 19] These numbers suggest that patients that are detected with AF by screening, indeed have a lower burden of symptoms.

Strengths and limitations

To the best of our knowledge this is the first study to compare AF-like symptoms in screen-detected AF patients with those without screen-detected AF in a screening setting in daily primary practice. Moreover, we used a questionnaire to assess symptoms just before the screening was done and to enable also the assessment of symptoms not presented to the GP.

For this study we included all patients aged ≥65 years that were screened for AF when they visited the GP practice during one study year. These results are therefore generalizable to that (selected) population.

Conclusion

Older community people who experience palpitations and shortness of breath should receive special attention to uncover AF in primary care. To a lesser

extend this applies to those with skipped heartbeats, lightheadedness and chest discomfort, while dizziness on the other hand seems not to be related to AF.

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Competing Interests

Prof. FH Rutten, Prof. AW Hoes, dr. M Hollander and mrs F. Kaasenbrood report an institutional unrestricted grant from Boehringer Ingelheim, during the conduct of the study. Dr. R. Tieleman reports grants and personal fees from Boehringer Ingelheim and personal fees from Pfizer/ BMS and Daiichi Sankyo, outside the submitted work. In addition, Dr. R. Tieleman has a patent filled by Applied Biomedical Systems with royalties paid. Prof. A Hoes chairs a large (around 500 employees) research and teaching institute within our University Medical Center that performs both investigator- and industry-driven research projects with a number of pharmaceutical and diagnostic companies. In addition, some of his members of staff receive unrestricted grants for research projects from a number of companies. It is our explicit policy to work with several companies and not to focus on one or two industrial partners. He receives no personal payment from any industrial partner. Other authors have nothing to disclose.

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Diagnosing atrial fibrillation with a single-lead electrocardiogram: Diagnostic performance, and inter-reader variability between cardiologists and general practitioners

Femke Kaasenbrood
Monika Hollander
Robert G. Tieleman
Marco Alings
Martin E. W. Hemels
Clemens G. K. M. Fauser
Nicolaas P.A. Zuithoff
Marcel A.J. Landman
Jeanette Caljouw-Vos
Annette Hoogveld
Jeroen Schaap
Jan-Eize Lindeboom
Karin S. Blankestijn
Arno W. Hoes
Frans H. Rutten

Submitted

7

Abstract

Background Atrial fibrillation (AF) may occur without overt symptoms, and single-lead electrocardiography (ECG) screening devices are helpful for detecting AF. We aimed to assess the performance of the interpretation of single-lead ECG data provided by such a device.

Methods We included 106 individuals that visited a cardiac outpatient clinic. All were tested for AF with the MyDiagnostick® (a hand-held single-lead ECG device) and underwent immediately afterwards a 12-lead ECG. Four general practitioners (GPs) and four cardiologists reviewed the 106 single-lead ECGs blinded to the 12-lead ECG. They subsequently reviewed the 12-lead ECGs, blinded to (own interpretation of) the single-lead ECG. The physicians were divided in four pairs based on experience in interpreting ECG data. The reference standard was an expert panel of three rhythm cardiologists assessing the 12-lead ECG.

Results AF prevalence was 39.6% and the light result of the MyDiagnostick® had a diagnostic accuracy (proportion correctly classified results) of 91.4%. The diagnostic accuracy of single-lead ECG interpretation by two regular GPs was 86.2%, by two experienced GPs 91.5%, by two regular cardiologists 91.0%, and by two rhythm cardiologists 90.9%. For the 12-lead ECG interpretation, the diagnostic accuracies of the four types of physicians were overall higher with 88.1%, 95.3%, 96.3%, and 98.6%, respectively.

Conclusion The diagnostic accuracy of the light signaling of the device was good and comparable to the physician's interpretation of its single-lead ECG. In clinical practice, it is safest to immediately perform a 12-lead ECG in case the MyDiagnostick® suggests AF, or otherwise single-lead ECG registration should be interpreted by a physician experienced in interpreting single-lead ECGs.

Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia and its prevalence increases with age, affecting 8% of those aged at least 65 years.[1] It is associated with an increased risk of ischaemic stroke, heart failure and death.[2 3] It is speculated that up to 30% of AF is 'asymptomatic', and notably paroxysmal AF makes diagnosing a challenge. [4-6] Current guidelines recommend opportunistic screening for AF in primary care in patients by pulse palpation, followed by a subsequent 12-lead electrocardiogram (ECG) in case of irregularity.[4 7 8] Many screening devices have been developed to help general practitioners (GPs) detect AF with a single time-point measurement. Blood pressure monitors with heart rhythm registration, and single-lead ECG devices showed to have good performance compared to a 12-lead ECG interpreted by a single or at the best two cardiologist(s) as the reference standard.[9]

In case of suspected AF, a 12-lead ECG should follow immediately after screening to confirm AF status. However, in everyday primary care practice this is not always feasible; such 12-lead ECG is often performed some hours to days later, with the risk of missing paroxysmal AF. Single-lead ECG devices are potentially attractive because they provide (i) a light result of whether AF is likely present based on an incorporated computer algorithm based on R-R intervals, and (ii) the recording can be transported to a computer for visual interpretation by a health care provider. The AF-SCREEN International Collaboration recommends to use these devices to screen for AF, since a one minute single-lead ECG can confirm AF status.[10] However, the European Heart Rhythm Association (EHRA) emphasizes the difficulties with interpreting these single-lead ECGs, because it lacks i) registration of multiple leads and ii) clear recognition of the p-waves, which is often not visible in lead I or artificially enlarged by the device with the risk of enlarging an artifact.[4 11 12] If AF confirmation on the single-lead ECG by health care provider is accurate to define AF status, a 12-lead ECG recording is not necessary.[10] Research on the diagnostic performance of interpretation of single-lead ECGs by physicians is needed to know whether we could do without a 12-lead ECG in daily practice.

The MyDiagnostick® is one of several types of hand-held single-lead ECG devices. The diagnostic test performance for detection of AF based on the light result of the MyDiagnostick® was previously evaluated in two studies, both using a subsequent 12-lead ECG interpreted by a single cardiologist as the reference standard.[13 14] They mentioned sensitivity of 93.8% and 100%, specificity of 92.9% and 95.9% and diagnostic accuracy of 93.4% and 96.9%

in populations with a prevalence of AF of 53.0% and 27.6% respectively.[8] [9] The interpretation of the MyDiagnostick® single-lead ECG registration by experienced electrophysiologists was found to have a sensitivity of 81.8-89.5% and specificity of 94.2-95.7% compared to the blinded interpretation of a 6/12-lead ECG by the same electrophysiologists in a population with a 7.5% AF prevalence.[15] Interpretation of 500 single-lead ECGs, derived from Omron and Merlin by four cardiologists had mean sensitivity and specificity of 93.9% and 90.0% respectively, in a sample of the general population aged ≥75 years if compared to an immediately followed 12-lead ECG interpreted by two cardiologists as the reference.[16]

These previous studies on the performance of single-lead ECG interpretations didn't compare the results to a physician's interpretation of an immediately recorded 12-lead ECGs. Also, these studies do not consider general practitioners for interpretation of the ECG registration, while often screening is done in primary care. GPs have the option to interpret a single- or 12-lead ECG him/herself or consult an experienced colleague, or ask a cardiologist to interpret either type of ECG registration. Information about the interpretation of different health care workers is needed as guidance for the practical use of single-lead devices in primary care.

We assessed the diagnostic performance of i) the light result of the MyDiagnostick®, ii) the interpretation of the single-lead ECG of the MyDiagnostick® by general practitioners and cardiologists, knowing the light result (visible on the pdf of the one minute rhythm strip) as would be in everyday clinical practice, and finally iii) the interpretation of immediately followed 12-lead ECGs by both types of physicians.

Methods

Study design and study population

A random sample of 106 patients was included who visited the cardiology outpatient clinic of the Martini hospital Groningen for routine consultations. ECGs were performed first by MyDiagnostick® for one minute, followed immediately by a standard 12-lead ECG. All single-lead ECGs and 12-lead ECGs were stored on the computer. Patients with an activated pacemaker rhythm were excluded from the analyses.

The study complied with the Data protection law of the Netherlands. All data of participants were cared for in a de-identified manner.

MyDiagnostick®

The MyDiagnostick® (Applied Biomedical Systems BV, the Netherlands) is a rod-shaped single-lead ECG device that has two electrodes at the ends. While holding the device with both hands during one minute, a lead I ECG is recorded. An incorporated algorithm within the device measures (ir)regularity of the RR intervals and based on that reveals either a red or green light. A green light may be interpreted as sinus rhythm, and a red light (irregularity for more than 75% of 60 seconds) as probably AF. Of course, it may also indicate frequent premature beats or (substantial) sinus arrhythmia, i.e. due to breathing effects. The rhythm strip recording may be downloaded from the computer for manual interpretation.

Readers

Eight healthcare professionals interpreted the 106 single-lead ECGs: four general practitioners (GPs), two of them experienced in ECG reading (experienced GPs), two general cardiologists and two rhythm cardiologists. The readers interpreted the ECG results independently, and each was blinded for patient identifiers and clinical information. They were, however, not blinded for the result of the light signal of the MyDiagnostick®, as is usual in everyday practice. They were asked to place remarks if they were uncertain about their decision (e.g. doubts, technical issues). At a later moment, all healthcare professionals also assessed the 12-lead ECGs of the 106 patients, blinded for the results of the MyDiagnostick® (red/green light) and single-lead ECG.

