Nicole Verbiest - van Gurp

Detection of atrial fibrillation

Evaluation of diagnostic methods and
primary care based opportunistic screening

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Colophon

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Detection of atrial fibrillation

Evaluation of diagnostic methods and primary care based opportunistic screening

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Voor Gerard, Thijmen en Merel

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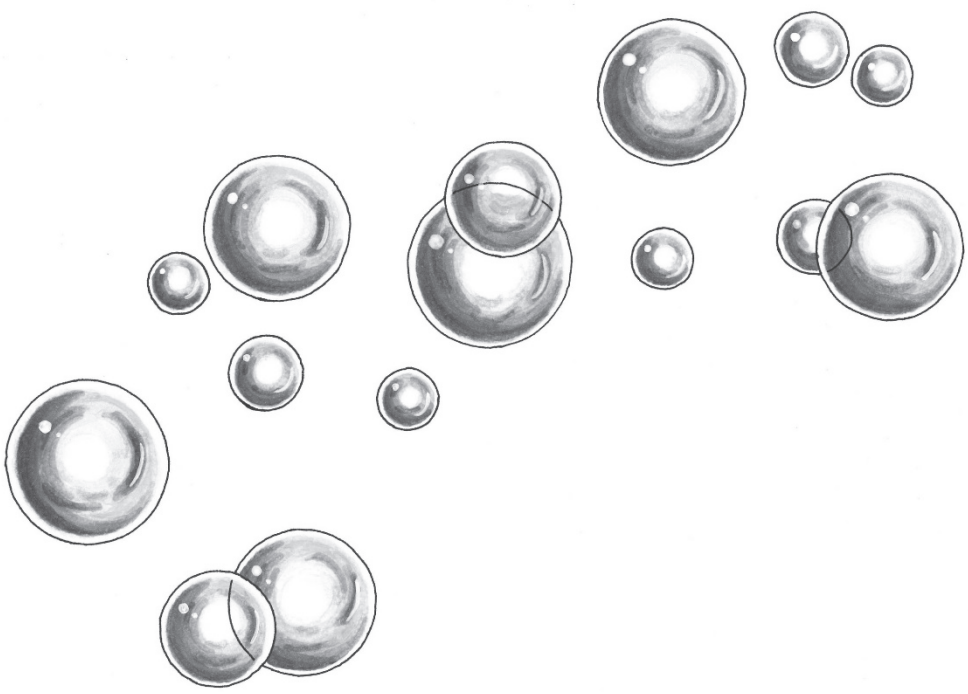
Chapter 1

General introduction



General introduction

Atrial fibrillation (AF) is an arrhythmia that can present with symptoms but can also be asymptomatic. AF can cause serious comorbidity such as a stroke. This is easily preventable with medication. However, patients with AF may elude diagnosis when they have no symptoms, or if the arrhythmia occurs intermittently. So how can we find these patients? This thesis concerns the detection of AF and how to improve it. It describes current care, opportunistic screening (case-finding), and various diagnostic devices in different settings.

What is atrial fibrillation?

AF is caused by a disturbance in the electrophysiological signals in the heart. In sinus rhythm, the sinus node produces regular impulses that go from the atria, through the atrioventricular (AV) node to the ventricles.[1] This electric process causes contraction of the atria, followed by contraction of the ventricles. In AF, impulses arise disorderly and in quick succession, from varying places in the atria. The AV node is overwhelmed by the amount of impulses from the atria; the time between two subsequent impulses is too short for it to recover. Consequently, not all impulses arriving at the AV node are transferred to the ventricles. Instead, impulses pass through from the atria to the ventricles in an irregular manner. Together, this results in a very fast and ineffective contraction (fibrillation) of the atria and an irregular and fast contraction of the ventricles. This changes the blood flow, which can cause thrombi that can lead to a stroke. Also, due to the fast contraction, the cardiac muscle can become stretched, thickened, or stiff, known as cardiomyopathy. As a result, the heart may have trouble pumping the blood effectively through the body and thus cause heart failure.

Heart failure is not only a possible complication of AF, but it can also be a risk factor for developing AF. Other factors that increase the risk of developing of AF are hypertension and age.[1] The overall prevalence of AF is approximately 1%, and increases with age.[2-4] AF can give rise to symptoms such as palpitations, dyspnoea, light-headedness, collapse or chest pain.[5] However, AF can also occur without symptoms, which is called ‘silent AF’. During physical examination, medical professionals can detect an irregular rhythm or tachycardia with pulse palpation or auscultation of the heart. A pulse deficit might be present, in which the heart rhythm is so fast that not every contraction heard during auscultation, reaches the periphery as a palpable heartbeat. AF can be diagnosed by means of

electrocardiography (ECG); the p-waves that represent atrial contraction in normal sinus rhythm are absent, and the QRS-complexes representing ventricular action appear irregularly. If the rhythm alternates between sinus rhythm and AF, it is called paroxysmal AF. Paroxysmal AF can progress to persistent and permanent AF in time.

Importance of early diagnosis

Severe possible consequences of AF are stroke and heart failure; 15-30% of all ischemic strokes are AF related.[6-8] In 4-14% of patients admitted for stroke, AF is newly diagnosed because of this event.[6, 9, 10] Strokes caused by AF have a higher mortality than other strokes, and lead to higher morbidity.[11] Independent of the occurrence of strokes, overall mortality is still higher in patients with AF than in patients without AF. It is very important to detect AF in an early stage before any complications occur.

AF can be treated in different ways. In rate control, oral medication is used to treat the tachycardia by slowing the frequency.[12] Rate control decreases symptoms, but does not terminate the arrhythmia. The aim of rhythm control is to restore sinus rhythm by means of chemic or electric cardioversion or ablation. However, studies have not unequivocally demonstrated that rhythm control reduces stroke risk.[13, 14] A meta-analysis shows a trend towards favouring rate control over rhythm control in preventing complications of AF.[15] Another meta-analysis found no differences in mortality between rhythm and rate control in older patients with AF.[14] However, the most important treatment for AF is anticoagulant therapy, which can prevent 60% of AF-related strokes.[16] The CHA_2DS_2VASc score helps to determine whether anticoagulants are needed.[17] How patients are treated, depends on several factors such as age, medical history, duration of AF and the preference of the patient.

For treatment to be installed, first AF needs to be diagnosed. However, the detection of AF can be problematic, as it can be silent or paroxysmal; patients without symptoms lack the trigger to seek medical care, and patients with paroxysmal AF may be in sinus rhythm when the rhythm is assessed. Screening might increase AF detection rate. Gaining insight in everyday healthcare could also help find ways to improve AF detection. Obviously, we do not know how many patients are not yet diagnosed and are still at increased risk of getting a severe stroke. One could say that patients found with screening, are the ones that would have remained undetected otherwise. The yield of screening therefore approximates of the number of yet undetected patients. Depending on screening method, population, and region, the yield may differ.

Screening for AF

Improving AF detection has high priority for scientists; in the past two decades several screening studies were performed.[18, 19] In 1998, screening by means of a single-lead ECG in British primary care detected AF in 5.4% of patients.[20] A randomised controlled trial (RCT) compared opportunistic and systematic screening, favouring the latter due to a higher yield of AF (1.3% and 4.5%, respectively).[21] Inhabitants of Japan underwent annual systematic screening by means of an ECG from 1983, in 2004 this was shown to be cost-effective.[22] At the start of our research in 2013, the 'Screening For AF in the Elderly' (SAFE) study was the only RCT on this topic that compared both systematic and opportunistic screening with usual care.[23] It was performed in the United Kingdom from 2001 to 2003 among almost fifteen thousand patients. It showed that screening increased the incidence of AF as compared with usual care.[24] Opportunistic screening (or case-finding) was as effective, but less expensive than systematic screening. After the SAFE-study, other studies showed a beneficial effect of screening as well. Pre-operative screening in 2012 by means of an ECG yielded 0.7% previously undiagnosed AF among patients aged ≥65 years in Australia.[25] In 2012 a Swedish study describes screening for silent paroxysmal AF after the occurrence of a stroke or transient ischemic attack; the researchers used 24-hour ECG recording and intermittent rhythm registrations for 30 days and diagnosed AF in 6.8% of patients.[26] In 2013 another screening study in Sweden among patients of 75 and 76 years old, yielded previously undiagnosed silent AF in 1% of patients.[27] In the same year prolonged screening in Germany after a stroke with a seven-day Holter revealed paroxysmal AF in 12.6% of patients.[28] However, only one study compared screening for AF with usual care. To demonstrate the effect of screening, more high-level evidence was required.

Devices for AF-detection

The SAFE study used radial pulse palpation as a screening tool. In asymptomatic patients it has a high sensitivity, but low specificity.[29, 30] The negative predictive value is high: a normal pulse almost rules out AF. Of all patients with an irregular pulse, only one out of six has AF; the positive predictive value is low.[31] Therefore, an irregular pulse needs to be followed by a 12-lead ECG to confirm or refute the diagnosis AF. When using radial pulse palpation as a screening tool, this would result in many 12-lead ECG's. Performing those is costly and time-consuming.

After publication of the SAFE study, several devices were developed to improve and facilitate detection of AF. An electronic blood pressure monitor with built-in AF detection algorithm ('eBPM'), as recommended by the British NICE-guideline (WatchBP Home A, Microlife, Widnau, Switzerland) seemed reliable in detecting AF, with both high sensitivity (97%) and specificity (94%).[32] Single-lead ECG devices ('handheld ECG') also looked promising in detecting AF, with a high sensitivity (94-100%) and specificity (90-99%).[33-36] Some of these devices are equipped with an AF detection algorithm and others require a visual review of the rhythm strip. An example of a single-lead ECG device with integrated AF detection function is the MyDiagnostick (MyDiagnostick Medical B.V., Maastricht, The Netherlands). A head-to-head comparison of different AF detection devices had not yet been performed in a screening setting.

Aim and research questions

The aim of this thesis was to investigate whether the detection of AF can be improved. We first explored current practice of cardiologists and general practitioners (GPs). In the second part of this thesis, we describe a cluster RCT on opportunistic screening, called the 'Detecting and Diagnosing Atrial Fibrillation' (D_2AF) study. A cohort study and two diagnostic accuracy studies were embedded in this trial. We conclude with an evaluation of consumer-led use of devices for AF detection, to see what might be the future of AF detection.

The main research questions are:

1. Can current practice of cardiologists and GPs be improved, to increase AF detection rate? If so, in what way?
2. What are the diagnostic characteristics of three methods – radial pulse palpation and measurements with two devices with built-in detection algorithm, namely an electronic blood pressure monitor and a single-lead ECG device – for AF detection in an opportunistic screening setting?
3. What are the diagnostic characteristics of a single-lead ECG device with AF detection algorithm, when used trice daily at home with continuous Holter monitoring as reference standard to detect AF in patients with a negative 12-lead ECG?
4. Does opportunistic screening for AF in general practice among patients of 65 years and older improve AF detection rate?
5. What is the opinion of health care professionals on consumer-led use of wearables, devices, and apps for detection of AF?

Outline of the dissertation

Case vignette studies, exploring current practice

Chapter 2

We present the results of a case vignette study, exploring cardiologists' diagnostic choices in six AF related case vignettes and compare it to the guidelines. Gaining insight in the current diagnostic process might give clues for improvement.

Chapter 3

As a sequel to chapter 2, we now focus on GPs in a similar case vignette study. Besides exploring their diagnostic choices regarding AF, we also inquire after perceived knowledge and experience for AF detection and available diagnostic tools. Furthermore, we gauge their support for screening, should it prove to be effective.

D_2AF study

Chapter 4

Here we present the protocol of the D_2AF study, a cluster RCT comparing opportunistic screening for AF with usual care. Results of the trial can be found in chapter 8. Within the trial, several studies are embedded, the results of which are described in chapter 5-7.

Chapter 5

This chapter focusses on the pathway to diagnose AF in everyday health care. We performed a cohort study, embedded in the control arm of the RCT. Describing the way AF is diagnosed in usual care, might give clues for how to improve it.

Chapter 6

A 12-lead ECG is too laborious and time-consuming for opportunistic screening purposes in general practice. In this chapter we describe a diagnostic accuracy study. We compare diagnostic test characteristics of three screening tools, individually and in different combinations:

1) radial pulse palpation,
2) eBPM (WatchBP Home A),
3) Handheld ECG (MyDiagnostick).

The two devices both have a built-in AF detection algorithm. The tests are performed at the general practice. They are followed by a 12-lead ECG if one or more tests are positive and in a random sample of 10% of patients with three negative tests.

Chapter 7
If AF is not diagnosed in the consulting room, paroxysmal AF is not yet ruled out. To gain insight in the amount of patients eluding diagnosis after opportunistic screening at a single time point, we performed home measurements. For two weeks, patients with a negative 12-lead ECG used the handheld ECG three times a day and wore a Holter. We present the yield of this method and the diagnostic accuracy of trice daily measurements with the handheld ECG.

Chapter 8
To determine the yield of opportunistic screening for AF, we performed a cluster RCT in 96 general practices. In one arm we selected patients with the intention to screen, in the other arm usual care was performed. After one year, we compared the percentage of new AF diagnoses in both groups, to see if opportunistic screening improved AF detection rate.

AF-SCREEN collaboration
Chapter 9
During the D_2AF study, the market for wearables, devices, and apps advanced. A variety of such tools is now directly available to consumers. To evaluate how medical professionals think of this development, the AF-SCREEN international collaboration – a group promoting discussion and research about screening for AF – distributed a survey among health care workers.

General discussion and impact
Chapter 10
This chapter places our findings in a broader context. We discuss our main findings, methodological and practical considerations and implications for practice and future research.

Chapter 11
An important part of research is to make the translation to daily practice. In this chapter we describe the scientific and societal impact of our study.