Reference standard

For the reference standard one additional rhythm cardiologist interpreted all 12-lead ECGs, besides the two previous mentioned rhythm cardiologists. Thus, the reference standard was the independent interpretation of the 12-lead ECG by three rhythm cardiologists. They were blinded for the results of the MyDiagnostick® (green or red light), and for the single-lead registration. In case of disagreement, they were asked to re-assess the 12-lead ECGs with the knowledge that there was disagreement among them, but without representing their previous interpretation of these specific ECGs. The score of the majority of the second assessment of these three experts was used as the final outcome (yes/no AF).

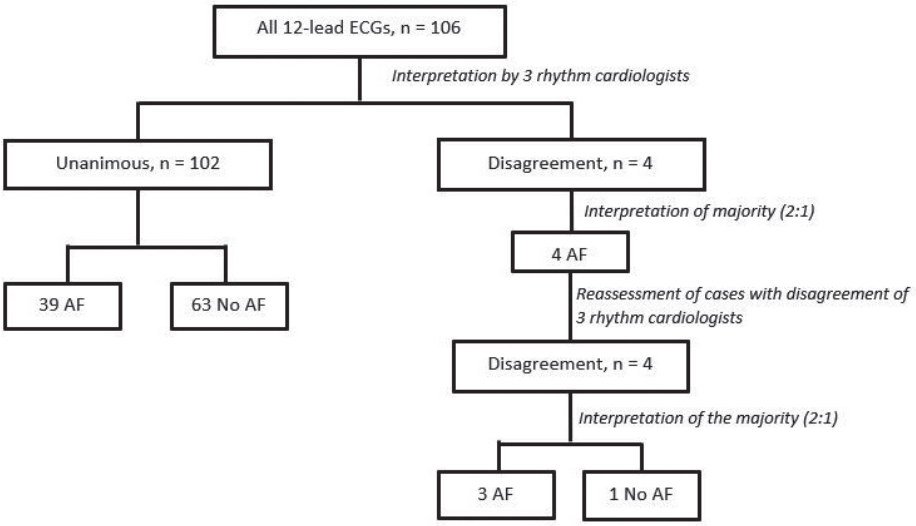

Figure 1. Flow chart of the assessment of the reference standard: 12-lead ECG recorded at the same moment as MyDiagnostick® measurement and interpreted by three rhythm cardiologists.

Data analyses

We first estimated the accuracy and sensitivity, specificity, negative and positive predictive value for the MyDiagnostick® light and the interpretation of the single- and 12-lead ECG with 95% confidence intervals (CIs) of GPs (categorized as regular GPs (n=2) and ECG-reading experienced GPs (n=2)), cardiologists (categorized in regular (n=2) and rhythm cardiologists (n=2)). This was done with a mixed logistic regression model, because all physicians analyzed the same single-lead ECGs and 12-lead ECGs in the same patients. We included random components in the model to account for the variability and covariance of sensitivity and specificity due to the assessment by multiple physicians. We subsequently used the same analysis to estimate PPV and NPV for AF prevalence of 2.0%, assuming that sensitivity and specificity would be stable. In some calculations the random component in the model was close to zero and in these cases we subsequently removed the random component from the model. We calculated diagnostic accuracy by dividing the number of correct interpretations (true negatives and true positives) by all interpretations (true negatives, true positives, false positives and false negatives). Cohen's and Fleiss' kappa (κ) was used to evaluate agreement between readers.[17] Analyses were performed with SAS (version 9.4) and Microsoft Excel 2010.

In case a reader could not decide on the presence or absence of AF on the single-lead ECG, it was classified as 'not interpretable', and these registrations were excluded from the analysis.

Results

The prevalence of AF in the 106 patients was 39.6%. In 102 cases (96.2%) the three rhythm expert cardiologists reached first round full agreement; AF in 39 cases (38.2%) and no AF in 63 cases (61.8%). Of the remaining four 12-lead ECGs (3.8%), three were classified as AF (see figure 1) by the majority of the experts after reassessment of the ECG.

Overall performance of the signaling of the MyDiagnostick® and the interpretation of single-lead ECG and 12-lead ECG

Table 1 shows the diagnostic performance of (i) the light result derived from the MyDiagnostick®, (ii) the readings of the single-lead ECG and (iii) the 12–lead ECG, all compared to the reference standard. The diagnostic performance of the single-lead and 12-lead ECGs are the mean of all the eight health care professionals (Table 1).

For the light signal the diagnostic accuracy was 91.4% and sensitivity and specificity were 90.5% and 92.2%, respectively. For the single-lead ECG interpretation the mean diagnostic accuracy was 90.2%, and the sensitivity and specificity were 85.9% and 93.7%, respectively. For 12-lead ECG interpretation the mean diagnostic accuracy was 95.2%, and sensitivity and specificity were 95.1% and 97.3%. Predictive values are shown in table 1 for AF prevalence of this study (39.6%).

Table 1. Overall diagnostic performance for detecting or excluding AF on 106 MyDiagnostick® light signal, MyDiagnostick®-generated single-lead ECGs interpreted by eight health care providers, and the immediately recorded 12-lead ECGs interpreted by eight health care providers, each compared to the reference standard; 12-lead ECGs interpreted by three expert cardiologists

	NPV (95% CI)	PPV (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy*	Kappa#	NI
Light	93.7 (85.9-98.0)	88.4 (76.7-95.7)	90.5 (79.2-96.9)	92.2 (84.0-97.1)	91.4		0
Single-lead	90.8 (87.7-93.2)	89.7 (85.6-92.8)	85.9 (79.0 -90.9)	93.7 (90.5-95.9)	90.2	0.79	8
12-lead	96.7 (94.3-98.2)	95.6 (92.0-97.6)	95.1 (90.4-97.6)	97.3 (94.6-98.6)	95.2	0.81	0

Abbreviations: Light = light result from the MyDiagnostick®; Single-lead = interpretation of single-lead ECG by all eight health care professionals combined; 12-lead = interpretation of 12-lead ECG by all eight health care professionals combined; NPV= negative predictive value; PPV= positive predictive value; 95% CI= 95% confidence interval; N.I. = not interpretable (reader could not define AF status based on single-lead ECG); * Accuracy = number of true positive results + number of true negative results / number of all results; # Kappa = Cohen's Kappa represents variation in interpretations within group of readers.

Inter-reader differences in the interpretation of the single-lead ECGs

The diagnostic accuracy was 86.2% for regular GPs, 91.5% for experienced GPs, 91.0% for regular cardiologists, and 90.9% for rhythm cardiologists. Sensitivity, specificity and predictive values are listed in table 2 stratified per profession.

Of the in total 848 single-lead ECG interpretations 8*106 readings), 103 (12.1%) were considered 'uncertain' by one or more readers. Two GPs (one regular and one experienced) considered together 71 interpretations as 'uncertain', which was 68.9% of all 'uncertain' interpretations. Reasons mentioned for 'uncertainty' were (i) poor quality of the recordings (35.0%), (ii) very subtle irregularity (27.2%), (iii) narrowness of a single-lead without clear p-wave (19.4%), and (iv) unspecified (18.4%). As expected, the interpretation on presence or absence of AF was more often incorrect in 'uncertain' cases as compared to the single-lead ECG interpretations considered interpretable; 32.0% versus 7.9%. (Data not shown)

Table 2. Diagnostic performance for detecting or excluding AF on 106 MyDiagnostick®-generated single-lead ECGs by different health care providers (knowing also the light signal result) compared to 12-lead ECGs interpreted by three expert cardiologists (reference standard)

Reader	NPV (95% CI)	PPV (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy*	Kappa#	N.I.
RC	92.8 (86.3-96.4)	88.4 (79.1-93.9)	89.8 (75.9-96.1)	92.2 (84.1-96.4)	90.9	0.82	3
Car	91.0 (84.3-95.0)	91.3 (82.3-95.9)	86.2 (70.5-94.2)	94.7 (87.6-97.8)	91.0	0.82	1
EGP	92.4 (86.0-96.0)	90.4 (81.4-95.3)	88.6 (74.1-95.5)	93.9 (86.6-97.4)	91.5	0.88	0
GP	85.9 (78.1-91.2)	88.6 (78.2-94.4)	76.6 (57.1-89.0)	93.9 (86.5-97.4)	86.2	0.57	4

Reference standard: 3 rhythm cardiologists' interpretation on presence/absence of AF on 12-lead ECG. Abbreviations: RC = Rhythm cardiologist; Car = Cardiologist; EGP = Expert General Practitioner; GP = General Practitioner; NPV= negative predictive value; PPV= positive predictive value; 95% CI= 95% confidence interval; N.I. = not interpretable (reader could not define AF status based on single-lead ECG); * Accuracy = number of true positive results + number of true negative results / number of all results; # Kappa = Cohen's Kappa represents variation in interpretations within group of readers.

Inter-reader differences in the interpretation of the 12-lead ECG

Table 3 shows the diagnostic performance of four groups of health care providers in the interpreting 12-lead ECG recordings. The diagnostic accuracy was 88.1% for regular GPs, 95.3% for experienced GPs, 96.3% for regular cardiologists and 98.6% for rhythm cardiologists. Sensitivity, specificity and predictive values are listed in table 3 stratified per profession.