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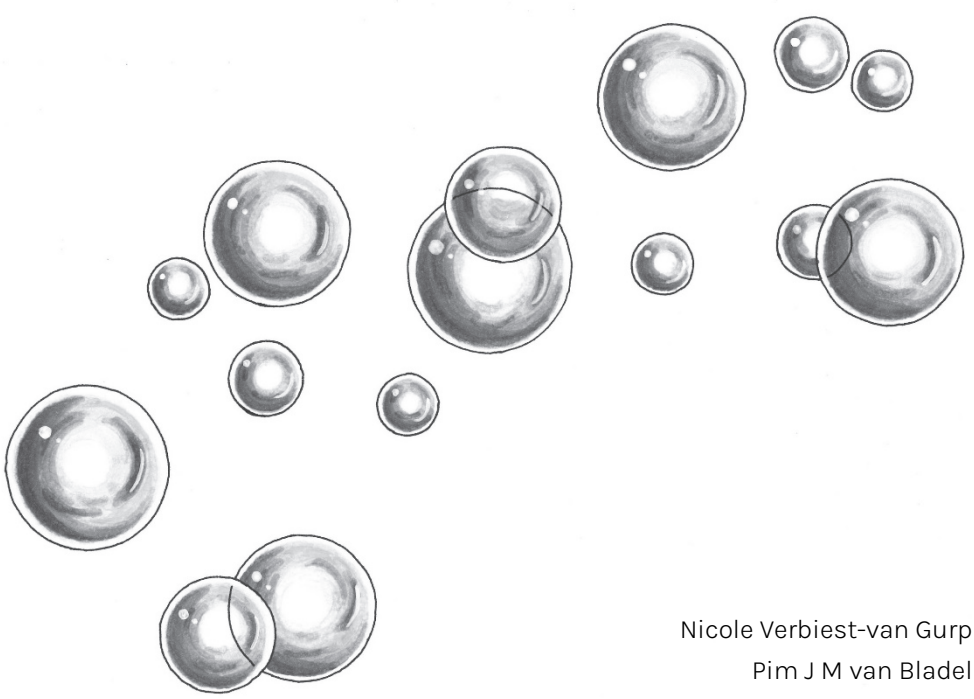
Chapter 2

Current practice of Dutch cardiologists in detecting and diagnosing atrial fibrillation: results of an online case vignette study



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Neth Heart J 2017;25(10):567–573

Abstract

Introduction

Detection of atrial fibrillation (AF) is important given the risk of complications, such as stroke and heart failure, and the need for preventive measures. Detection is complicated because AF can be silent or paroxysmal. Describing current practice may give clues to improve AF detection. The aim of this study was to describe how cardiologists currently detect AF.

Methods

Between December 2014 and May 2015, we sent Dutch cardiologists an online questionnaire. Firstly, we asked which tools for detection of AF their department has. Secondly, we presented six case vignettes related to AF, in which they could choose a diagnostic tool. Thirdly, we compared the results with current guidelines.

Results

We approached 90 cardiology departments and 48 (53%) completed the questionnaire. In asymptomatic patients with risk factors according to CHA_2DS_2-VASc, 40% of the cardiologists would screen for AF. In patients with signs or symptoms of AF, all but one cardiologist would start a diagnostic process. In both vignettes describing patients with non-frequent symptoms, 46% and 54% of the responders would use short-term (i.e. 24- or 48-hour) electrocardiographic monitoring, 48% and 27% would use longterm (i.e. 7 day, 14 day or one month) monitoring. In both cases describing patients with frequent symptoms, 85% of the responders would use short-term and 15% and 4% longterm monitoring.

Conclusion

Dutch cardiologists have access to a wide variety of ambulatory arrhythmia monitoring tools. Nearly half of the cardiologists would perform opportunistic screening. In cases with non-frequent symptoms, monitoring duration was shorter than recommended by NICE.

Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia with serious potential consequences such as stroke and heart failure. AF affects 1–2% of the total population.[1, 2] Prevalence increases with age to approximately 7–8% in people aged 65 years and over.[3] It may remain undetected for a long time because it is often asymptomatic or paroxysmal. In 14% of patients presenting with stroke, AF is first diagnosed after the stroke has already occurred.[4] Early detection of AF is imperative, since adequate antithrombotic treatment reduces the risk of stroke in AF by 60%.[5]
The European Society of Cardiology (ESC) recommends opportunistic screening in patients aged 65 years and over, systematic ECG screening may be considered in patients aged 75 years and over.[6] The National Institute for Health and Care Excellence (NICE) advises using a sphygmomanometer with a built-in AF detection algorithm in people with suspected hypertension and those being screened or monitored for it.[7] If signs or symptoms are suggestive of AF, ECG registration should be performed. The specific technique (e. g. 12-lead ECG, Holter, patient- or auto-triggered event recorder) and monitoring duration depend on the symptom frequency. Despite the recommendations in these guidelines AF often remains undetected, as shown in various screening studies.[3, 8]
Several new techniques have been introduced to improve detection of AF, e. g. single-lead ECG, modified sphygmomanometers and finger-probe devices.[9, 10] We are currently conducting a trial to test the effectiveness of case-finding of AF by general practitioners (GPs), using some of these new techniques.[11] Part of the study will describe 'usual care' by GPs, i.e. how GPs currently diagnose AF. The European Heart Rhythm Association Survey has revealed a wide variation of practice among cardiologists regarding the detection of AF.[12] They investigated diagnosis and management of silent AF but addressed neither the detection of AF in patients with signs or symptoms nor the use of newer techniques.
The current case vignette study has three objectives. Firstly, we identify the diagnostic techniques currently available to cardiologists. Secondly, we describe the diagnostic tools that cardiologists use to detect and diagnose AF in different situations, varying by risk factor, signs and symptoms and symptom-frequency. Thirdly, we compare our results with the recommendations of the ESC and NICE guidelines.[6, 13]

Methods

Study design and setting

Between December 2014 and May 2015 we sent Dutch cardiologists an online questionnaire. Cardiology departments were extracted from a list of all Dutch hospitals provided by the National Institute for Public Health and Environment (RIVM) website.[14] Outpatient clinics, hospitals without cardiology departments and hospitals sharing cardiologists were not eligible. We approached the remaining 90 groups by telephone to obtain an e-mail address of one cardiologist
who would represent the cardiology department. Subsequently, we sent an e-mail with a link to the online questionnaire to those who consented (n = 85). If there was no response, we sent a maximum of nine reminders. Additionally, we approached four cardiologists from non-responding departments using a personal message.

Online questionnaire

We used Formdesk to present the questionnaire online. Questions were multiple choice with a free text box for comments. A practicing cardiologist from a general hospital (HK) tested the pre-final version of the questionnaire.

Table 1 Description of six case vignettes on atrial fibrillation (AF) used in the online questionnaire

	A	B	C	D	E	F
Risk factors for AF (CHA_2DS_2-VASc[a])	X					
No symptoms[b] of AF	X	X				
Non-frequent symptoms of AF (<1/24 hours)			X	X		
Frequent symptoms of AF (≥1/24 hours)					X	X
Signs of AF during physical examination[c]		X		X		X

a) Congestive heart failure, hypertension, age of 65–74 or >74, diabetes, stroke, TIA, thromboembolism, vascular disease, female sex

b) Dyspnea, exercise intolerance, chest pain, palpitations, dizziness and/or syncope

c) Irregular pulse, pulse deficit or a varying loudness of the first heart sound

The first question concerned the ECG techniques that the department were currently using. This inventory was followed by questions regarding six case vignettes with varying characteristics related to AF (risk factors, signs and

symptoms and symptom frequency), as shown in Table 1. The vignettes described the key elements of a case pointwise. The survey concluded with a question on the use of echocardiography.
The questions on the case vignettes were divided into two sets. In each case, we first asked whether the cardiologist would start a diagnostic process to detect AF, and if so, which technique he or she would use. In a second set of questions, the cases in which the cardiologist started a diagnostic process with a 12-lead ECG were presented again. We asked if he or she would continue the diagnostic process if the result was negative, and if so, with which technique.

Data analysis

We used IBM SPSS Statistics 21 for descriptive statistics. Because of the use of obligatory fields in the questionnaire, missing values did not occur. As we used two sets of questions in which respondents could choose to apply monitoring, we combined both sets of answers to evaluate the total number of respondents who would apply monitoring. We dichotomised the monitoring duration of Holter and event recording into short-term (i.e. 24- and 48-hour) and longterm (i.e. 7 day, 14 day and one month) monitoring. We used McNemar's test to investigate the correlation between symptom frequency and monitoring duration.
Free text comments were categorised by theme. We compared the answers of the cardiologists with the ESC and NICE guidelines.[6, 13]

Results

Study population

Cardiologists from five (out of eight) university hospitals and 43 (out of 82) general hospitals completed the questionnaire (total response rate 48/90, 53%). The participating departments were well distributed over the Netherlands, as shown in figure 1.

Available techniques

Whereas ECG and Holter devices were universally available, this was not the case for other diagnostic devices (figure 2). Single-lead ECG was available to 10% of the respondents.

Figure 1 Geographic distribution of responding (n = 48, blue) and non-responding cardiology departments (n = 42, pink)

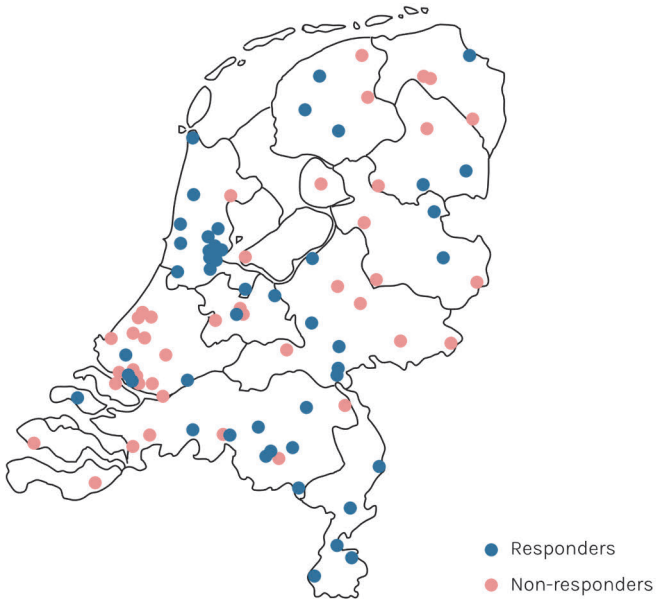
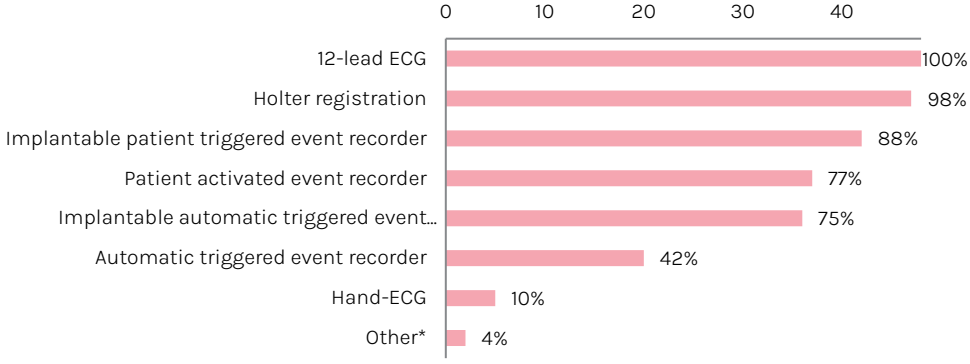
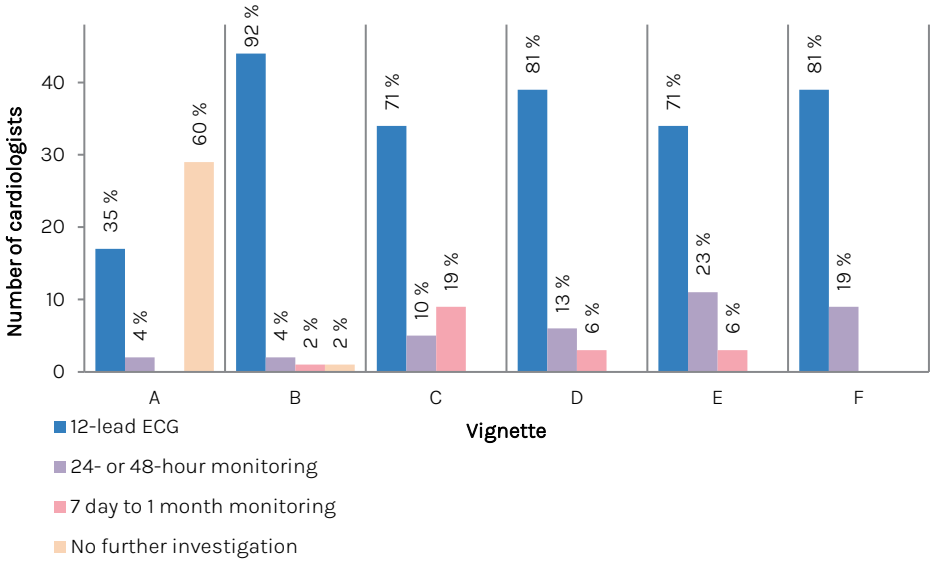


Figure 2 Techniques for ECG registration available at the responding cardiology departments (n=48)



* This category consisted of the NUUBO® (wireless ECG recording) and teaching the patients to feel their own pulse.

Figure 3 The initially applied diagnostic technique for each case vignette* (n = 48 cardiology departments).



* See Table 1 for case vignette descriptions

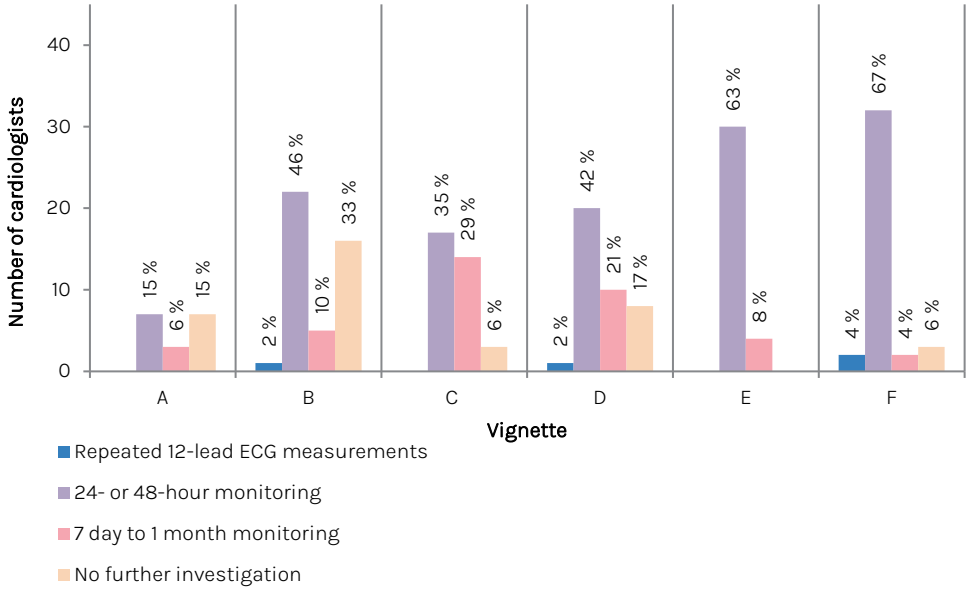
Initial diagnostics

In a patient without signs or symptoms indicative of AF (vignette A), 40% (19/48) of the cardiologists would start a diagnostic process. Three cardiologists stated that they do not see asymptomatic patients. In a patient presenting with signs of AF during physical examination (vignette B), 98% (47/48) of the cardiologists would initiate further diagnostics. In those cases with varying combinations of signs and symptoms (vignettes C, D, E, F) all cardiologists said they would start the diagnostic process. In all cases, 80% of the cardiologists who initiated the diagnostic work-up would start with an ECG. Details are shown in figure 3. Six cardiologists commented that all patients attending the cardiology department routinely undergo a 12-lead ECG.