Table 3. Diagnostic performance of health care providers interpreting a 12-lead ECG compared to the reference standard (three expert cardiologists' interpretation on presence or absence of AF on 12-lead ECG) in 106 cases.

Reader	NPV (95% CI)	PPV (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy*	Kappa#
RC	98.4 (93.8-99.6)	98.8 (91.9-99.8)	97.8 (89.3-99.6)	99.2 (93.8-99.9)	98.6	0.94
Car	96.9 (81.8-98.9)	95.3 (87.8-98.3)	95.6 (85.5-98.8)	97.0 (91.0-99.0)	96.3	0.92
EGP	98.4 (83.7-99.6)	91.2 (82.9-95.7)	97.8 (89.2-99.6)	93.9 (86.6-97.3)	95.3	0.88
GP	86.7 (79.3-91.8)	92.6 (83.0-97.0)	76.7 (57.3-88.9)	96.2 (89.9-98.6)	88.1	0.52

Reference standard: 3 rhythm cardiologists' interpretation on presence or absence of AF on 12-lead ECG. Abbreviations: RC = Rhythm cardiologist; Car = Cardiologist; EGP = Expert General Practitioner; GP = General Practitioner; NPV= negative predictive value; PPV= positive predictive value; 95% CI= 95% confidence interval; * Accuracy = number of true positive results + number of true negative results / number of all results; # Kappa = Cohen's Kappa represents variation in interpretations within group of readers.

Discussion

The light signal of the hand-held single-lead device MyDiagnostick® has a diagnostic accuracy (percentage of correctly identified patients) of 91.4%. The diagnostic accuracy of the interpretation of the single-lead ECG from MyDiagnostick® by GPs and cardiologists (knowing the result of the light signal) was slightly worse than only the light signal (90.2%). The diagnostic accuracy of interpretation of the 12-lead ECG by GPs and cardiologists was the highest (95.2%). The regular GPs performed worse in interpreting both single-lead ECGs and 12-lead ECGs than experienced GPs, cardiologists and rhythm cardiologists.

Two previous studies assessed the light signal results of the MyDiagnostick® and they mentioned a sensitivity of 93.8% and 100%, respectively, and specificity of 92.9% and 95.9%, respectively. This in a population in which the prevalence of AF was 53.0% and 27.6%, respectively.[13 14] In both studies, the reference standard was a 12-lead ECG recorded immediately after holding the MyDiagnostick® and interpreted by a single cardiologist blinded for the single-lead results. In our study with a prevalence of AF of 39.6% we had a similar sensitivity and specificity of 90.5% and 92.2%, respectively.

The interpretation of a single-lead ECG is more difficult than that of 'standard' 12-lead ECG because only the latter in general enables the recognition of p-waves if present and to a lesser extend amplitude of QRS-complex is reduced in single-lead recordings.[4] Since, this shortcoming is related to measuring only lead I with a single lead device, it is therefore related to all single-lead ECGs, making our results generalizable to other single-lead ECG devices.[15 16 18] In our study all physicians could better interpret a 12-lead ECG than a single-lead ECG, even with knowing the light signal result in the latter case. In general, a 12-lead ECG following a red signal seems a safer option than interpreting the single-lead registration of the MyDiagnostick®. Physicians are not used to interpreting single-lead ECG data and in this study the interpreter had serious doubts about their interpretation in 12.1% of the single-lead ECGs. Previous studies reported documented 'not interpretable rates' of 3.9% and 7.2% of single-lead registrations. [15 16]

Misinterpretations of single-lead ECG devices have important consequences. False positive AF may result in unnecessarily prescribing oral anticoagulants, without clear benefit while risking serious bleeds. On the other hand, based on a false negative diagnosis a patient will not be prescribed oral anticoagulants and is thus exposed to increased thrombo-embolic risks, e.g. ischaemic stroke.[3] False positives are less likely to be corrected over time (an ECG at a later stage with sinus rhythm may result in interpreting the previous reading as paroxysmal AF) than false negatives (an ECG at a later stage showing AF will immediately be followed by initiation of oral anticoagulants if the stroke/thromboembolic risk is considered high enough).

It is important to realize that our reference standard is not completely flawless. Our three experienced rhythm cardiologists disagreed on four cases (3.8%). In the SAFE study, the disagreement among two cardiologists interpreting more than 2500 12-lead ECGs from a primary care population (prevalence of AF of 8.4%) on presence or absence of AF was much lower with 0.27%.[8] If the interpretation of a single (expert) cardiologist's interpretation of a 12-lead ECG is used as the reference standard, it will be very likely that some ECGs will be misclassified in a few cases.[7 8 13-15 18]

Interpreting our results, one has to realize that in a screening setting, e.g. .in primary care, the prevalence of AF is low (around 2%) and therefore high NPV and low PPV may be expected. In every day primary care practice this would mean it is safe to consider a green light as absence of AF, at least for that very moment, while a red light needs to be confirmed, before considering initiation of anticoagulant therapy. Preferably a 12-lead ECG recording should follow a

positive signal of the MyDiagnostick® in everyday clinical practice and it should be performed immediately after screening, because otherwise paroxysmal AF while holding the single-lead device could be missed.[6] If this is not feasible, it is tempting to use single-lead ECG to determine AF status. Based on this study, one should be warned that interpretation is difficult and should only be performed by a health care professional with experience in interpreting single-lead ECG recordings.

Strengths and limitations

To our knowledge, this is the first study in which the light result of a hand-held ECG device are compares with the interpretation of the single-lead ECG, and 12-lead ECG by multiple health care professionals all against a robust reference standard (3 rhythm cardiologists). We believe this provides relevant information for everyday practice.

In the present study we used ECG registrations from a random sample of patients who had visited the outpatient cardiology clinic for routine controls. As a result, relatively more difficult to interpret AF cases could have been included as compared to a primary care setting, because prescription of rate-reducing drugs was relatively common, and this may have affected the heart rate and severity of the irregularity.

It is important to emphasize that the prevalence of AF in our study population was much higher (39.6%) than may be expected in a primary care population (around 8% in population aged >65 years and around 2% in a screening setting).[13 14 19]

We used a mixed logistic regression model with a random intercept to analyze pairs of sensitivity and specificity and pairs of PPV and NPV. The design of the study, however, is strictly speaking cross-nested, for which an additional random component for patients should have been be included. This analysis proved not estimable, most likely due to the high values for sensitivities, specificities, PPV and NPV.

Conclusions

The diagnostic accuracy of the light signaling of the MyDiagnostick® was good and comparable to the physician's interpretation its single-lead ECG. For clinical practice, it doesn't have extra value to interpret a single-lead ECG next to the light signaling of the MyDiagnostick®. In case of a red light, however, it is safest to immediately perform a 12-lead ECG, or otherwise let its single lead ECG registration be interpreted by a physician with vast experience with interpreting rhythm strips.

Author contributions

FK, MHo, AHoe, RT, KB and FR contributed to the conception or design of the work. MHo, MA, MHe, CF, ML, JC, AHoo, JS, JL and FR analyzed single-lead ECGs and 12-lead ECG for the research. FK, MHo, RT, MA, MHe, CF, ML, JC, AHoo, JS, JL, KB, AHoe and FR contributed to the interpretation of the results. NZ contributed to the analysis. FK and KB drafted the manuscript. All critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Declaration of conflict of interest

Dr. Alings reports personal fees from Bayer, Boehringer Ingelheim, BristolMeyerSquib BMS, Daiichi Sankyo, Pfizer and Sanofi, outside the submitted work as a member of advisory board. Dr. Rutten, dr. Hollander and mrs Kaasenbrood report an institutional unrestricted grant from Boehringer Ingelheim, during the conduct of the study. Dr. Tieleman reports grants and personal fees from Boehringer Ingelheim and personal fees from Pfizer/ BMS and Daiichi Sankyo, outside the submitted work. In addition, Dr. Tieleman has a patent filled by Applied Biomedical Systems with royalties paid. Other authors have nothing to disclose.

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General discussion: Should we screen for atrial fibrillation in primary care?

Main findings of this thesis

This thesis focuses on screening for atrial fibrillation (AF) in primary care. Before we try to answer the question "should we screen for AF in primary care", we summarize the main results of the thesis based on the research objectives formulated in the Introduction (chapter 1):

1. To provide insight in the effectiveness and feasibility of two possible strategies for AF screening in primary care: (i) 'mass' AF screening during flu vaccination and (ii) opportunistic screening of those aged ≥65 years when visiting the GP practice.
2. To explore whether patients with screen-detected AF more often experience AF-related signs and symptoms than patients without AF.
3. To investigate whether a one minute single-lead ECG recorded by a hand-held ECG device accurately diagnoses AF.

Ad 1. Effectiveness and feasibility of two strategies to screen for AF in primary care.

- The first strategy included screening for AF in older community people during influenza vaccination sessions in primary care. In chapter 2 we showed that such screening with a hand-held single-lead ECG device resulted in screening 35% of the eligible population, with a yield of 1.1% newly detected AF cases within the screened population.[2] The highest yield of newly detected AF (4.9%) was in the oldest age category (≥85 years). The vast majority of screen-detected cases fulfilled the criteria for anticoagulation; 78% had a CHA_2DS_2-VASc score ≥2, 19% had a CHA_2DS_2-VASc score of 1, and 3% a score of zero.