Monitoring duration

Figure 4 shows what the subsequent actions of the cardiologists would be if the 12-lead ECG did not confirm AF. In both cases with non-frequent symptoms, i.e. C and D, 46% (22/48) and 54% (26/48) of the cardiologists, respectively, would use short-term monitoring, whereas 48% (23/48) and 27% (13/48) would use long-term

Figure 4 The subsequent diagnostic actions for each case vignette* in which a 12-lead ECG was chosen as the initial diagnostic test but did not reveal atrial fibrillation (n = 48 cardiology departments).



* See Table 1 for case vignette descriptions

monitoring. In the two vignettes with frequent symptoms, i.e. E and F, these percentages were 85% (41/48, both cases) for short-term monitoring and 15% (7/48) and 4% (2/48) for long-term monitoring. Commenting on vignettes C, D, E and F some cardiologists said that they would instigate long-term monitoring if short-term monitoring provided negative results. We observed a significant negative correlation between symptom frequency and the chosen monitoring duration ($p < 0.01$).

Echocardiography

Almost all participating cardiologists (47/48; 98%) would perform an echocardiogram after diagnosing AF. Reasons to perform echocardiography were to find a possible cause of AF by investigating left ventricular function, atrial and ventricular dimensions and valvular function, and to look for cardiomyopathy.

Monitoring duration as indicated by cardiologists was overall shorter than recommended by the NICE guideline (details in Table 2).

Table 2 Guidelines on diagnosis of atrial fibrillation (AF) and responses of cardiologists on case vignettes

	ESC	NICE	Responding cardiologists (%)				
			12-lead ECG		Ambulatory monitoring		
			Yes	No	Short*	Long†	None
Only risk factors	Pulse taking / rhythm strip	Sphygmomanometer with AF-detection	35	65	19	6	75
Non-frequent symptoms	No advice	Event recorder	71	29	46	48	6
Frequent symptoms	No advice	24-hour Holter	71	29	85	15	0
Signs	ECG	ECG	92	8	50	10	40
Signs & non-frequent symptoms	ECG	ECG. If negative: event recorder	81	19	54	27	19
Signs & frequent symptoms	ECG	ECG. If negative: 24-hour Holter	69	31	85	4	10

* 24- and 48-hour

† Seven days, 14 days and one month

Discussion

Our study showed that Dutch cardiologists have a wide variety of ambulatory arrhythmia monitoring tools at their disposal. Nearly half of the cardiologists would perform opportunistic screening using ECG in patients with only risk factors for AF without signs and symptoms. In case of non-frequent symptoms, indicated monitoring duration was often shorter than recommended by the NICE guideline.

Available techniques

Several studies show positive results regarding the use of new devices for AF detection.[9, 10] Our study showed that few cardiologists have a single lead ECG device. One cardiologist used a NUUBO wireless device. Perhaps the availability of numerous other techniques makes the less extensive – but also less informative – techniques less useful for cardiologists.

Opportunistic screening

In patients with signs or symptoms indicative of AF, practically all cardiologists would start a diagnostic process, mostly with 12-lead ECG. The actions of the cardiologists are in excellent agreement with the guidelines on this matter.[6, 13]
In a patient without signs or symptoms but with risk factors for complications of AF, 40% of respondents would initiate the diagnostic process. The European Heart Rhythm Association Survey found a comparable percentage; 40–50% of cardiology departments (n = 33) screened for AF in patients aged 65 years and over or who had diabetes mellitus, hypertension or heart failure.[12] Several studies have addressed the clinical consequences of AF found by screening.[15] It remains controversial whether anticoagulation therapy can reduce stroke risk in asymptomatic patients as much as in symptomatic patients. Both the ESC and the NICE guidelines advise performing opportunistic screening for AF.[6, 13]

Monitoring duration

In the cases with signs of AF during physical examination, some cardiologists would not continue the diagnostic process if the 12-lead ECG was negative. They commented that the signs could not be caused by AF because this was not shown on the 12-lead ECG. However, cardiologists who would continue, commented that AF might have been present during physical examination, but may already have disappeared when starting ECG registration. In this case, prolonged monitoring might still reveal paroxysmal AF. As the case vignette did not clearly state if the symptoms were still present during the 12-lead ECG, both explanations could be correct. The NICE guideline recommends prolonged monitoring in every patient with suspected AF if it is not revealed by a 12-lead ECG.[13] In a study of patients with embolic stroke or TIA, 12-lead ECG at admission revealed that 2.7% (4/149) had AF.[16] However, a total of 12.1% (18/149) was diagnosed with AF later on using repeated 12-lead ECG, Holter or event-loop recording. This means that 82% (18/22) of the patients would have been missed if one were to rely on a single 12-lead ECG.
The cardiologists who would continue the diagnostic process most often used 24- or 48-hour Holter, and less often would apply long-term monitoring. However, a Dutch study showed that a minimum recording time of two weeks seems necessary to detect paroxysmal AF.[17] After two weeks of recording, 83.3% of the relevant diagnoses could be established. The ESC guideline does not make recommendations on the diagnosis of paroxysmal AF.[6] The NICE guideline advises ambulant ECG registration for 24 hours in cases where symptoms occur daily, and

event recording in cases experiencing fewer episodes.[13] Whereas in our study symptom frequency was negatively correlated with monitoring frequency, the cardiologists would still use 24- to 48-hour monitoring more often than monitoring of longer duration if symptoms were non-frequent. A possible explanation is that the burden on the patient increases with a longer monitoring duration and the patient may thus refuse it. Cardiologists may first offer a short period of monitoring, possibly followed by longterm monitoring if no AF is found. Though a stepwise approach could be considered patient-friendly, it is also laborious to perform and interpret multiple tests on each patient.

The European Heart Rhythm Association Survey investigated diagnostic preferences in European hospitals regarding the use of event recorders.[18] Sixty-four percent of centres preferred 24-or 48-hour Holter and 17% preferred event recording if palpitations occurred once a week or more. If palpitations occurred less often than once a week, 40% of the centres preferred an event recorder and 36% preferred Holter monitoring. Our results are consistent with other research describing current practice, even though they are inconsistent with the NICE guideline.

Strengths and limitations

More than 50% of the cardiology departments responded and completed the questionnaire. For an online questionnaire among health care professionals approached by e-mail, we consider the response acceptable.[19] We found no difference in participation between general and university hospitals. Non-responding departments were spread across the Netherlands. Therefore, we consider nonresponse bias to be irrelevant.

Some details of our study require attention. The different case vignettes provide an overview of the key decisions in the diagnostic process. Further differentiation of symptoms and history would have provided more specific information and insight into the actual variation in the diagnostic process. However, by doing so we would also have complicated the results and would have compromised generalisability.

Pulse palpation and the use of a sphygmomanometer with an AF detection algorithm are part of the recommendation for opportunistic screening for AF by ESC and NICE, respectively. Positive results on either test can be considered as a sign of AF during physical examination. In each case vignette we mentioned the presence of signs but did not mention whether these two tests were performed. Therefore, our results regarding case-finding only apply to the use of ECG and ECG monitoring.

Regarding implantable event recorders, the answer options provided were patient-triggered or automatically- triggered devices. However, in reality this distinction is arbitrary, as they are often two aspects of the same device. It would have been sufficient to provide one option, i.e. implantable event recorder.

Implications for practice

On most topics, the answers cardiologists gave are in agreement with current guidelines. Yet, detection of AF may improve by opting for a longer duration of monitoring in cases with non-frequent symptoms, and by considering opportunistic screening in high-risk patients.

The responsibility for detecting and diagnosing AF lies not only with cardiologists but also with GPs. Due to the observed variety in diagnostic approach to AF by cardiologists, we advise GPs and cardiologists working in the same region to make collaborative agreements on their roles in detecting and diagnosing AF.

Conclusion

Dutch cardiologists have access to a wide variety of ambulatory arrhythmia monitoring tools. Nearly half of the responding cardiologists would perform opportunistic screening for AF. In cases with non-frequent symptoms, duration of monitoring was often shorter than recommended by the NICE guideline.

Declarations

Acknowledgements

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Competing interests

N. Verbiest-van Gurp, P. J. M. van Bladel, H. A. M. van Kesteren, P. M. G. Erkens and H. E. J. H. Stoffers declare that they have no competing interests.

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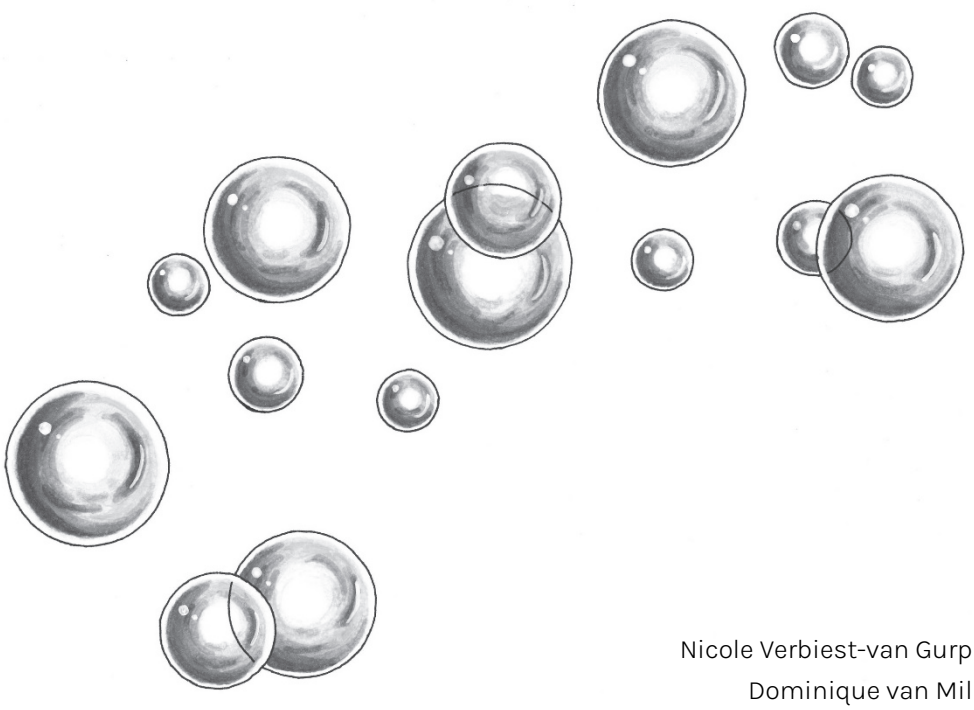
Chapter 3

How do Dutch general practitioners detect and diagnose atrial fibrillation? Results of an online case vignette study



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BMC Fam Pract 2019;20(1):175

Abstract

Background

Detection and treatment of atrial fibrillation (AF) are important given the serious health consequences. AF may be silent or paroxysmal and remain undetected. It is unclear whether general practitioners (GPs) have appropriate equipment and optimally utilise it to detect AF. This case vignette study aimed to describe current practice and to explore possible improvements to optimise AF detection.

Methods

Between June and July 2017, we performed an online case vignette study among Dutch GPs. We aimed at obtaining at least 75 responses to the questionnaire. We collected demographics and asked GPs' opinion on their knowledge and experience in diagnosing AF. GPs could indicate which diagnostic tools they have for AF. In six case vignettes with varying symptom frequency and physical signs, they could make diagnostic choices. The last questions covered screening and actions after diagnosing AF. We compared the answers to the Dutch guideline for GPs on AF.

Results

Seventy-six GPs completed the questionnaire. Seventy-four GPs (97%) thought they have enough knowledge and 72 (95%) enough experience to diagnose AF. Seventy-four GPs (97%) could order or perform ECGs without the interference of a cardiologist. In case of frequent symptoms of AF, 36–40% would choose short-term (i.e. 24–48 h) and 11–19% long-term (i.e. 7 days, 14 days or 1 month) monitoring. In case of non-frequent symptoms, 29–31% would choose short-term and 21–30% long-term monitoring. If opportunistic screening in primary care proves to be effective, 83% (58/70) will support it.

Conclusion

Responding GPs report to have adequate equipment, knowledge, and experience to detect and diagnose AF. Almost all participants can order ECGs. Reported monitoring duration was shorter than recommended by the guideline. AF detection could improve by increasing the monitoring duration.

Background

Atrial fibrillation (AF) can have serious health consequences such as stroke and heart failure. Adequate antithrombotic treatment reduces the risk of stroke by 60%.[1, 2] Unfortunately, AF often remains undetected and untreated, because it can be asymptomatic or paroxysmal. Many studies involving screening and new devices aimed to find ways to increase the AF detection rate.[3-8] A current example of such a study in Dutch primary care is D_2AF (Detecting and Diagnosing Atrial Fibrillation), a multicentre cluster randomised controlled trial with nested diagnostic studies.[9] The intervention practices of D_2AF perform opportunistic screening for AF, and the control practices provide usual care.

Innovations such as screening are not the only way to increase AF detection rate; this might also be accomplished by optimising current practice. However, it is unclear how general practitioners (GPs) currently detect and diagnose AF. In the optimal situation GPs would have knowledge and experience regarding AF, adhere to the guideline and have access to diagnostic devices, i.e. 12-lead ECG and preferably also an ambulatory device.

We therefore undertook a survey to explore whether GPs have appropriate equipment and optimally exploit their diagnostic tools for AF detection. This study aimed to describe current practice to see if improvement is possible, in order to optimise the detection of AF.

Methods

Study design and setting

For this case vignette study, using six case vignettes with varying characteristics related to AF, we laid our focus on achieving a representative sample of GPs. We performed a sample size calculation to determine the number of responses needed. A sample size of 75 had an acceptable margin of error of 0.11 from the 95% CI in a conservative calculation based on a proportion of 0.5, i.e. the width of the 95%CI does not exceed 0.22. For a proportion of 0.5 this means that the lower limit of the 95%CI is equal to or higher than 0.5–0.11 = 0.39 and the upper limit is equal to or lower than 0.5 + 0.11 = 0.61.

In June and July 2017, we sent our survey to a surplus of GPs (n = 385), accounting for the expected low response.[10, 11] This was a random selection of e-mail addresses

of GPs from the database of the Department of Family Medicine of Maastricht University, covering the south-eastern part of the Netherlands. To improve the geographical spread, we also used GPs who had participated in the control arm of the nationwide D_2AF study (n = 25).[9] We excluded GP trainees, current participants in the control arm of the D_2AF study and all participants in the intervention arm. We sent one general reminder to both responders and non-responders, and a maximum of five reminders to non-responding D_2AF GPs. No further invitations were sent after the required sample had been achieved. We offered participants a 10-euro gift card. The Medical Ethics Review Committee of Maastricht University Medical Centre waived formal review because the Medical Research Involving Human Subjects Act (WMO) does not apply.

Online questionnaire

The questionnaire was adapted from a previous version for cardiologists to fit the situation of GPs.[12] For example, we removed 'implanted devices' from the answering options. Questions were multiple choice with room for comments, the language was Dutch. Two GPs and the communication expert of the department of general practice tested the pre-final version. We used Formdesk to present the questionnaire online.

The questionnaire consisted of several parts. Firstly, we inquired after the demographics of respondents and their practice. Subsequently, we asked their opinion on their knowledge and experience in diagnosing AF on a five-point Likert scale. After that, they could indicate which diagnostic devices they have and use to diagnose AF. This was followed by questions on six case vignettes with varying characteristics related to AF (risk factors, signs and symptoms and symptom frequency), as shown in Table 1. These key elements cover the situations in which a GP could be inclined to start a diagnostic process for AF and in which the GP had different diagnostic options according to the guideline.[13] The vignettes described these elements pointwise. The survey concluded with questions on screening and actions after diagnosing AF.

We divided the questions on the case vignettes into two sets. In each case, we first asked whether the GP would start a diagnostic process to detect AF, and if so, with what technique. In the second set of questions, the cases in which the GP would start a diagnostic process with a 12-lead ECG were presented again. We asked if he or she would continue the diagnostic process if the results were negative, and if so,

with what technique. If the GP chose Holter or event recording, then he or she had to indicate the monitoring duration.

Table 1 Description of six case vignettes on atrial fibrillation (AF) used in the online questionnaire

	A	B	C	D	E	F
Risk factors for AF (CHA_2DS_2-VASc*)	X					
No symptoms† of AF	X	X				
Non-frequent symptoms of AF (<1/24 hours)			X	X		
Frequent symptoms of AF (≥1/24 hours)					X	X
Signs of AF during physical examination‡		X		X		X

* Congestive heart failure, hypertension, age of 65–74 or >74, diabetes, stroke, TIA, thromboembolism, vascular disease, female sex

† Dyspnea, exercise intolerance, chest pain, palpitations, dizziness and/or syncope

‡ Irregular pulse, pulse deficit or a varying loudness of the first heart sound

Data analysis

We used IBM SPSS Statistics 25 for descriptive statistics and analysis. We performed an independent samples T-test to investigate if the experience of GPs in years is related to whether they consider treating patients themselves. We used McNemar's test to investigate the association between symptom frequency and monitoring duration. As we used two sets of questions in which respondents could choose to apply monitoring, we combined both sets of answers to evaluate the total number of respondents who would apply monitoring. We dichotomised monitoring duration of both Holter and event recording into short-term (i.e. 24 and 48 h) and long-term (i.e. 7 days, 14 days and 1 month) monitoring. Often Holter is short-term and event recording long-term monitoring, but not necessarily.

Free comments were categorised by theme. We compared the answers of GPs with the guideline of the Dutch College of General Practitioners.[13] Missing values were assumed to be missing at random.

Results

Study population

We terminated data collection after 76 responses. Respondents' characteristics are shown in Table 2 and their geographic distribution in figure 1. D_2AF GPs were older than the other GPs (mean age 54.8 vs. 49.2 years, p = 0.023), but did not differ in other characteristics.

Table 2 Characteristics of responding GPs and their practice

Characteristic	n = 76
Respondents	
Male, n (%)	47 (61.8)
Age in years, mean (range)*	50.7 (30-66)
Years of experience, mean (range)*	19.3 (3-39)
Practices	
Number of GPs, mean (range)†	2.99 (1-8)
Number of patients, mean (range)	4,496 (1,300-11,000)

* One GP did not fill in the questions for age and years of experience

† Three GPs did not fill in the question on 'number of GPs'

Diagnostic equipment

Ninety-seven percent of responding GPs (74/76) felt that they have enough knowledge and 95% (72/76) judged they have enough experience to diagnose AF. GPs have a wide variety of diagnostic techniques at their disposal (see figure 2 for details). Ninety-seven percent of GPs (74/76) could order ECGs without the interference of a cardiologist. Eighty-four percent of them (62/74) had an ECG device in-house.

Techniques GPs actually used to diagnose AF were ECGs (72/76, 95%), Holter registrations (37/76, 49%), patient-activated event recorders (33/76, 43%), automatically-triggered event recorders (1/73, 1%), hand-ECGs (7/74, 9%) and sphygmomanometers with AF-detection algorithm (15/75, 20%). Due to missing answers in the questions on the three last devices, the denominator is below 76.

Almost all GPs with access to a 12-lead ECG device use it to diagnose AF, whereas approximately half of the GPs with access to monitoring devices like Holters and event recorders seem to use those techniques.

Figure 1 Geographic distribution of responding D2AF GPs (n = 20, green) and non D2AF GPs (n = 56, orange)

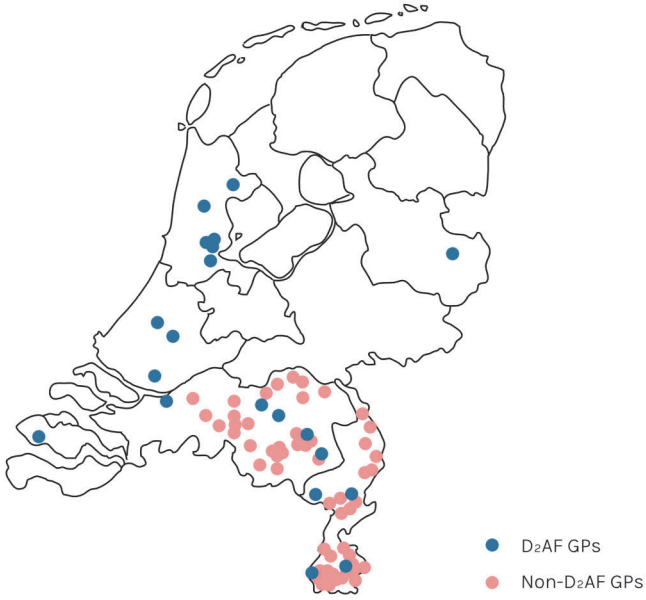
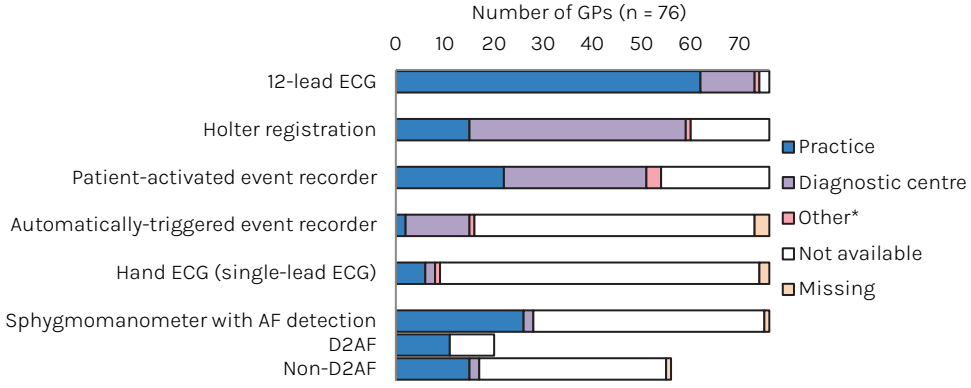


Figure 2 Availability and location of diagnostic devices in AF detection for the GP.



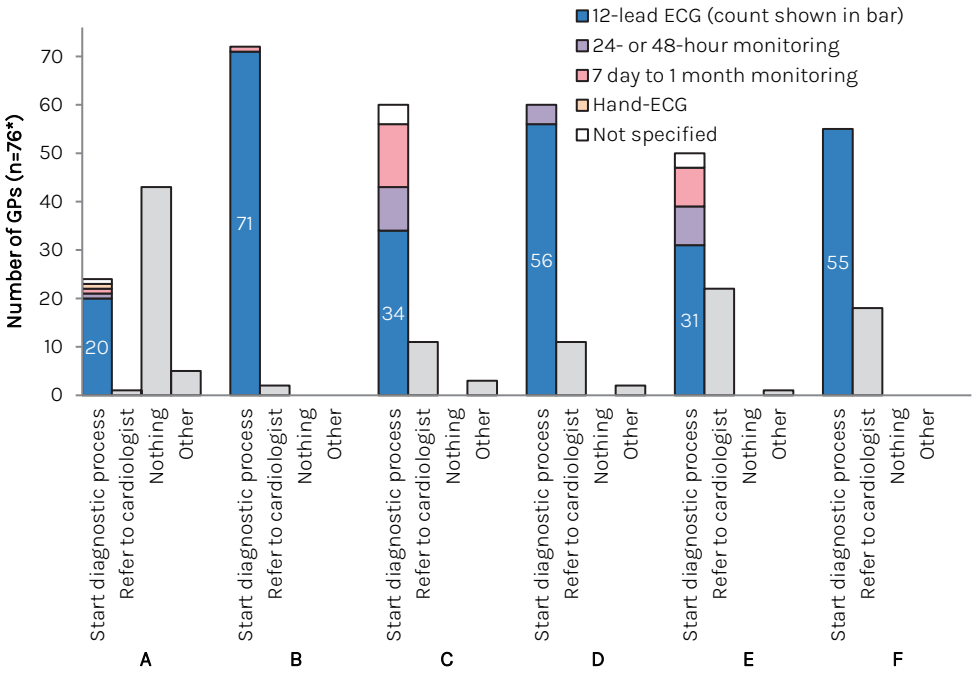
* Other consisted of pulse palpation, auscultation and determination of the presence of pulse deficit. The availability of the sphygmomanometer is split up for D2AF and non-D2AF GPs, as the former got a sphygmomanometer with AF detection as a gift for participation in the D2AF study

Diagnostic process

In all vignettes, except vignette A (a patient without signs or symptoms indicative of AF), all GPs would undertake action, either by starting the diagnostic process, referral or something else, as shown in figure 3. In vignette A, 33% of GPs (24/73) would start the diagnostic process, and 59% (43/73) would do nothing. In all cases, the majority preferred starting the diagnostic process above direct referral to the cardiologist. Most GPs started with a 12-lead ECG. One GP indicated to consider a single lead ECG as a solitary diagnostic tool for frail homebound elderly.

Figure 4 shows the subsequent actions of respondents whose initial action was to perform a 12-lead ECG, given the results were negative for AF. In all cases, the majority chose to continue the diagnostic process. GPs would refer patients to a cardiologist more often in case of signs of AF during physical examination (vignette B, D and F; n = 13, 13 and 11), than when patients did not show any signs (vignette A, C and E; n = 1, 2 and 1).

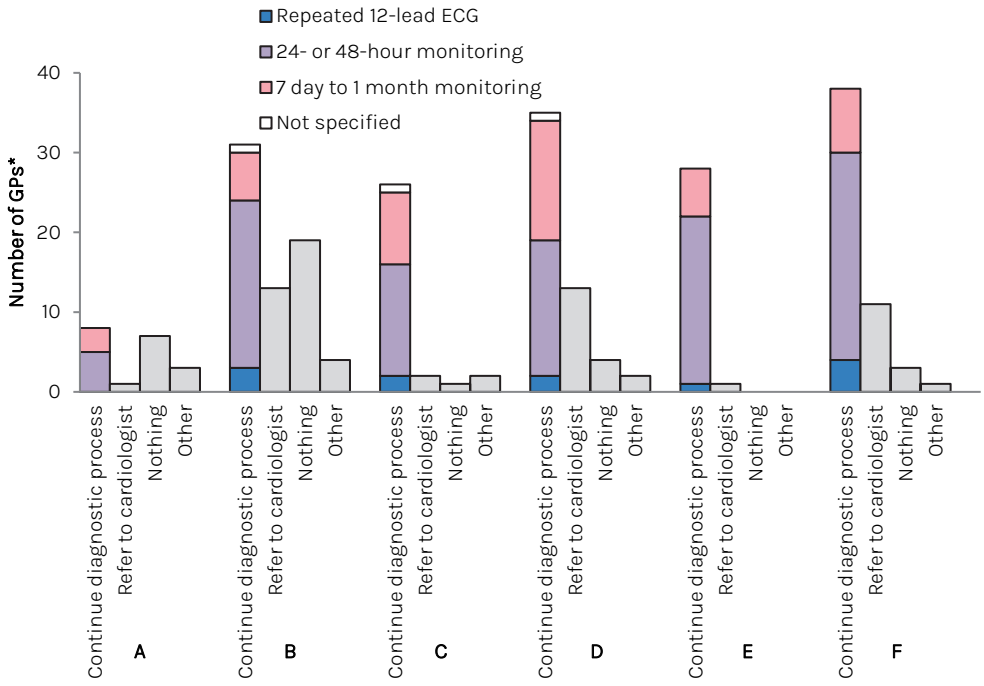
Figure 3 Initial action of GPs per case vignette.



* Three GPs did not answer the question for vignette A, D, E and F (n = 73), and two GPs did not answer the question for vignette B and C (n = 74)

GPs preferred short-term above long-term monitoring in all cases. In case of frequent symptoms of AF (vignette E, F), respectively 40 and 36% of GPs would choose short-term monitoring at any moment in the diagnostic process, and 19 and 11% would choose longterm monitoring. In case of non-frequent symptoms (vignette C, D) respectively 31 and 29% would choose short-term and 30 and 21% would choose long-term monitoring. Symptom frequency and the chosen monitoring duration were negatively associated in vignette C and vignette E ($p = 0.031$); i.e. GPs chose long-term monitoring 1.5 times more often in case of non-frequent symptoms than in case of frequent symptoms, and they chose short-term monitoring 1.3 times more often in case of frequent symptoms than in case of non-frequent symptoms. This association was not statistically significant for vignette D and vignette F ($p = 0.125$).