  In chapter 3 we showed that such a 'seasonal influenza vaccination' strategy is cost-effective in 99.8% of the simulations, and even cost saving in 61.9% of the simulations.[3]
- The second strategy included opportunistic screening with a hand-held single-lead ECG device in those aged ≥65 years who visit the GP practice. We performed a pragmatic cluster-randomized trial, in which we provided intervention practices with screening devices and left the use of the screening tool at their discretion. Fifteen intervention practices were compared to 16 control practices providing usual care. In chapter 4 we showed that after one year, there was no significant difference in the rate of newly detected AF between the screening and usual care group (1.43% vs. 1.37%). On average, the intervention GP practices screened only 10.7% (range 0.0% to 39.0%) of all patients aged ≥65 years enlisted in the practice.

Ad 2. Do patients with screen-detected AF more often experience AF-related signs and symptoms than patients without AF?

- In the case-control study presented in chapter 5 we explored whether patients with screen-detected AF visited the GP with susceptive signs or symptoms more often than those without AF. For that purpose we scrutinized medical files of 61 screen-detected AF patients (cases) and 244 age- and gender matched controls up to two years previous to diagnosis and determined whether they visited the GP practice with one of following symptoms or signs: shortness of breath, fatigue, dizziness, chest pain, (near)syncope, symptoms suspicious for TIA/minor stroke, and palpation of an irregular pulse. In 44.3% of screen-detected AF cases one or more AF-related symptom or sign was presented to and recorded by the GP. This was 34.0% (p=0.14) in 244 age- and sex-matched controls. Palpitations and an irregular pulse were both significantly more often recorded in cases than controls: 9.8% vs. 3.7% (OR 3.2, 95% CI 1.1 to 9.7) and 9.8% vs. 0.4% (OR 26.5, 95% CI 3.1-224.7), respectively.
- In chapter 6 we compared the results of a questionnaire about AF-related symptoms administered to patients screened for AF, between screen-detected AF patients and those who had no AF at screening. Significantly more screen-detected AF patients experienced palpitations (32.0%) and shortness of breath (36.0%) than those without AF (11.7% and 15.8%, respectively). Dizziness was reported less frequently by patients with screen-detected AF (4.0% vs. 13.2%, p=0.18). In total, 36.0% of screen-detected AF patients did not report any AF-related symptom, compared with 56% in patients without AF.

  In conclusion; older community-dwelling people who experience palpitations, shortness of breath and/or have an irregular pulse should be considered for AF detection, although, palpitations and shortness of breath are common in this age category.

Ad 3. Does a one minute single-lead ECG recorded by a hand-held ECG device accurately diagnose AF?

- In chapter 7, we compared (i) the instant light result (red or green) of the MyDiagnostick®, with (ii) the physician's interpretation of the single-lead ECG recording of the MyDiagnostick® and (iii) the physician's interpretation of a simultaneously made 12-lead ECG. The interpretation of the 12-lead ECGs by a panel of three experienced rhythm cardiologists was the reference standard (they disagreed on AF status in four of the 106 ECGs; 3.8%). Four GPs and four cardiologists were asked to assess AF status in 106

cardiology outpatients (prevalence of AF based on the three experts 39.6%) by interpreting the single-lead ECG registration of the MyDiagnostick® and the simultaneously made 12-lead ECG, blinded to their own interpretation of either registration. The instant light signal result of the MyDiagnostick® was almost as accurate in identifying AF status as the interpretation of the single-lead ECGs by cardiologists or GPs; 11.6% vs. 10.3% of all positive results were false positives and 6.3% vs. 9.2% of all negative results were false negatives. Moreover, we found that GPs and cardiologists were better in interpreting a 12-lead ECG (average accuracy 95.2%) than in interpreting a single-lead ECG registration (average accuracy 90.2%). When screening for AF in a primary care setting, the AF prevalence is very low (around 2%) and as a result the amount of false positive results will increase, whereas the false negative results will be reduced. From these findings we can conclude that in general the light signal of the MyDiagnostick® is sufficient (no interpretation of the 1 minute single-lead ECG needed), but that a red signal should be followed preferably by a 12-lead ECG or a single-lead ECG should be interpreted by an experienced physician.

Should we screen for AF in primary care?

In patients with AF the risk of stroke is around five times higher than in those without AF. Oral anticoagulation (OAC) reduces this risk on average by 66%. Up to one third of AF cases is expected to be undetected in usual care according to a meta-analysis that was reported in 2013.[4] Guidelines recommend opportunistic pulse palpation in adults aged ≥65 years during blood pressure measurement, and recording a 12-lead ECG in case of irregularity; a strategy aimed at improving AF detection.[1 5]

Many previous screening studies suggested that there is ample room for improvement of AF detection in primary care by screening those aged ≥65 years.[4 6] However, there are signals that the detection of AF in primary care has already improved over the last decade, possibly due to improved awareness of undetected AF, the recommendation in guidelines to screen for undetected AF and the stimulating effect of the introduction of direct OACs (chapter 4). The question of whether (and how) screening for AF should be implemented remains topical, considering the availability of easy to use screening devices on top of already improved care as usual (i.e. with more frequent pulse palpating) subjects ≥65 years.

In this chapter I will discuss the potential of screening for AF and follow the Wilson and Jungner criteria as a guidance.[7]

Table 1. Principles of early detection for disease by Wilson and Jungner (1968) applied to atrial fibrillation, using five categories: ++, +, +/-, - or --.

Wilson and Jungner Criteria[7]			
1.	The condition sought should be an important health problem	++	AF is an important health problem; it is common among people aged ≥65 years and it increases the risk of stroke, heart failure and all-cause mortality.
2.	There should be an accepted treatment for patients with recognized disease	++	Anticoagulants reduce the risk of stroke on average by 66%. Treatment is based on stroke risk, most often assessed with the CHA_2DS_2-VASc score. Screen- and regularly detected AF cases are recommended OAC if the CHA_2DS_2-VASc score≥2 and may be considered if score=1 (or 2 in women).
3.	Facilities for diagnosis and treatment should be available	++	Most important ingredients for AF screening are available in primary care, but the devices are seldom used.
4.	There should be a latent or early symptomatic stage	++	There is a latent stage of AF.
5.	There should be a suitable test or examination	+	Many single lead screening devices are available, but these often produce too many false positive results which may (i) cause patient anxiety, and (ii) place a burden on health services because a 12-lead ECG should follow.
6.	The test should be acceptable to the population	++	Available screening devices are well accepted by the public and health care workers.
7.	The natural history of the condition, including development from latent to declared disease, should be adequately understood	+	The disease course is in general known, but it is unclear whether AF patients detected with screening would also have been detected in usual care, and if so, after how much delay
8.	There should be an agreed policy on who to treat as patients	+	Patients receive stroke prevention based on the CHA_2DS_2-VASc score and rate or rhythm control is based on certain patient criteria.
9.	The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole	++	Screening is inexpensive and prevention of stroke very cost-effective. Depending on how the screening is executed it is likely to be cost-effective.
10.	Case finding should be a continuing process and not a "once and for all" project	++	This is possible in screening for AF.

1. AF should be an important health problem

Atrial fibrillation (AF) is the most common cardiac arrhythmia with a prevalence of 1-2% among the general population, steeply increasing with age to up to 8% of those aged ≥65 years, and even 18% in those aged ≥85 years.[8 9] The annual number of new cases of AF globally in 2010 was estimated at close to 5 million.[8 10]

AF is the leading cause of stroke, accounting for almost 40% of all strokes, and at least for 50% of strokes in the elderly aged ≥80 years.[11] In 11.5% of ischaemic stroke cases, AF was diagnosed afterwards, after monitoring the heart rhythm for at least 12 hours.[12] Furthermore, AF doubles the risk of heart failure and increases all-cause mortality with 50%.[13 14] AF has significant impact on healthcare costs, mainly driven by hospitalizations, stroke, and loss of productivity. It is estimated that AF accounts for 1% of the National Health Service budget in the United Kingdom, and $16 to 26 billion dollars of annual US expenses.[15 16]

It is evident that AF is an important disease and health care problem.

2. There should be an accepted treatment for patients with recognized AF

Treatment of AF includes (i) rate and rhythm control to improve symptoms and preservation of left ventricle function, e.g. drugs, cardioversion, catheter ablation and/or AF surgery, (ii) cardiovascular risk reduction, e.g. lifestyle changes and treatment of underlying CV conditions and (iii) stroke prevention with oral anticoagulants.[1]

Treatment with anticoagulants (vitamin-K anticoagulants (VKA) or non-vitamin-K anticoagulants (NOAC)) reduces stroke risk with around 66% at the expense of at least 1% major bleedings yearly including 0.3% intracranial bleeds.[17] The CHA_2DS_2-VASc score - consisting of the following items -Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, previous Stroke or TIA, Vascular disease, Age 65 to 75 years, and Sex category (female one point)- was developed with the aim to help clinicians select those requiring anticoagulant treatment.[1 5 18] Although treatment with (N)OACs is not extensively studied in screen-detected AF,[19] several studies showed that the prognosis of recognized AF is not dependent on presence or absence of symptoms [20 21 22] and therefore the same criteria for anticoagulation are recommended by guidelines. [23 24]

In conclusion, there are adequate treatment options for AF patients. Similar treatment strategies are recommended for clinically diagnosed and screen-detected AF patients, irrespective of the fact that clear evidence in screen-detected AF is lacking.

3. Facilities for diagnosis and treatment should be available

For more intensified opportunistic screening in primary care, easy to use and accurate screening devices should be available, as is personnel to perform the screening. In addition, easy access to a cardiologist for consultation should be organized.

Availability of diagnostic devices
During an educational meeting on cardiovascular disease in 2019, we asked 67 general practitioners to fill out a short multiple-choice questionnaire on AF detection in primary care. Ninety percent answered that they applied pulse palpation during every blood pressure measurement and ordered a 12-lead ECG in case of irregularity. Only 5% used a screening device, and 5% did not pay special attention to early detection. Thus, diagnostic screening devices, e.g. MyDiagnostick®, AliveCor® and blood pressure devices with AF detection function are not yet common practice. Besides this, the majority of GP practices has a 12-lead ECG device or can order a 12-lead ECG recording at a primary care diagnostic center or a cardiology outpatient clinic.

Personnel
Practice nurses could be involved to execute AF screening, when it is blended to existing primary care disease management programs (e.g. for type 2 diabetes, CV risk management, and COPD) or included in other prevention strategies, such as the yearly influenza vaccination. Sixty-five percent of the 67 GPs considered it worthwhile to let practice nurses participate in AF detection, and 61% considered training of the nurses for that purpose worthwhile. This seems feasible, since we managed to educate four research nurses by a 30 minute training for AF screening during influenza vaccination sessions with the MyDiagnostick®.[2] Practice nurses could be trained similarly.

Consultation of a cardiologist
Easy consultation of a cardiologist is important in a screening program, and this was agreed upon by 61% of the GPs who answered the questionnaire.

Financial incentives
Currently, there is no financial incentive for AF screening. Half of the GPs who filled out the questionnaire considered financial compensation important. On a scale from 0-100 (0=not important, 100=certainly needed) their mean score was 49.5, with 18% of them scoring 100.

In conclusion, the most important ingredients for AF screening are available in primary care, but devices are seldom used.

4. There should be a latent or early symptomatic stage

Suggestive symptoms of AF are palpitations, shortness of breath, tiredness, but also dizziness, chest pain, and (pre-) syncope,[25] but patients may be asymptomatic. Multiple studies showed that often AF remains unrecognized in usual care, primarily

because many patients with AF-associated symptoms do not present these to a doctor or because the attending health care professionals do not recognize the symptoms as being potentially caused by AF and consequently, the necessary diagnostic test are not performed. We found that 44.3% of screen-detected AF patients did not visit the GP with any AF-associated symptom or sign in two years prior to diagnosis (chapter 5). With a questionnaire immediately before screening 36.0% of patients with screen-detected AF reported no AF-suggestive symptom in the previous month (chapter 6). The remaining proportion of screen-detected AF patients experienced AF-associated symptoms prior to screening, but were not yet diagnosed with AF. In these patients AF could be detected more often by providing adequate information to patients on when to present AF-related symptoms to their GP and by convincing GPs to more often test for AF in everyday care.[6 26 27] Overall, screening or case-finding may uncover undetected AF, also in those with (non-presented or unrecognized) symptoms (see table 3).

In conclusion, there is a latent stage of AF, and opportunistic screening is helpful to uncover these patients.

5. There should be a suitable test or examination

Screening for AF can be performed by pulse palpation, or with one of many screening devices (table 2).[28] Importantly, false positive cases and to a lesser extent false negatives should be considered. We showed in the primary care setting that the MyDiagnostick® had a positive predictive value of 36%; which means that 64% of all positive results are false positives (chapter 2 and 4). [29] False positive results may cause patient anxiety, but importantly place a burden on health services because of extra unplanned 12-lead ECGs and cardiologist consultations (see also figure 1).

Hand-held single-lead ECG devices provide the possibility to transport the single-lead ECG recording for human interpretation, which seems attractive in primary care because it can bypass the two-step process of recording an additional 12-lead ECG after finding a positive result at screening. Importantly, because the ECG data is recorded at the exact moment of screening, it prevents conflicting results in case of paroxysmal AF. However, the risks of false positive and false negative results with interpretation of a single-lead ECG are higher than with a 12-lead ECGs (chapter 7). False positive results may result in unnecessary treatment with (N)OACs and therefore impose unnecessary bleeding risks. In patients with false negative results AF may remain undetected over a long period of time, lacking protection from oral anticoagulants, but false negative results might be corrected over time (see figure 1).[30]

In conclusion, many screening devices are available for AF screening, but false positive results can induce a burden on the health care system.

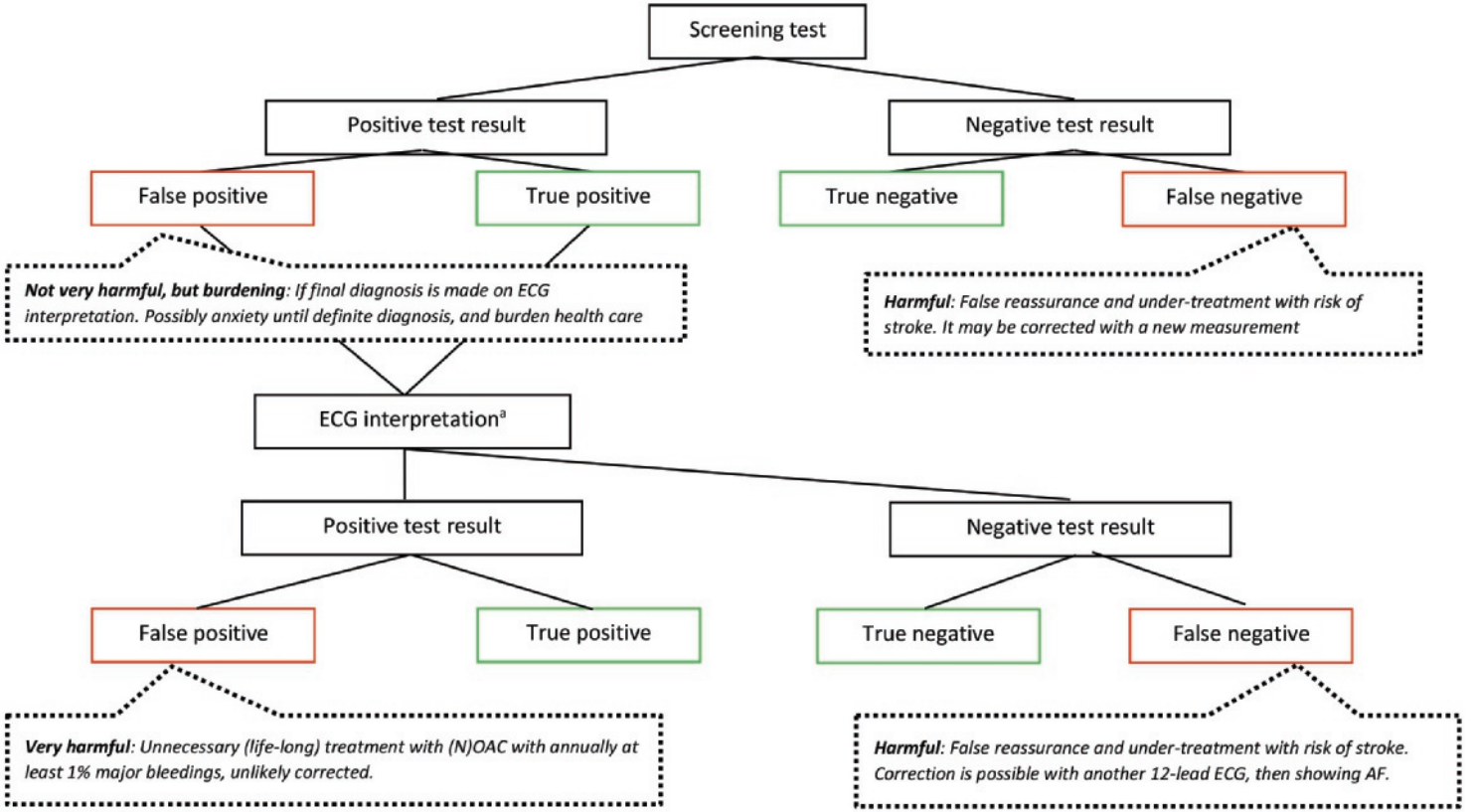

Figure 1. Diagnostic cascade of screening for AF with a device
[a] Either interpretation of 12-lead ECG or single-lead ECG.

Table 2. Diagnostic accuracy of screening devices with a 12-lead ECG interpreted by one or two cardiologists as a reference test.

Screening test	Number of patients included	AF prevalence	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV
Pulse palpation [a, 28]	16,159	7.8%	0.92 (0.85-0.96)	0.82 (0.76-0.88)	0.30	0.99
Automatic blood pressure monitor[a, 28]	2,637	14.3%	0.98 (0.92-1.00)	0.92 (0.88-0.95)	0.68	1.00
Finger photoplethysmography[b, 60]	219	N.A.	0.96	0.94	0.93	0.96
Single-lead ECG devices[a, 28]	14,147	10.3%	0.91 (0.86-0.94)	0.95 (0.92-0.97)	0.68	0.99
Single-lead ECG smartphone (Alivecor®)[61 62, c]	457	12.2%.	0.95	0.99	0.93	0.99

PPV, positive predictive value. NPV, negative predictive value. [a]A meta-analysis presenting pooled sensitivity and specificity of diagnostic screening devices. We calculated weighted mean AF prevalence and PPV and NPV based on this prevalence. [b]Data from a single study performed in 219 patients, mean age 66 years, 12-lead ECG interpreted by a single cardiologist as reference test. [c]We calculated weighted means for AF prevalence, sensitivity, specificity, PPV and NPV for these two studies.