Figure 4 Subsequent action per case vignette of GPs after a negative initial 12-lead ECG.



* See numbers of GPs whose initial action was to start with a 12-lead ECG in the blue bar of figure 3. One GP did not answer the question for vignette A (n = 19), four GPs did not answer the question for vignette B (n = 67), three GPs did not answer the question for vignette C (n = 31), two GPs did not answer the question for vignette D (n = 54), E (n = 29) and F (n = 53)

In case of non-frequent symptoms, some GPs opted to instruct the patient to go for an ECG when the complaints occur.

Actions after diagnosis

Almost all GPs would apply echocardiography (52/71, 73%). Thirty-seven percent (26/71) would refer the patient to a cardiologist who would then become the most responsible physician. Twenty-one percent of GPs (15/71) would refer the patient to a diagnostic centre, and 15% (11/71) would refer to a cardiologist only to perform echocardiography. Five GPs did not answer this question.

After diagnosing AF, 83% of GPs (59/71) would consider treating a patient themselves and 17% (12/71) would not. Often mentioned factors in this decision were patients age (41/71), the extent of complaints of AF (15/71), comorbidity (10/71), and other cardiac diseases (10/71). Five GPs did not answer this question. We found no significant association between years of experience and considering to start treatment themselves (p = 0.095).

Table 3 Comparison of GPs responses to the vignettes with the Dutch guideline on AF diagnosis (n = 76)*

Case vignette	Guideline	Responding GPs (n)						
		12-lead ECG			Ambulatory monitoring			
		Yes	No†	Missing	Holter	Event recorder	None‡	Missing
A: Only risk factors	No diagnostic tests	20	**53**	3	7	4	61	4
B: Signs	ECG	**71**	3	2	24	6	40	6
C: Non-frequent symptoms	ECG or event recorder. If negative ECG: event recorder	**34**	40	2	24	**26**	21	5
D: Signs & non-frequent symptoms	ECG or event recorder	**56**	17	3	24	**14**	33	5
E: Frequent symptoms	ECG or Holter. If negative ECG: Holter	**31**	42	3	**25**	19	27	5
F: Signs & frequent symptoms	ECG or Holter	**55**	18	3	**21**	13	37	5

* Bold numbers indicate the guidelines' recommendation

† In this case 'no' means the GP did not choose to start the diagnostic process (for example would refer the patient to a cardiologist) or the GP would start the diagnostic process, but not with an ECG

‡ In this case 'none' means the GP did not start/continue the diagnostic process or did continue but chose something else, e.g. a repeated ECG measurement

Comparison with guideline

Monitoring duration was shorter than recommended by the guideline (see Table 3 for details). The guideline does not recommend any form of screening for AF, the majority of GPs adheres to that advice by not applying any diagnostic tests in vignette A. If opportunistic screening in primary care proves to be effective, 83% (58/70) will support it. A 12-lead ECG is the first choice diagnostic test; most GPs follow this advice.

Discussion

In this study, GPs report that they are adequately equipped with devices, knowledge and experience to detect and diagnose AF. GPs adhere reasonably well to the guidelines in case vignettes concerning AF. Reported monitoring duration is often shorter than recommended. All GPs would undertake action in case a patient has signs or symptoms, and only a few would be satisfied if such a patient had a negative 12-lead ECG.

Diagnostic equipment

In our study, 97% of GPs could order 12-lead ECGs, of whom 84% could do this in-house. These results are similar to the results of a study in the United Kingdom, which reported that all GPs had access to an ECG machine, of whom 81% (39/48) had an ECG device in their practice.[14] Taggar et al. identified access to the required equipment as a barrier for opportunistic screening, among others.[14] That does not match our findings, as Dutch GPs seem well equipped with diagnostic devices and our respondents did not mention that barrier. Taggar et al. did not further explore the current use of the diagnostic devices in practice. Our search revealed no additional articles on the availability of devices, nor on current practice of AF detection.

GPs judged that they have sufficient knowledge and experience to diagnose AF. Research by Compiet et al. shows that the diagnostic accuracy of GPs to detect AF is indeed high (96%).[15] When comparing current results to our previous study among cardiologists, we see that monitoring devices are more often available to cardiologists than to GPs, as is to be expected.[12] Holter devices were available to 98% of cardiologists and 79% (60/76) of GPs, patient triggered event recorders were

available to 77 and 71% (54/76), and automatically triggered event recorders to 42 and 22% (22/73), respectively.

Diagnostic process

GPs chose shorter monitoring duration in case of frequent symptoms and vice versa. However, the chosen monitoring duration was still shorter than recommended in the guideline. In case of non-frequent symptoms, long-term monitoring is indicated, whereas more often short-term was chosen. Several studies show that short-term recording is not sufficient to diagnose paroxysmal arrhythmias in case of non-frequent symptoms.[16, 17] Our previous study showed that cardiologists also choose a shorter monitoring duration than recommended.[12] A possible reason for this is the assumed discomfort of long-term monitoring for patients. As shown in our current study, a lack of devices cannot explain this, as monitoring devices are readily available. Apart from innovating diagnostic methods and techniques, it might thus be worthwhile to optimise current care by extending the monitoring duration in order to improve AF detection. That might be a cheaper and less timeconsuming way to improve AF detection rate than screening. Therefore, barriers to long-term monitoring should be identified and dealt with. Nevertheless, newer and less burdensome devices might be a solution.[18]

Strengths and limitations

To the best of our knowledge, this study is the first to explore the current practice of GPs regarding detection of AF. We compared the GPs' reported actions with the current Dutch guideline. Two months after concluding our data collection, a revised version of this guideline appeared. We checked the two versions for differences in diagnostic recommendations and found none. Therefore, we consider our study results up-to-date. We did not compare GPs' responses to other guidelines, because we wanted to compare them to the guideline they use in practice.

We asked GPs to assess the adequacy of their knowledge and experience regarding AF. Although GPs were very confident of their knowledge and skills, we need to be careful to draw firm conclusions, as self-assessment of competence by physicians is not necessarily accurate.[19] As compared to empirical studies using data from medical records, case vignette studies may have a lower validity regarding behaviour of GPs, but they are an efficient and well-accepted technique to explore choice behaviour and attitudes with a higher validity than regular questionnaires.[20, 21]

Our study sample was small, but met our predefined sample size. Compared to the Dutch GP population (mean age 48 years, 49% male);[22] our population was a little older (50.7 years) and counted more men (61.8%).

Conclusion

Responding GPs stated to have adequate equipment, knowledge and experience to detect and diagnose AF. A 12-lead ECG is the preferred diagnostic tool by the majority of GPs, and most GPs can order or perform ECGs, without having to refer to a cardiologist. Duration of monitoring was often shorter than recommended by the Dutch guideline, suggesting that there may be room for improving the detection rate of AF by increasing the monitoring duration.

Declarations

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Competing interests

The authors declare that they have no competing interests.

Ethical approval

The Medical Ethics Review Committee of Maastricht University Medical Centre waived formal review because the Medical Research Involving Human Subjects Act (WMO) does not apply (reference number 2017-0064). All participating GPs were informed of the aims of this survey, informed consent was not necessary.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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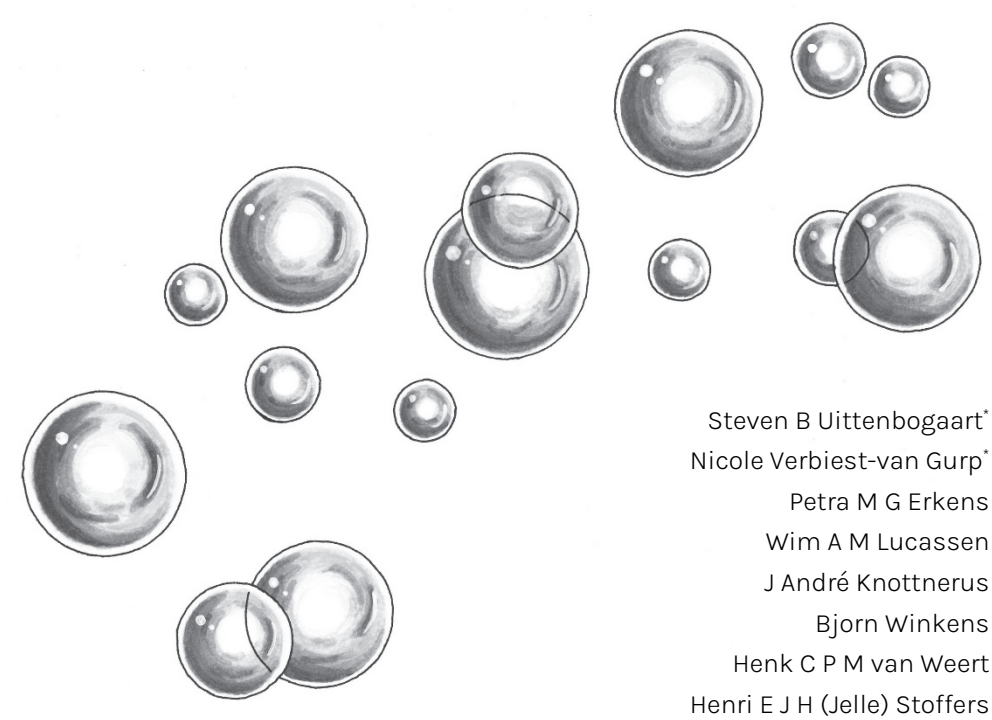
Chapter 4

Detecting and Diagnosing Atrial Fibrillation (D_2AF): combined design of a diagnostic accuracy study and a randomised screening trial in general practice



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Abstract

Background

Atrial fibrillation is a common cause of stroke and other morbidity. Adequate treatment with anticoagulants reduces the risk of stroke by 60 %. Early detection and treatment of atrial fibrillation could prevent strokes. Atrial fibrillation is often asymptomatic and/or paroxysmal.

Case-finding with pulse palpation is an effective screening method, but new methods for detecting atrial fibrillation have been developed. To detect paroxysmal atrial fibrillation ambulatory rhythm recording is needed. This study aims to determine the yield of case-finding for atrial fibrillation in primary care patients. In addition, it will determine the diagnostic accuracy of three different case-finding methods.

Methods/design

In a multicenter cluster randomised controlled trial, we compare an enhanced protocol for case-finding of atrial fibrillation with usual care. We recruit 96 practices. We include primary care patients aged 65 years or older not diagnosed with atrial fibrillation. Within each practice, a cluster of 200 patients is randomly selected and marked. Practices are evenly randomised to intervention or control group.

The allocation is not blinded. When a marked patient visits an intervention practice, the case-finding protocol starts, consisting of: pulse palpation, sphygmomanometer with automated atrial fibrillation detection and handheld single-lead electrocardiogram (ECG). All patients with at least 1 positive test and a random sample of patients with negative tests receive a 12-lead ECG. Patients without atrial fibrillation on the 12-lead ECG, undergo additional continuous Holter and use the handheld single-lead ECG at home for 2 weeks.

Control practices provide care as usual.

The study runs for 1 year in each cluster. The primary outcomes are the difference in detection rate of new AF between intervention and control practices and the accuracy of three index tests to diagnose AF. We are currently recruiting practices.

The 'Detecting and Diagnosing Atrial Fibrillation' (D_2AF) study will determine the yield of an intensive case-finding strategy and the diagnostic accuracy of three index tests to diagnose atrial fibrillation in a primary care setting.

Background

Atrial fibrillation (AF) is a common cardiac arrhythmia, associated with substantial health risks. AF increases mortality, reduces the quality of life and increases the risk of heart failure. Moreover, AF is an important risk factor for stroke. Prevalence of AF increases with age, from 1 % in the general population up to 7–8 % in people over 65 years old.[1, 2] With increasing age, patients also have a higher risk of stroke.[3] Up to 30 % of ischemic strokes are AF-related.[4-6] Treatment with oral anticoagulants reduces the risk of stroke by 60 %.[7, 8] However, in nearly a quarter of patients with stroke AF is detected after this event.[9] If we can detect AF before a stroke occurs and start anticoagulant therapy when appropriate, we may be able to prevent more than half of AF-related strokes.[4, 6, 9-11]

Although AF can be a symptomatic condition with patients experiencing palpitations, exercise intolerance or fatigue, AF often is asymptomatic[12] and remains undetected. Furthermore, patients can have recurrent intermittent episodes of AF, paroxysmal AF (pAF). As with persistent AF, the risk of stroke is substantially increased in patients with pAF.[13, 14] Therefore, detecting pAF is as important as detecting persistent AF, but more challenging.

To establish the diagnosis of AF, an electrocardiogram (ECG) recording – either on a regular 12-lead ECG or a 30-second rhythm strip – has to be made showing irregular RR intervals without distinct P waves. When used as screening tools, ECG and ambulatory rhythm recording are costly and time-consuming. Case-finding in general practice using pulse palpation, improved the detection of AF compared with care as usual (incidence of AF 1.63 % versus 1.04 %, difference 0.59 %, 95 % CI 0.20 % to 0.98 %).[15] Opportunistic screening in patients aged 65 years and over was as effective as systematic screening but at lower costs.[15]

Recently, new methods for detecting AF have been developed.[16] One development is the equipment of automatic sphygmomanometers with an algorithm for irregular beat detection (eBPM-AF). The National Institute for Health and Care Excellence (NICE) guideline advocates the use of one of these devices, i.e. the Microlife® WatchBP Home A device.[17] Other methods use a single-lead ECG. The MyDiagnostick (Applied Biomedical Systems® (ABS), Maastricht, The Netherlands) is an example of a handheld ECG device, which records a single-lead ECG (left-right arm).[18]

To detect cases of pAF, ambulatory rhythm recording is needed.[19] Traditionally, either 24-hour Holter or event recording is used. In post-stroke patients, a 30-day period of automatically triggered event recording increased the detection rate of pAF 5-fold

compared with a 24-hour Holter (detection rate of 16.1 % versus 3.2 %).[20] In primary care patients with palpitations, monitoring for 14 days diagnosed about 80 % of relevant arrhythmias.[19]

New developments have enabled the use of continuous ECG registrations for longer periods (continuous Holter) and make loop recording unnecessary. In general, ambulatory rhythm recording is used in symptomatic patients or as part of follow-up after stroke. There is insufficient evidence about the effectiveness of ambulatory rhythm registration for the detection of AF in asymptomatic patients (in general practice). This is a major evidence gap and further research is recommended.[21, 22]

The 'Detecting and Diagnosing Atrial Fibrillation' (D_2AF) study investigates whether enhanced opportunistic case-finding – using pulse palpation, single-lead handheld ECG and eBPM-AF – increases detection of AF in general practice patients of 65 years and over. Additionally, the study determines the most effective method of case-finding by comparing the diagnostic yield of pulse palpitation, handheld ECG and eBPM-AF alone and in combination.