6. The test should be acceptable to the population

An Australian qualitative study on the experience of users of the single-lead ECG device AliveCor® Heart Monitor for iPhone (iECG) reported that GPs appreciate the portability and instant results of the iECG.[31] They believed that such a device would add value to usual care, and they felt reassured if patient had a negative result with the device. Patients felt attracted to the technology and impressed seeing their heartbeat on an iECG. It is, however, questionable whether the public and also GPs are sufficiently aware of the consequences of false positive results. The devices mentioned under 5 seem acceptable to the population and they are already in use by GPs as well as by the public.

In conclusion, screening devices are accepted by the public and health care workers.

7. The natural history of AF, including development from latent to declared AF, should be adequately understood

Notably in the beginning of the disease, AF may occur in paroxysms, and over time progress to persistent or permanent AF ('AF becomes AF'). Some authors suggest that undetected AF is mainly paroxysmal, because continuous AF is more likely to remain unnoticed by patients, while others speculate that symptoms become noticed if AF is present at least 20-40% of the time. [25 32-34] These conflicting speculations indicate that it is yet unknown why some patients remain undetected.

It is also unclear whether AF patients detected with screening would also have been detected in usual care, and if so, after how much delay.

In conclusion, the natural history of AF is partly understood and there is large heterogeneity in the development and disease trajectory of AF. It remains unknown what proportion of latent AF will develop into manifest AF.

8. There should be an agreed policy on whom to treat

Regarding OAC, there is much uniformity because most physicians apply the CHA_2DS_2-VASc in any patient with AF whether paroxysmal, permanent, or screen-detected. There is, however, an ongoing debate about whether AF patients with a relative low risk of an ischaemic event would benefit from (N)OAC treatment. Therefore, it remains undefined whether or not men with CHA_2DS_2-VASc score 1 and women with a score 2 should receive anticoagulants. [1 5]

9. The cost of case finding should be economically balanced in relation to possible expenditure on medical care as a whole

Because screening is inexpensive and the prevention of stroke very effective, screening is easily cost-effective. The cost-effectiveness of screening for AF

in primary care has been studied in six countries: Japan, UK, Sweden, Ireland, Australia and the Netherlands.[35-40] Two studies used a hand-held single lead ECG device and the remaining evaluated pulse palpation with subsequent 12-lead ECG in case of irregularity. Most studies showed that screening for AF would probably be cost-effective. We showed that screening for AF with a single-lead ECG device during influenza vaccination in Dutch primary care in people aged ≥65 was almost certainly cost-effective (99.8% of the simulations) with a willingness to pay 20,000 euro/quality adjusted life year, and probably even cost saving (61.9% of the simulations).[3]

Nevertheless, we have to realize that the cost-effectiveness of screening strategies critically depends on the yield of AF detection. If the yield of screening is low and close to care as usual, then cost-effectiveness will be reduced.

10. Case finding should be a continuing process and not a "once and for all" project

Because adults contact the GP on average 7 times a year, repetitive screening seems feasible in primary care.[41] More screening moments increase the likelihood of detecting AF, notably because AF can occur in paroxysms.[42] Also because every year there are around 1.5-3.0% new incident cases in those aged ≥65 years.[9] Repetitive screening is also useful to uncover AF in those previously labeled incorrectly as no AF (false negatives). It is however not known how frequent we should screen to reach the most optimal yield of AF detection in primary care.

In conclusion, screening for AF can be applied continuously in primary care.

Based on the aforementioned; how should we screen for AF in primary care?

It is clear that primary care seems an appropriate setting for AF screening, but leaving the screening with a hand-held ECG device at the discretion of the GP does not result in more newly detected cased than care as usual (chapter 4). Thus, a programmatic approach is needed. Other studies also showed that a programmatic approach is more effective than leaving screening at discretion of physicians (table 3). We consider yearly inviting people aged ≥65 years for screening (e.g. with a hand-held single-lead ECG device) during influenza vaccination the best option. In addition, practice nurses could use a screening device during routine visits of patients participating in one of the primary care disease management programs. However, positive results at screening should always be checked to prevent false positive results; either with a directly recorded 12-lead ECG or a single-lead ECG derived from a hand-held ECG device interpreted by an experienced physician. Financial incentives seem necessary to facilitate the implementation of AF screening in primary care in the Netherlands.

Table 3. Overview of AF screening studies in primary care and community

First author (year of publication)	Country	Selection and number of participants	Screening rate[a]	Age in years	Diagnostic method	New AF cases (%)	Usual care detection rate[b]	Start (N) OAC in eligible cases
Studies in Primary care								
Quinn (2018)[43]	Canada	Opportunistic selecting of 2,010 patients visiting the GP practice with trained staff conducting the screening. All eligible patients included	95%	≥65	At a single time-point (i) Pulse palpation, (ii) Single-lead ECG (heart check) ánd (iii) blood-pressure device (Watch Home-A®). In case of positive result: confirmation by 12-lead ECG.	14 (0.7%)	N.A.	77%
Gonzalez (2017)[44]	Spain	Cluster RCT during 18 months comparing screening with pulse palpation (n=5,465) to focusing on AF symptoms (n=1,525 symptom-focused)	N.A.	≥65	At a single time-point. (i) Irregular pulse was followed by 12-lead ECG (ii) GPs focused on AF symptom detection	Pulse palpation: 61 (1.1%). Symptom-focused: 104 (6.8%)	-	N.A.
Kaasenbrood[2] (2016)	Netherlands	Screening during influenza vaccination sessions. 3,269 were actually screened	34.6%	Mainly elderly	Single time-point measurement with hand-held single-lead ECG MyDiagnostick®	37 (1.1%)	-	75%
Smyth[39] (2016)	Ireland	GPs were asked to screen during routine consultations and 6,527 were screened	30%	≥65	Single time-point pulse palpation	55 (0.8%)	-	65%

Table 3. Continued.

First author (year of publication)	Country	Selection and number of participants	Screening rate[a]	Age in years	Diagnostic method	New AF cases (%)	Usual care detection rate[b]	Start (N) OAC in eligible cases
Studies in Primary care								
Benito[26] (2015)	Spain	RCT during 2 years. In intervention arm 463 patients with ≥1 AF risk factor visited the GP nurse for screening. 465 included in control arm receiving CAU.	Screening: 26.7% CAU: 84.4%	All ages	Intermittent in intervention arm; 12-lead ECG every 6 months and instructions on pulse palpation	Scr: 11 (2.4%) CAU: 6 (1.3%)	Scr: 9.1% CAU: 100%	Scr: 100% CAU: 100%
Bury[45] (2015)	Ireland	Invited by post to attend screening. 566 actually screened.	56%	≥70	Single time-point a 3-lead ECG during 2 minutes	12 (2.1%)	-	78%
Kearley[46] (2014)	UK	Invited to receive multiple diagnostic measurements at a single time-point. 889 actually screened.	N.A.	≥75	Single time-point (i) Single-lead ECG Omron and (ii) Single-lead ECG Merlin and (iii) WatchBP monitor®	12 (1.3%)	-	N.A.
Lowres[37] (2014)	Australia	Performed at pharmacy, 891 actually screened.	N.A.	≥65	Single time-point single-lead ECG iECG AliveCor®	10 (1.1%)	-	60%
Clua-Espuny[47] (2013)	Spain	Invited by phone, researchers conducted screening in 952 people	N.A.	≥60	Single time-point 12-lead ECG	23 (2.4%)	-	76%
Rhys[38] (2013)	UK	Screening during influenza vaccination, 552 screened.	N.A.	≥65	Single time-point pulse palpation. In those with irregular pulse only 57% showed up for confirmatory 12-lead ECG.	2 (0.4%)	-	N.A.

Table 3. Continued.

First author (year of publication)	Country	Selection and number of participants	Screening rate[a]	Age in years	Diagnostic method	New AF cases (%)	Usual care detection rate[b]	Start (N) OAC in eligible cases
Studies in Primary care								
Wiesel[48] (2013)	US	Patients with ≥1 risk factor for AF were invited and 139 actually screened.	N.A.	All ages	Intermittent during 30 days AF-detect BP monitor® ECG event monitor	2 (1.4%)	-	50%
Fitzmaurice[6] (2007)	UK	3-arm cluster RCT during one year. In one intervention arm 4,562 patients invited by post, in opportunistic arm 4,575 flagged in GP file, and 4,513 in control arm received CAU. All eligible patients were included	Syst: 53% Opp: 69%	≥65	Single time-point (i) Opportunistic Pulse palpation or (ii) Systematically a 12-lead ECG	Syst: 74 (1.6%) Opp: 75 (1.6%) Ctrl: 47 (1.0%)	Syst: 30% Opp: 32% Ctrl: 100%	N.A.
Morgan[27] (2002)	UK	Cluster RCT during 1 year; systematic arm invited 1,499 patients by post and opportunistic arm flagged 1,502 in GP file. All eligible patients were included	Syst: 73% Opp: 29%	65-100	Single time-point pulse palpation	Syst: 12 (0.8%) Opp: 7 (0.5%)	-	N.A.
Wheeldon[49] (1998)	UK	Patients were invited by post to attend screening and 1,147 were screened	85%	≥65	Single time-point 12-lead ECG	5 (0.4%)	-	N.A.

Table 3. Continued.

First author (year of publication)	Country	Selection and number of participants	Screening rate[a]	Age in years	Diagnostic method	New AF cases (%)	Usual care detection rate[b]	Start (N) OAC in eligible cases
Studies in Primary care								
Hill[50] (1987)	UK	Patients were invited by post to attend screening and 799 were screened	81%	≥65	Single time-point 12-lead ECG	10 (1.3%)	-	N.A.
Studies in community								
Soni (2019)[51]	India	Residents of villages were approached by the research group for screening and 2,074 were screened.	90%	≥40	Intermittent. Three times during five days a single-lead ECG Kardia®, AliveCor®	First screening 22 (1.1%) Intermittent 11 (0.5%)	-	N.A.
Proietti (2016)[52]	Belgium	Results of five times Belgian Heart Rhythm Week invitations (2010-2014). All aged ≥18 were invited by advertisement through media, hospitals and GP practices. Research nurse conducted the screening among 52,741	64% (of those enrolled in program)	≥18	Single time-point Omron®, HeartScan® HCG-801	603 (1.1%)	-	N.A.
Svennberg[24] (2015)	Sweden	All inhabitants of Stockholm County and Halland region were invited by mail and a research nurse conducted screening. 7,173 actually screened	54%	75-76	Intermittent single-lead ECG during 2 weeks	Initial screening 37 (0.5%) Intermittent 181 (2.5%)	-	93%

Table 3. Continued.

First author (year of publication)	Country	Selection and number of participants	Screening rate[a]	Age in years	Diagnostic method	New AF cases (%)	Usual care detection rate[b]	Start (N) OAC in eligible cases
Studies in community								
LePage[53] (2015)	Island	General public was invited for a free heart screening event. 989 actually screened	N.A.	12–99	Single time-point single-lead ECG (iECG AliveCor®)	2 (0.2%)	-	N.A.
Li (2015)[54]	China	Inhabitants of Shanghai participated in comprehensive program and 3,922 actually screened	83%	≥60	Intermittent, twice a year a 12-lead ECG during a median follow-up of 3.8 year	34 (0.9%)	-	N.A.
Virtanen[55] (2014)	Finland	Inhabitants of Lieto were invited by post to participate in a program in which a nurse gave instructions on self pulse palpation. 139 were screened	21%	≥75	(i) Single time-point 12-lead ECG and (ii) Intermittent pulse palpation twice daily during one month	Initial screening 2 (1.0%) Intermittent 2 (1.4%)	25% (1 case)	N.A.
Engdahl[42] (2013)	Sweden	All inhabitants of Halmstad were invited by mail and a research nurse conducted screening. Those with $CHADS_2$ ≥2 received intermittent measurements at home. N=767 (of whom 419 were intermittently screened)	64%	75-76	(i) Single time-point 12-lead ECG and (ii) Intermittent a single-lead ECG twice daily during 2 weeks	Initial screening 10 (1.3%) Intermittent 30 (7.2%)	-	76%

Table 3. Continued.

First author (year of publication)	Country	Selection and number of participants	Screening rate[a]	Age in years	Diagnostic method	New AF cases (%)	Usual care detection rate[b]	Start (N) OAC in eligible cases
Studies in community								
Frewen[56] (2013)	Ireland	4,890 inhabitants were recruited as a part of a longitudinal study.	N.A.	≥50	Single time-point 10-min 3-lead ECG Medilog Darwin®	45 (0.9%)	-	N.A.
Sanmartin[57] (2013)	Spain	Inhabitants were invited by post, screening performed by nurse in 1,486	17%	≥65	Single time-point, pulse palpation	17 (1.1%)	-	N.A.
Claes[58] (2012)	Belgium	Inhabitants invited to attend a nationwide-organized voluntary screening program and 10,691 were screened	79%	≥40	Single time-point, single-lead ECG Omron HCG-801®	161 (1.5%)	-	N.A.
Schnabel[59] (2012)	Germany	Inhabitants invited to take part in a five-hour examination for a study on cardiovascular disease prevalence. 4,864 screened	60%	35-74	Single time-point, 12-lead ECG	25 (0.5%)	-	N.A.

CAU = Care as usual. [a]Rate of those actually undergoing screening among all invited for screening. [b]Rate of those newly detected in CAU, not with screening among those that were included in the study.

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Appendices

Summary

Atrial fibrillation (AF) is a common cardiac arrhythmia and the prevalence increases with age up to 8% of those aged 65 years and older, and it is expected to even rise in the near future. AF increases the risk for ischemic stroke around five-fold and the risk of death two-fold and is associated with other cardiovascular problems, notably heart failure. Treatment with anticoagulants, (vitamin K antagonist (VKA) or non-vitamin K oral anticoagulants (NOAC)) can reduce the stroke risk with 66%.

Early detection of AF is key to start treatment as early as possible. However, around one third of AF patients do not experience symptoms, making diagnosing AF a challenge. Screening of those with increased risk is an option, and primary care seems the most appropriate setting given the frequency in which people visit the general practitioner (GP) practice and the opportunity to make a 12-lead electrocardiogram (ECG) for confirming the diagnosis. We explored two possible strategies to conduct screening; 'mass' screening at a single time point, e.g. during flu vaccination, and opportunistic screening with a hand-held single-lead ECG device provided to community people aged ≥65 years attending the general practice for any reason. Moreover, we addressed important questions about diagnostic accuracy of the hand-held single-lead ECG device we used for screening.

The research objectives of this thesis were:

1. To provide insight in the effectiveness and feasibility of two possible strategies for AF screening in primary care: (i) 'mass' AF screening during flu vaccination and (ii) opportunistic screening of those aged ≥65 years when visiting the GP practice.
2. To explore whether patients with screen-detected AF more often experience AF-related signs and symptoms than patients without AF.
3. To investigate whether a one minute single-lead ECG recorded by a hand-held ECG device accurately diagnoses AF.

Ad 1. Effectiveness and feasibility of two strategies to screen for AF in primary care.
In **chapter 2** we examined a programmatic approach in which research nurses screened for AF during influenza vaccination in primary care practices. With this programmatic approach 35% of the population that visited the influenza vaccination sessions was screened and 1.1% of them was newly detected with AF. All screen-detected AF cases were aged ≥60 years and detection rate increased

with age up to 4.9% in those aged ≥85 years. The vast majority of these cases were eligible for anticoagulation treatment (19% had a CHA_2DS_2-VASc score of 1, and 78% a CHA_2DS_2-VASc score of 2 or more). In **chapter 3** we found that this screening approach was almost definitely cost-effective (nearly 99.8% of the simulations) and most likely cost saving (62% of the simulations) for identifying new cases of AF in the population aged ≥65 years in the Netherlands.

In **chapter 4** we examined an opportunistic approach in which screening was left at discretion of coworkers of GP practices. In a cluster randomized trial 15 intervention GP practices used the same hand-held single-lead ECG devices at their own discretion to screen all patients aged at least 65 years that visited the practice and 16 control practices provided usual care. The coworkers of intervention practices managed to screen 11% of the eligible population during one study year. Even though the yield was high in the screened group (28 of 919; 3.0%), this did not result in an increased AF detection rate when compared to usual care (both 1.4% during one study year). Patients that were selected for screening by GP practices had more comorbidities, e.g. hypertension, type 2 diabetes and COPD as compared to patients that were not screened.

Ad 2. Do patients with screen-detected AF more often experience AF-related signs and symptoms than patients without AF?

In **chapter 5** we found that 44% of the patients with screen-detected AF consulted the general practice with AF signs or symptoms two years prior to diagnosis, but this was overall not significantly more than age- and gender matched controls (34%). Signs and symptoms included shortness of breath, fatigue, dizziness, chest pain, (near)syncope, symptoms suspicious for TIA/minor stroke, and palpation of an irregular pulse. Palpitations and an irregular pulse were significantly more prevalent in screen-detected cases than controls: 9.8% vs. 3.7% and 9.8% vs. 0.4%, respectively.

In **chapter 6** we describe a study in which patients filled out a questionnaire just before screening about presence of AF-related symptoms during the past month; palpitations, skipped heart beats, shortness of breath, chest discomfort, dizziness and/or lightheadedness. AF was detected in 3.0% of all patients aged ≥65 years that were screened. Patients with screen-detected AF reported significantly more often AF-related symptoms than those without AF (64.0% versus 44.2%). Most frequently reported were palpitations (32.0% versus 11.7%) and shortness of breath (36.0% versus 15.8%), while dizziness occurred more often among patients without AF (4.0% versus 13.2%). Patients

who experienced palpitations or shortness of breath had a twice or more chance of AF at screening; 7.2% and 6.0%, respectively.

Ad 3. Does a one minute single-lead ECG recorded by a hand-held ECG device accurately diagnose AF?