Methods

Design

We perform a multicenter cluster randomised controlled trial (RCT) comparing enhanced case-finding of AF with usual care. In each practice, the study runs for 1 year. In the intervention arm, we run a diagnostic study comparing 3 different methods for case-finding of AF with a composite reference standard consisting of a 12-lead ECG and a 2 week Holter. This way, we determine the yield of each method individually and combined to detect unknown AF. Figure 1 shows a flowchart of the study design.

Participants: practices and patients

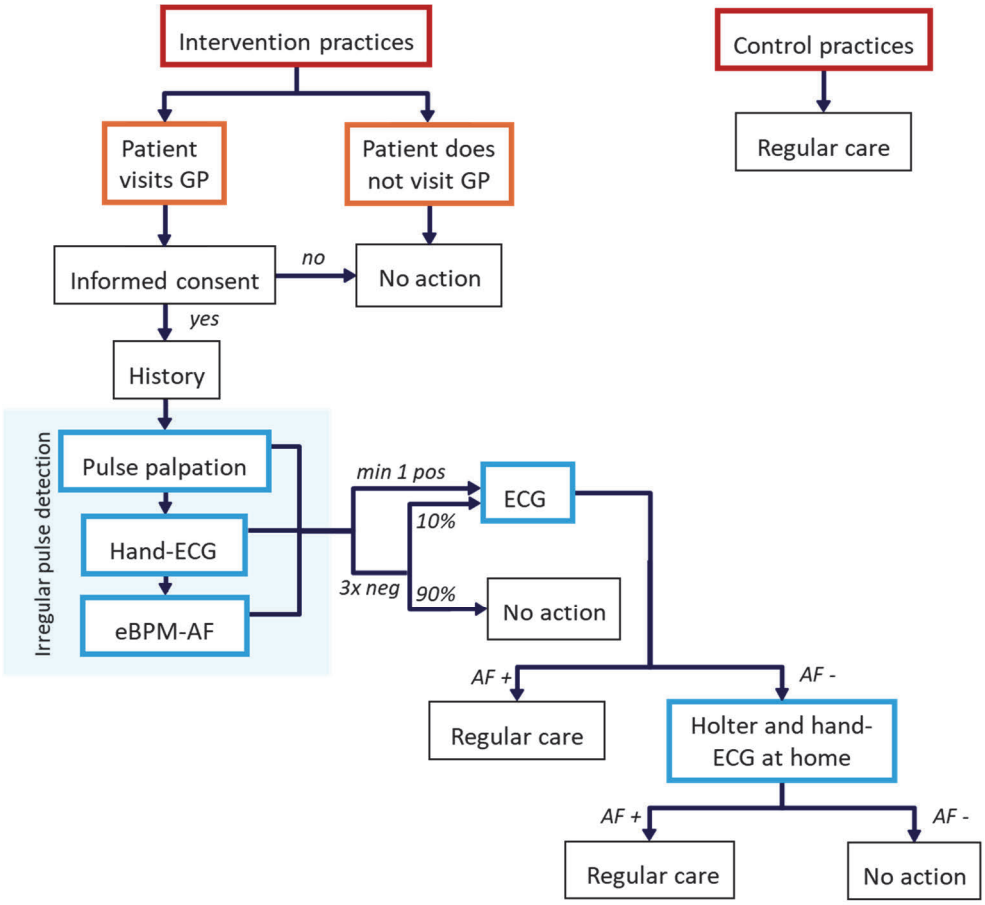
General practices are recruited across The Netherlands. We regard two or more general practices sharing facilities as one practice. Within each practice, we form one cluster by selecting a random fixed sample of two hundred patients out of the eligible patients.

The inclusion criterion for selection of the cohort is an age of 65 years and over; the exclusion criterion is previously documented AF. Additional criteria are applied only to patients in the intervention group for whom case-finding would be inappropriate

(see intervention practices). After selection of the study cohort, we extract the medical files to determine the baseline characteristics (e.g. age, sex and medical history including heart disease, hypertension, previous stroke/transient ischaemic attack (TIA), diabetes).

All data are entered into our secured trial management system. This system also gathers all other data during the study. Investigators enter data directly into the system using electronic case record forms (eCRF).

Figure 1 Study design of 'Detecting and Diagnosing Atrial Fibrillation' D_2AF. GP, general practitioner; hand-ECG, handheld ECG device; eBPM-AF, automatic sphygmomanometer with an algorithm for irregular beat detection; ECG, electrocardiogram



Cluster randomisation

Clusters are evenly allocated to either the intervention or the control group using stratified randomisation. To stratify clusters, we determine the prevalence of AF in all patients aged 65 years and over in participating clusters using International Classification of Primary Care (ICPC)-codes in the medical files. Subsequently, we stratify clusters in high-prevalence and low-prevalence clusters. As a cut-off we use the average prevalence of AF in the associated general practices of the 2 universities involved in this study: 8.05 %. We use computerised randomisation in permuted blocks of random sizes. After randomisation, the investigator informs the participating practices of the allocation.

Intervention practices

In each practice, the selected 200 patients are marked in the medical records of the practice before the start of the study. When a marked patient makes an appointment for a consultation at the practice we ask him or her to participate. The sub-investigator (practice nurse, practice assistant or general practitioner) does not carry out the intervention in patients not suited for case-finding based on the following criteria:

- having a pacemaker or implantable cardioverter-defibrillator (ICD)
- legal incompetence or inability to give informed consent
- suffering from a terminal illness (as defined by the general practitioner)
- inability to come to the practice to participate in the diagnostic process; for instance, a patient who is chronically bedridden. Patients who cannot visit the practice due to a temporary situation (such as the flu) are not excluded

The reason is noted in the trial management system. All patients who undergo the case-finding protocol in the intervention group will be asked written informed consent. We do not ask informed consent in the control group since we merely analyse these patients on a group level. They receive care as usual and we do not want to trigger additional awareness of AF.

Diagnostic tests

The sub-investigator collects the baseline information on the patient history, weight, length and current symptoms indicative of AF. Subsequently, the sub-investigator performs the following three index tests in all study patients:

- *Pulse palpation*: manual palpation of the radial artery in the wrist with the fingertips for a minimum of 15 seconds. The frequency is registered. The

heart rhythm is classified as 'regular', 'one to three skipped or extra beats' or 'irregular'. Both 'one to three skipped or extra beats' and 'irregular' are regarded as a positive result. The filling pressure is classified as 'equal' or 'unequal'.

- *eBPM-AF*: the WatchBP Home A (Microlife®, Widnau, Switzerland) is an electronic sphygmomanometer with an algorithm for irregular beat detection. The algorithm calculates the irregularity index based on the interval time between heartbeats and indicates an irregular pulse if the threshold is exceeded. A cuff is applied around the patient's left or right upper arm. The cuff inflates and deflates automatically after pressing the 'ON' button. The display shows the average of three blood pressure measurements. If an irregular pulse is detected in at least two out of three measurements, an icon on the display saying 'Afib' starts blinking.[17] If the device is not able to correctly analyse the rhythm this is noted in the eCRF.
- *Handheld ECG at the practice*: the MyDiagnostick (ABS, Maastricht, The Netherlands) is a 24-cm long bar with metallic electrodes at both ends. It records a single-lead ECG (left-right arm). The device switches on automatically when holding it with both hands. An automatic algorithm calculates a rhythm-score, periodicity-score and variability-score based on computed intervals between two R waves. If the threshold is exceeded, a red light indicates possible AF. The outcome of the handheld ECG is noted in the eCRF. If the device cannot make a recording this is registered. Recordings are stored locally and are uploaded as a PDF in the local PC application.[23]

The order in which the index tests are performed is set. Pulse palpation is performed and recorded first. Then, by an alternating pre-set order in the eCRF, both eBPM-AF and handheld ECG are performed and recorded.

All patients scoring positive on at least 1 of the 3 index tests will receive a 12-lead ECG in the same session as the index tests. To calculate sensitivity and specificity of the screening procedure, a random sample of 10 % of patients who score negative on all 3 index tests also receive a 12-lead ECG. An overview of these procedures can also be seen in figure 1. The sub-investigator is blinded to the ECG results while performing the index tests.

12-lead ECG: the 12-lead ECG device (Fysiologic®, Amsterdam, The Netherlands) is paperless and does not display the ECG. The ECG is transferred digitally and assessed by an experienced assessor, supervised by a cardiologist. In case the ECG

shows any serious clinically relevant abnormality, the general practitioner (GP) is notified immediately. A second cardiologist re-assesses all AF-diagnosed ECGs and a random sample of negative ECGs. Both cardiologists are provided with basic data such as age and gender but are blinded to all previous measurements. Any disagreement on diagnosis is solved by a third cardiologist. AF is defined as the absence of distinct P waves and a completely irregular RR interval.[24]

If a patient is diagnosed with AF, the study protocol is finished. Results of the ECG are reported back to the GP, who provides care at his discretion.

In patients in whom no AF is diagnosed on a 12-lead ECG, 2 additional tests are performed to detect pAF:

- *Handheld ECG at home*: the same device (MyDiagnostick, ABS, Maastricht, The Netherlands) as mentioned above is used, but the indication light is set off. Thus, the patient is blinded for the results of the test (light will not blink). The patient is instructed to use the handheld ECG three times a day at set times. After 2 weeks of recording, data are uploaded as PDF in the local PC-application. The MyDiagnostick can store up to 140 ECG strips.
- *Two-week Holter*: the same device (Fysiologic®, Amsterdam, The Netherlands) as for the 12-lead ECG is used. The wiring has four different patches instead of ten. With these 4 patches, leads V1 and V5 are obtained. The patient receives a small disposable shoulder bag to wear the device and several sets of patches with instructions so they can change them. After 2 weeks of continuous recording, data are transferred and assessed by an experienced assessor, supervised by a cardiologist. The number and duration of AF episodes are registered. In case the ECG shows any serious clinically relevant abnormalities, the GP is notified immediately. A second cardiologist, blinded to previous assessments re-assesses all AF-diagnosed Holters. Furthermore, a random sample of negative Holters is re-assessed. We define AF as any arrhythmia that has the characteristics of AF (see above) and lasts at least 30 seconds.[24]

Diagnoses 'atrial fibrillation'

To diagnose AF, we use a composite reference standard consisting of the results of the 12-lead ECG and the 2-week Holter as defined previously.

Besides cases found with our case-finding protocol, we will also perform computer searches of the medical records to identify all new cases of AF. We ask the sub-

investigator to report how the diagnosis was established in new cases of AF not detected with the intervention.

Quality of life

Little is known of the quality of life of asymptomatic AF patients. To investigate this, we use the EuroQol 5D (EQ-5D) questionnaire to measure quality of life. EQ-5D is a generic tool that assesses five dimensions of health-related quality of life by use of a questionnaire and a visual analogue scale.[25] We opt for 1000 patients in the intervention practices to participate: all patients with newly diagnosed AF saturated with a random sample of patients not diagnosed with AF. The reason for the visit may affect quality of life at the time of the visit. Therefore, we delay the timing of the questionnaire until the end of the study year.

Control practices

In each practice, the selected 200 patients are marked in the medical records of the practice before the start of the study, but the marking is blinded to the sub-investigators. Neither the sub-investigators nor the patients are aware of participation in the study. The control practices perform 'usual care' at the discretion of the GP. Currently, the guideline on AF of the Dutch College of General Practitioners does not recommend screening for AF. Pulse palpation is not carried out systematically.

At the end of the study year, we perform computer searches of the medical records to identify all new cases of AF in the control practices. We evaluate the route that led to the diagnosis of AF. To that end, we will study the patients' files to determine the path by which the diagnosis AF is made.

End of the study

The study ends when all clusters have finished their 1-year study period.

Outcome measures

Primary outcome measures

1. The yield of a case-finding strategy for AF (including paroxysmal and asymptomatic AF) compared with care as usual.
2. The diagnostic accuracy (sensitivity and specificity) of each of the three index tests (pulse palpation, eBPM-AF and handheld ECG) to diagnose AF

and the accuracy of various combinations of case-finding strategies with the results of the 12-lead ECG and 2-week Holter as reference standard.

Secondary outcome measures

1. The incidence and prevalence of AF (including paroxysmal and asymptomatic) in patients aged 65 years and over in Dutch general practice.
2. The diagnostic accuracy (sensitivity and specificity) of the handheld ECG at home to detect pAF with the 2-weeks Holter as the reference standard.
3. The quality of life of patients with newly detected asymptomatic AF compared with healthy controls as measured with the EQ-5D.

Sample size calculation

The primary outcome is the difference in the detection rate of new AF in 1 year between intervention and control practices. We estimate that the yearly incidence of new AF in the Netherlands in patients aged 65 and over is 1.3 % and assume that this is the detection rate in control practices.[26] In previous research among a similar group of patients the odds ratio (OR) of newly identified AF by opportunistic screening compared with no screening in the control group was 1.61 (95 % CI 1.14–2.29).[15] In that study, ECG was offered if the pulse of the patient was irregular. Since we will provide a more extensive diagnostic programme of various diagnostic methods, it is likely that we will find a higher detection rate of (paroxysmal and asymptomatic) AF. We assume that an OR of 1.8 is reasonable. The detection rate in the intervention group is estimated at 2.32 %.[27] To detect an absolute difference of 1.02 % in the detection rate of new cases of AF between the intervention and control arm of the study with 80 % power at a significance level of 5 %, we will need 2701 patients in each group.[28] Outcomes for individuals within clusters may be correlated as we will randomise practices (i.e. clusters). To take into account the effect of cluster randomisation we calculate a design effect of 2.99 based on fixed cluster sizes of 200 patients and an intracluster correlation coefficient (ICC) of 0.01.[29, 30] In a study comparable to ours, an ICC of 0.0027 between practices was found at the end of the study.[15] Increasing the sample size by a design effect of 2.99 the number of required inclusions becomes 8076 patients per group. Additionally, we take into account a loss to follow-up of 15 %. After correcting for loss to follow-up we get a total of 9501 patients. We decided on 48 even cluster sizes of 200 patients

which makes a total of 9600 patients. Our sample size and study design are comparable to the study by Hobbs et al..[22]

Statistical analysis

We analyse data on an intention-to-screen basis. We evaluate the outcomes of the intervention on a patient level.

Primary study outcomes

1. The difference in yield of new AF in 1 year between intervention and control practices is estimated by calculating the difference in detection rate of new AF (new cases of AF after 1 year within the clusters/all patients in the clusters) between intervention and control practices. We use logistic mixed-effects models with practice as random factor for statistical analysis, since this accounts for the correlation between patients within the same practice. In case the outcome (AF yes/no) is missing for a patient, the patient is excluded from the analysis (list-wise deletion). We use multiple imputation to obtain complete datasets and to see whether the original analysis is influenced by these missing data: i.e. to see whether the difference in detection rates between intervention and control groups is similar for both the original analysis (list-wise deletion) and the multiple imputation analysis.
2. Diagnostic test characteristics of the different index tests to diagnose AF are compared with the results of the 12-lead ECG and 2-weeks Holter (composite reference standard). Sensitivity and specificity of each technique are calculated (including the corresponding 95 % confidence intervals). Because not all patients receive the reference standard, diagnostic parameters are estimated by converting studied numbers (i.e. results of test and reference standard) to the source population by multiplying them with the sample factor. For this, we use inversed probability weighting.[31] In the intervention group, we expect an incidence of AF of 2–3 %. This would result in sufficient numbers in all cells of the imaginary diagnostic 2x2 tables. We compare the diagnostic characteristics of the index tests to each other. We evaluate each method separately and in different combinations.

Secondary study outcomes

1. We use descriptive statistics in both intervention and control practices to provide current AF prevalence and incidence figures in Dutch general practice.
2. The diagnostic test characteristics of the handheld ECG device for home monitoring using the 2-week Holter as reference standard are reported in a 2x2 table. Sensitivity and specificity (including the corresponding 95 % confidence intervals) are calculated.
3. We use descriptive statistics to describe the outcomes of the quality of life of patients with asymptomatic AF and healthy controls.

Categorical data are presented by number of patients (%) and numerical data by mean (SD) or median (interquartile range, IQR), where appropriate. IBM SPSS (SPSS Inc., Chicago, IL, USA) for Windows and SAS (SAS Institute, Cary, NC, USA) will be used to analyse the data.

Discussion

The 'Detecting and Diagnosing Atrial Fibrillation' (D_2AF) study is the first case-finding study to detect AF in general practice not only using pulse palpation but also new methods like a single-lead handheld ECG – to be used at the office and at the patient's home – and an electronic sphygmomanometer with the ability to detect AF while measuring the blood pressure.

In a systematic review, Lowres et al. showed that screening for AF at one moment can identify previously undiagnosed AF.[32] The incidence of previously undiagnosed AF in patients of 65 years and over was 1.4 % (CI 1.2–1.6 %). However, when using pulse palpation or 12-lead ECG at only one moment, one risks missing pAF. A systematic screening programme in a 75-year-old Swedish population showed that 2 weeks of additional intermittent ECG recording using a single-lead ECG twice daily (after a negative 12-lead ECG) revealed newly found pAF in 7.4 % of screened patients.[33] The D_2AF study uses new diagnostic methods and intermittent ECG recording to detect persistent and paroxysmal AF. By comparing the new methods (eBPM-AF and handheld ECG) and pulse palpation, we will be able to determine the diagnostic gain of each method separately and of combined strategies. Furthermore, we will determine the gain of using the handheld ECG at home for a prolonged period.

We use cluster randomisation to prevent control patients from being contaminated with awareness of AF detection or with the availability of additional equipment. We use a fixed sample size of 200 patients, as a compromise between statistical power and an acceptable workload for the general practices.

We focus on patients aged 65 years and over, because of the increasing prevalence of AF with age from about 1 % in the whole population to about 5 % in people aged over 65.[34] Moreover, detecting AF in this age group has treatment consequences in most patients. According to the CHA_2DS_2VASc score all women and most men of 65 years and over with AF are eligible for anticoagulation. By recruiting in different regions, we include practices with diversity in organisation and patients characteristics, such as ethnicity.

Besides the actual prevalence in the patient group, the efforts the doctors made to detect AF in the past determines the registered prevalence of AF in each cluster. Therefore, we expect the registered prevalence of AF in each practice to correlate negatively with the chance of detecting new AF. We will use prevalence of AF in patients aged 65 years and older as our stratification variable to equalise the chance of finding new AF in the intervention and control practices.

We use a case-finding protocol, which means that only patients making an appointment for a consultation are asked to participate. We preferred this method to systematic screening, where all patients are asked to participate. One of the reasons is that Hobbs et al. showed case-finding to be as effective as systematic screening.[15]

In the intervention arm, we run a diagnostic study to determine the test characteristics of different case-finding methods for AF. Ideally, one should perform the reference standard in all patients. We considered this as too costly, time-consuming and interruptive for both patients and practices. Therefore, we decided to perform the composite reference test only in patients with a positive case-finding test and a small random group of patients with negative tests.

AF is an important risk factor for stroke, and early detection is desirable to enable prevention of serious complications. The D_2AF study will provide valuable evidence on the efficacy of case-finding and on the best methods for detecting AF.

Trial status

The trial has started September 2015 in the first practices. We are currently completing the recruitment of practices.

Declarations

Funding

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Competing interests

The authors declare that they have no competing interests.

Ethical approval

The D_2AF study proposal was approved by the medical ethical board of the Academic Medical Center in Amsterdam (dated 14 November 2014, number NL48215.018.14). The D_2AF study is registered at The Netherlands Trial Register (NTR number NTR4914).

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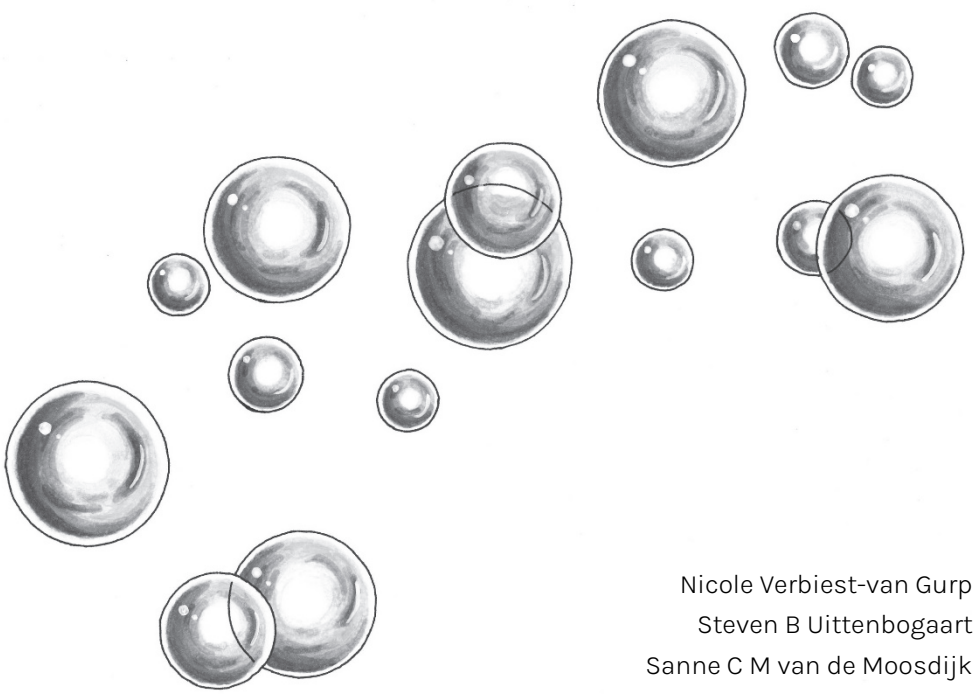
Chapter 5

How is atrial fibrillation detected in everyday healthcare? Results of a cohort study



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Abstract

Background

Atrial fibrillation (AF) is a common arrhythmia, with serious potential consequences when left untreated. For timely treatment, early detection is imperative. We explored how newly diagnosed AF is detected in patients aged ≥65 years in Dutch healthcare.

Methods

The cohort consisted of 9526 patients from 49 general practices in the usual care arm of the Detecting and Diagnosing Atrial Fibrillation (D_2AF) study. Patient selection started in 2015. Data collection ended in 2019. We automatically extracted data from the electronic medical records of the cohort and reviewed individual records of patients with AF.

Results

We included 258 patients with newly diagnosed AF. In 55.0% (142/258), the irregular heartbeat first presented in general practice, 16.3% (42/258) in cardiology. Cardiologists diagnosed most cases (47.3%, 122/258), followed by general practitioners (GPs, 33.7%, 87/258). Symptoms triggered AF detection in 64.7% (167/258) of patients, stroke in 3.5% (9/258). Overall, people aged 65-74 years more often presented with symptoms than people aged ≥75 years (73.5% vs. 60.6%, p=0.042). In 31.5% (81/258), AF was found incidentally ('silent AF'). Silent AF-patients were on average two years older than symptomatic AF-patients. Silent AF was less often diagnosed by a GP (21.0% vs. 39.0%, p=0.008) and more often by another physician (no GP or cardiologist, 34.6% vs. 11.9%, p<0.001). Most diagnoses were based on a 12-lead electrocardiogram (93.8%).

Conclusion

Diagnosing AF is a multidisciplinary process. Most often, the irregular heartbeat was detected by the GP, but cardiologists diagnosed most cases. One-third of all newly found AF was silent.

What's new

- Two thirds of patients are diagnosed with atrial fibrillation (AF) due to symptoms, whereas one third of patients has silent AF.
- General practitioners often are the first to detect an irregular heartbeat, whereas cardiologists most often diagnose AF.
- Diagnosing new AF is often a multidisciplinary process, in which not only the cardiologist, but also general practitioners and other physicians are frequently involved.
- The great majority of new AF diagnoses is based on a 12-lead electrocardiogram.

Introduction

Atrial fibrillation (AF) is a common arrhythmia among the elderly, associated with considerable comorbidity.[1-3] Up to a quarter of ischemic strokes is AF-related.[4, 5] Since adequate antithrombotic treatment reduces stroke risk in AF by 60%, early detection of AF is crucial.[6] However, detection of AF can be challenging. Approximately one-third of patients has no symptoms, so-called silent AF.[7, 8] Without symptoms, patients do not seek medical attention and physicians are not triggered to perform diagnostic tests. Silent AF can be discovered incidentally, for example when measuring blood pressure or through screening. Paroxysmal AF further complicates the detection due to its intermittent character. As a result, AF may remain undetected.

Exploring current practice could uncover possible strategies to improve AF detection. In Dutch health care, all inhabitants are enlisted with a general practitioner (GP). In case of health-related issues, this physician is consulted first. Outside office hours, patients can contact the out-of-hours primary care service. Not all general practices and out-of-hours services have a 12-lead ECG device.[9] Therefore, some GPs have to refer patients to the cardiologist to confirm AF. Previously, we investigated AF detection by Dutch GPs and cardiologists in two case vignette studies.[10, 11] GPs indicated to have adequate equipment, knowledge and experience to detect and diagnose AF. Cardiologists reported having access to a wide variety of diagnostic tools. Most GPs and cardiologists chose a shorter monitoring duration than the guidelines recommend for patients with symptoms less than once daily.[12, 13]

The present cohort study describes how AF is detected in people aged ≥65 years in everyday health care. We investigated what triggered the detection of AF, where the irregular heartbeat was first noticed, who diagnosed AF, and which diagnostic devices were used.

Methods

Design and setting

This study includes data from the 'usual care' control arm of the Detecting and Diagnosing Atrial Fibrillation (D_2AF) study, a cluster randomised controlled trial comparing opportunistic screening for AF with usual care.[14, 15] Participating practices were evenly distributed across the Netherlands (appendix 1).

Participants and data extraction

Patients were selected between October 2015 and September 2017. In each practice we randomly selected 200 patients aged ≥65 years, without an International Classification of Primary Care (ICPC) code for AF in the electronic medical record. In one small practice, only 189 patients met these criteria, bringing the total to 9789 patients. Both patients and health care workers were unaware of who had been selected, to avoid the observer's paradox (influencing usual care regarding AF detection due to awareness of the study). We extracted baseline characteristics from the electronic medical record of the cohort between May 2018 and January 2019. Follow-up time differed per practice.

To identify all newly diagnosed AF cases after the study period, we manually reviewed patient records with ICPC codes for AF, palpitations, paroxysmal tachycardia, ectopic heartbeats, other abnormal heartbeats, transient ischemic attack and stroke. We considered AF confirmed if it was recorded on a 12-lead ECG, Holter or event recorder. Recording time was not registered. Patients with atrial flutter were also included, since it has the same ICPC code, can cause the same symptoms, can convert into AF and also requires antithrombotic treatment.

Data collection

We entered pseudonymised data of patients with newly diagnosed AF in a cloud-based electronic case report form (Castor Electronic Data Capture, Ciwit BV, Amsterdam, the Netherlands) using checkboxes and free text. To track down what

triggered diagnosis, where the irregular heartbeat was detected, what medical professional diagnosed AF and which diagnostic tests were performed, we reviewed several sections of the medical record: journal, medical history, discharge letters, outpatient letters and medication overviews. In case of any doubt, data collectors (SU, SvdM, UvS, KC, YG) reached consensus by discussion.

Data analysis

We used IBM SPSS 25 Statistics to perform analyses. First, we compared baseline characteristics of those in the cohort who did or did not develop AF. Second, we analysed gender and age-related differences in the trigger for AF diagnosis, i.e. after stroke, due to symptoms or incidentally. Third, we compared those in whom AF diagnosis was found incidentally ('silent AF'), with those in whom the diagnosis was purposefully sought out due to symptoms or a stroke ('symptomatic AF'). We applied Chi-square to categorical variables and used Fisher's exact and Fisher-Freeman-Halton exact tests where appropriate. We applied independent-samples T-tests to numerical variables. A p-value of <0.05 was considered statistically significant. Free text comments were categorised by theme.