In **chapter 7** we determined accuracy of interpretation of single-lead ECGs derived by MyDiagnostick®; four general practitioners (GPs), and four cardiologists reviewed single-lead ECGs of 106 patients visiting a cardiology outpatient clinic. They subsequently reviewed 12-lead ECGs of the same 106 patients. The diagnostic accuracy of the light signaling of the device was good and comparable to the physician's interpretation of its single-lead ECG. However, all physicians were less good in diagnosing AF on a single-lead ECG than on a 12-lead ECG. Regular GPs performed worse than GPs with vast experience in ECG interpretation and cardiologists. In clinical practice, it is safest to immediately perform a 12-lead ECG in case the MyDiagnostick® suggests AF, or otherwise single-lead ECG registration should be interpreted by a physician experienced in interpreting single-lead ECGs.

Samenvatting

Atriumfibrilleren (AF) is een veel voorkomend hartritmestoornis. De prevalentie neemt toe met de leeftijd tot 8% van de 65-plussers en de verwachting is dat deze in de nabije toekomst zelfs zal stijgen. AF verhoogt het risico op ischemische beroerte ongeveer vijfmaal en het risico op de dood tweemaal en het wordt geassocieerd met andere cardiovasculaire problemen, met name hartfalen. Behandeling met anticoagulantia (vitamine K-antagonist (VKA) of niet-vitamine K orale anticoagulantia (NOAC)) kan het risico op een beroerte met 66% verminderen.

Vroege detectie van AF is belangrijk om zo snel mogelijk behandeling te starten. Ongeveer een derde van de AF patiënten heeft echter geen symptomen, waardoor het detecteren een uitdaging is. Daarom kan men screenen bij mensen met een verhoogd risico, en eerstelijnszorg lijkt de meest geschikte setting gezien de frequentie waarmee mensen de huisartsenpraktijk bezoeken en de mogelijkheid om een 12-afleidingen elektrocardiogram (ECG) te maken voor het bevestigen van de diagnose. We hebben twee mogelijke strategieën onderzocht om zulke screening uit te voeren; massale AF-screening tijdens griepvaccinatie, en opportunistische screening waarbij huisartspraktijken iedereen vanaf 65 jaar, die de hun praktijk bezocht, konden screenen met een hand-ECG-apparaat. Daarnaast hebben de diagnostische nauwkeurigheid onderzocht van het hand-ECG-apparaat dat we voor screening hebben gebruikt.

De onderzoeksdoelstellingen van dit proefschrift waren:
1. Inzicht verschaffen in de effectiviteit en haalbaarheid van twee mogelijke AF-screeningstrategieën in de huisartspraktijk: (i) massale AF-screening tijdens griepvaccinatie en (ii) opportunistische screening van personen vanaf 65 jaar bij een bezoek aan de huisartspraktijk.
2. Bepalen of patiënten met AF gedetecteerd bij screening vaker AF-gerelateerde signalen en symptomen ervaren dan patiënten zonder AF.
3. Onderzoeken of een ritmestrook van één minuut dat opgenomen is met een in de hand-ECG-apparaat, nauwkeurig AF diagnosticeert.

Ad 1. Effectiviteit en haalbaarheid van twee strategieën voor screening op AF in de eerste lijn.
In **hoofdstuk 2** hebben we een programmatische benadering onderzocht waarin onderzoeksverpleegkundigen screenden voor AF tijdens griepvaccinatie sessies in huisartspraktijken. Met deze programmatische benadering werd 35%

van de bezoekers van de griepvaccinatiesessies gescreend en 1.1% daarvan werd nieuw gedetecteerd met AF. Alle screen-gedetecteerde AF gevallen waren ≥60 jaar en de detectiegraad nam toe met de leeftijd tot 4.9% bij patiënten van ≥85 jaar. De grote meerderheid van deze gevallen kwam in aanmerking voor antistollingsbehandeling (19% had een CHA_2DS_2-VASc-score van 1 en 78% een CHA_2DS_2-VASc-score van 2 of meer). In **hoofdstuk 3** ontdekten we dat deze screening bijna zeker kosteneffectief was (in 99.8% van de simulaties) en hoogstwaarschijnlijk kostenbesparend (in 62% van de simulaties) voor het identificeren van nieuwe gevallen van AF bij de bevolking vanaf 65 jaar in Nederland.

In **hoofdstuk 4** onderzochten we een opportunistische benadering waarbij de screening werd overgelaten aan de medewerkers van huisartspraktijken. In een cluster-gerandomiseerde trial gebruikten 15 interventie huisartspraktijken een hand-ECG-apparaat om alle patiënten met een leeftijd vanaf 65 jaar die de praktijk bezochten te screenen en 16 controlepraktijken leverden gebruikelijke zorg. De medewerkers van interventiepraktijken slaagden erin gedurende een studiejaar 11% van de bevolking ≥65 jaar te screenen. Hoewel de opbrengst in de gescreende groep hoog was (28 van 919, 3.0%), resulteerde dit niet in een verhoogde AF-detectiegraad in vergelijking met de gebruikelijke zorg (beide 1.4% tijdens één studiejaar). Patiënten die waren geselecteerd voor screening door huisartspraktijken hadden meer co-morbiditeit, b.v. hypertensie, type 2 diabetes en COPD in vergelijking met patiënten die niet werden gescreend.

Ad 2. Hebben patiënten met screen-gedetecteerd AF vaker AF-gerelateerde signalen en symptomen dan patiënten zonder AF?

In **hoofdstuk 5** vonden we dat 44% van de patiënten met screen-gedetecteerd AF de huisartspraktijk raadpleegde met AF-signalen of -symptomen twee jaar voorafgaand aan de diagnose, maar dit was niet significant meer dan mensen zonder AF van eenzelfde leeftijd en geslacht (34%). Signalen en symptomen waren kortademigheid, vermoeidheid, duizeligheid, pijn op de borst, (bijna) syncope, symptomen die verdacht zijn voor TIA/ kleine beroerte en palpatie van een onregelmatige pols. Hartkloppingen en een onregelmatige pols kwamen significant meer voor in screen-gedetecteerde gevallen dan controles: respectievelijk 9.8% versus 3.7% en 9.8% versus 0.4%.

In **hoofdstuk 6** beschrijven we een onderzoek waarin patiënten vlak voor de screening een vragenlijst invulden over de aanwezigheid van AF-gerelateerde symptomen in de afgelopen maand; hartkloppingen, overgeslagen hartslagen, kortademigheid, pijn op de borst, licht in het hoofd en/ of duizeligheid.

AF werd gedetecteerd bij 3.0% van alle patiënten van ≥65 jaar die werden gescreend. Patiënten met screen-gedetecteerd AF rapporteerden significant vaker de AF-gerelateerde symptomen dan die zonder AF (64.0% versus 44.2%). Meest frequent gerapporteerd waren palpitaties (32.0% versus 11.7%) en kortademigheid (36.0% versus 15.8%), terwijl duizeligheid vaker voorkwam bij patiënten zonder AF (4.0% versus 13.2%). Patiënten met hartkloppingen of kortademigheid hadden bij screening tweemaal of meer kans op AF; Respectievelijk 7.2% en 6.0%.

Ad 3. Geeft een ritmestrook van één minuut dat is opgenomen met een hand-ECG-apparaat nauwkeurig de diagnose AF?
In **hoofdstuk 7** hebben we de nauwkeurigheid bepaald van interpretatie van ritmestroken opgenomen door de MyDiagnostick®; vier huisartsen en vier cardiologen beoordeelden ritmestroken van 106 patiënten die een cardiologische polikliniek bezochten. Ze beoordeelden vervolgens 12-afleidingen ECG's van dezelfde 106 patiënten. De diagnostische nauwkeurigheid van de lichtsignalering van het apparaat was goed en vergelijkbaar met de interpretatie van de ritmestrokendoor de artsen. Alle artsen waren echter minder goed in het diagnosticeren van AF op een ritmestrook dan op een 12-afleidingen ECG. Reguliere huisartsen presteerden slechter dan huisartsen met uitgebreide ervaring in ECG-interpretatie en cardiologen. In de klinische praktijk is het veiligst om onmiddellijk een 12-afleidingen ECG uit te voeren in het geval dat de MyDiagnostick® AF suggereert, of anders een ritmestrook te laten interpreteren door een arts die daar ervaring mee heeft.

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&

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Curriculum vitae

Femke Kaasenbrood was born in Utrecht, the Netherlands, on 5th of March 1988. After graduation from the "Christelijk Gymnasium Utrecht" in 2006, she studied Medicine at the University of Maastricht and graduated in 2013. She combined her medicine study with a honours program, which included research in the field of Alzheimer's disease. In 2013-2014 Femke worked as a resident at the emergency room of "St. Antonius Ziekenhuis" in Utrecht (location Leidsche Rijn). In 2014 she started working on the research described in this thesis, at the Julius center for Health Sciences and Primary Care of the University Medical Center Utrecht, under supervision of prof. dr. F.H. Rutten, prof. dr. A.W. Hoes, dr. M. Hollander and dr. R.G. Tieleman. She combines her PhD project with general practitioner vocational training at the Department of General Practice, Julius Center Utrecht. In 2018 she received a master's degree in Clinical Epidemiology at Utrecht University. Results of her PhD research are presented in the current thesis entitled 'Detection of atrial fibrillation in primary care'.

List of publications

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