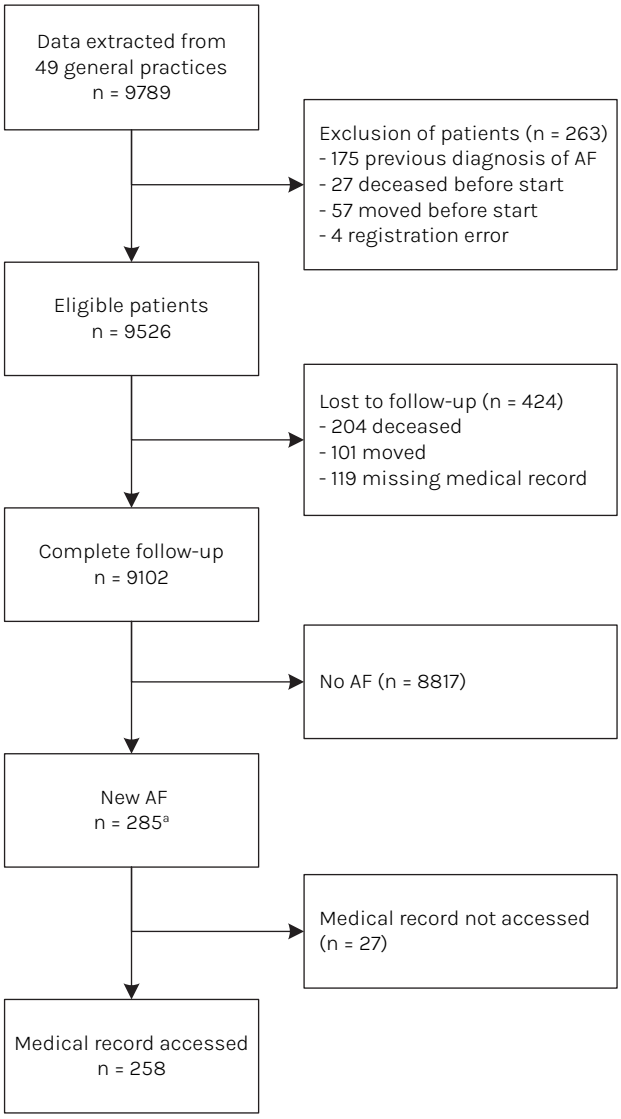
Results

Study population

We included 49 general practices and formed a cohort of 9526 patients (figure 1), of whom 285 (3.0%) had newly diagnosed AF. On average, patients with AF were older than those without AF, and more often had heart failure, hypertension, diabetes, and vascular diseases (table 1).

The mean time between defining the cohort and reviewing the medical records was 25.6±5.8 months. We could review the medical records of 258 patients with AF, of whom 23 had an atrial flutter. Women were diagnosed with AF at an older age than men (79.7 vs. 77.5 years, $p=0.014$). The mean CHA_2DS_2VASc score for patients with AF was 3.7±1.5, and it was higher in women than in men (4.2 vs. 3.2, $p<0.001$), due to one point for female sex.

Figure 1 Follow-up of the study cohort



AF: atrial fibrillation

a) We found more patients with new AF in the current study (n=285) than in the RCT (n=139), because of a longer follow-up.

Table 1 Baseline characteristics of the cohort, including a comparison of patients with and without new atrial fibrillation

	Cohort n=9526	New AF n=285	No AF n=9241	p-value
Age in years, mean (SD)	75.0 (6.9)	77.6 (7.1)	74.9 (6.9)	<0.001
Female, n (%)	5177 (54.3)	148 (51.9)	5029 (54.4)	0.406
Comorbidity, n (%)[a]	6080 (64.7)	215 (75.4)	5865 (64.4)	<0.001
Diabetes	1750 (18.6)	77 (27.0)	1673 (18.4)	<0.001
Heart failure	362 (3.9)	25 (8.8)	337 (3.7)	<0.001
Hypertension	4579 (48.7)	170 (59.6)	4409 (48.4)	<0.001
Previous stroke / TIA	911 (9.7)	36 (12.6)	875 (9.6)	0.089
Thromboembolism	431 (4.6)	15 (5.3)	416 (4.6)	0.579
Vascular disease[b]	1573 (16.7)	62 (21.8)	1511 (16.6)	0.021

AF: atrial fibrillation; TIA: transient ischemic attack

a) For 127 of 9526 patients (all in the group with no AF), comorbidity was missing.

b) Vascular disease includes peripheral vascular disease, myocardial infarction and angina pectoris

Table 2 Trigger for diagnosis of new atrial fibrillation, including a comparison between men and women and between two age groups

	All n=258	Gender Male n=120	Female n=138	p-value	Age groups 65-74 n=83	≥75 n=175	p-value
Symptoms, n (%)[a]	167 (64.7)	76 (63.3)	91 (65.9)	0.662	61 (73.5)	106 (60.6)	0.042
Palpitations	79 (30.6)	30 (25.0)	49 (35.5)	0.068	37 (44.6)	42 (24.0)	<0.001
Dyspnoea	73 (28.3)	33 (27.5)	40 (29.0)	0.792	16 (19.3)	57 (32.6)	0.027
Fatigue / malaise	40 (15.5)	16 (13.3)	24 (17.4)	0.369	13 (15.7)	27 (15.4)	0.961
Chest pain	35 (13.6)	17 (14.2)	18 (13.0)	0.793	15 (18.1)	20 (11.4)	0.145
Syncope / collapse	28 (10.9)	12 (10.0)	16 (11.6)	0.681	10 (12.0)	18 (10.3)	0.671
Dizziness	28 (10.9)	13 (10.8)	15 (10.9)	0.993	10 (12.0)	18 (10.3)	0.671
Other[b]	40 (15.5)	14 (11.7)	26 (18.8)	0.112	10 (12.0)	30 (17.1)	0.291
Stroke, n (%)	9 (3.5)	5 (4.2)	4 (2.9)	0.737[d]	0	9 (5.1)	0.062[d]
Incidental, n (%)[c]	81 (31.5)	39 (32.5)	42 (30.7)	0.751	21 (25.3)	60 (34.3)	0.163
Other, n (%)[c]	0	0	0	n.a.	0	0	n.a.

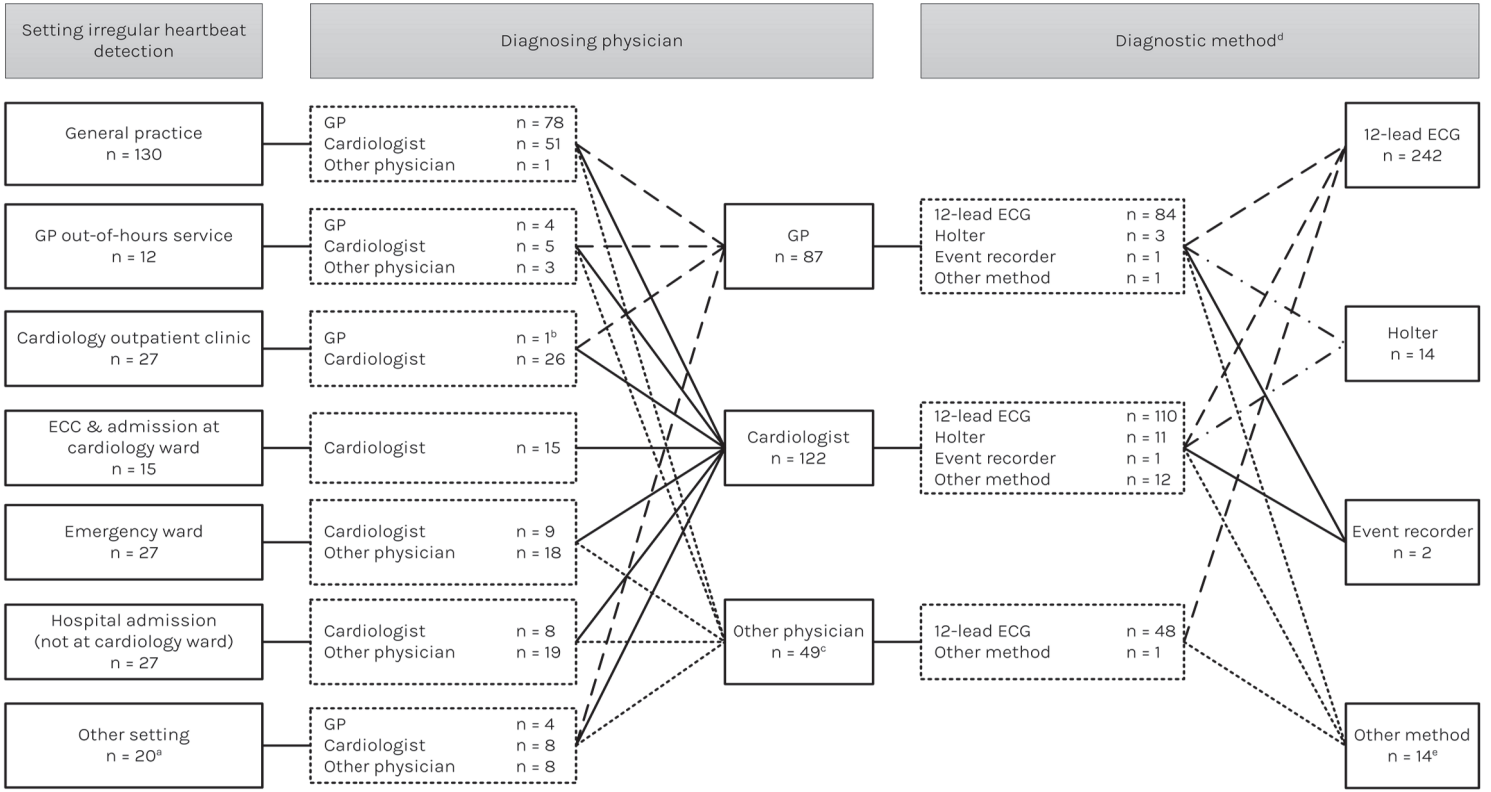
a) Patients could have more than one symptom.

b) Peripheral oedema (12), nausea/vomiting (9), diarrhoea (2), transpiration (4), exercise intolerance (2), back pain (3), cough (2), unstable feeling (1), anxiety (1), agitation (1), tremor (1), blurry sight (1), heavy feeling in the legs (1), unclear (6)

c) For one female patient, it was unclear whether it was incidental or another reason (n=257 in the first column and n=137 in the third column)

d) Fisher's Exact Test

Figure 2 The setting where an irregular heartbeat was first detected, the diagnosing physician and the diagnostic methods applied (n=258)



GP: general practitioner; ECG: electrocardiogram; ECC: emergency cardiac care department

a) Other settings: Outpatient clinic other than cardiology ward (7), pre-surgical screening (4), ambulance (7), driver license bureau (1), diabetes centre (1)

b) The irregular heart rate of this patient was detected in a cardiology outpatient clinic abroad, after which the GP in the Netherlands diagnosed AF and initiated treatment.

c) Other physicians: emergency physician (11), internist (9), neurologist (7), pulmonologist (4), geriatrician (4), surgeon (4), anaesthetist (2), ambulance personnel (2), intensivist (2), nephrologist (1), oncologist (1), orthopaedist (1), unclear (1)

d) Due to multiple answering options, observed numbers exceed 100%, in 12 cases, a combination of two diagnostic methods was applied and in one case three methods were applied.

e) Other methods: telemetry (3), pacemaker (3), cardiac stress test (3), unclear (5)

Table 3 Comparison of characteristics of patients whose diagnosis was found incidentally (silent AF) versus those of patients whose diagnosis was sought out purposefully due to symptoms or a stroke (symptomatic AF)

	Incidental diagnosis ('silent AF') n=81	AF-targeted diagnostics because of symptoms or stroke ('symptomatic AF') n=177	p-value
Age in years, mean (SD)	79.0 (6.8)	77.0 (7.0)	0.033
Female, n (%)	42 (51.9)	96 (54.2)	0.721
Comorbidity, n (%)	62 (76.5)	129 (72.9)	0.534
Diabetes	24 (29.6)	44 (24.9)	0.420
Heart failure	10 (12.3)	11 (6.2)	0.095
Hypertension	49 (60.5)	100 (56.5)	0.546
Previous stroke / TIA	11 (13.6)	25 (14.1)	0.907
Thromboembolism	3 (3.7)	10 (5.6)	0.760[a]
Vascular disease[b]	15 (18.5)	41 (23.2)	0.401
Atrial flutter, n (%)[c]	7 (8.6)	16 (9.0)	0.940
Setting irregular heartbeat detection, n (%)[d]			
General practice	22 (27.2)	108 (61.0)	<0.001
GP out-of-hours service	1 (1.2)	11 (6.2)	0.111[a]
Cardiology outpatient clinic	17 (21.0)	10 (5.6)	<0.001
ECC & admission at cardiology ward	0	15 (8.5)	0.004[a]
Emergency ward	10 (12.3)	17 (9.6)	0.504
Hospital admission (not cardiology ward)	20 (24.7)	7 (4.0)	<0.001
Other location	11 (13.6)	9 (5.1)	0.018
Diagnosing physician, n (%)[d]			
GP	18 (21.0)	69 (39.0)	0.008
Cardiologist	35 (43.2)	87 (49.2)	0.375
Other physician	28 (34.6)	21 (11.9)	<0.001
Diagnostic method, n (%)[e]			
12-lead ECG	75 (92.6)	167 (94.4)	0.587
Holter	3 (3.7)	11 (6.2)	0.409[a]
Event recorder	1 (1.2)	1 (0.6)	0.530[a]
Other method	7 (8.6)	7 (4.0)	0.123

AF: atrial fibrillation; TIA: transient ischemic attack; GP: general practitioner; ECG: electrocardiogram; ECC: emergency cardiac care department

a) Fisher's Exact Test

b) Peripheral vascular disease, myocardial infarction and angina pectoris

c) In the incidental diagnosis group, AF-classification was missing for 1 person (n=80)

d) For every patient, only one answering option could be filled in (exclusive categories). The setting of the irregular heartbeat detection and diagnosing physician were significantly different for patients found incidentally versus those in whom diagnosis was sought out deliberately (both p<0.001).

e) For every patient, multiple answering options could be filled in (non-exclusive categories).

Trigger for AF detection

Symptoms triggered AF detection in 167 (64.7%) and stroke in nine patients (3.5%). It was found incidentally in 81 patients (31.5%, table 2). Seventy-nine symptomatic patients (47.3%) presented with palpitations. Dyspnoea was the second most common symptom (73, 43.7%). Overall, people aged ≥75 years were less often detected due to symptoms than 65-74 year olds (60.6% vs. 73.5%, p=0.042); palpitations occurred less frequently (24.0% vs. 44.6%, p<0.001) and dyspnoea more frequently (32.6% vs. 19.3%, p=0.027) in the older age group.

Setting irregular heartbeat detection

In 142 cases (55.0%), the irregular heartbeat was detected in general practice, either during working hours or at the out-of-hours service (figure 2). In 42 cases (16.3%), it was first noted at a cardiology department, either at the emergency cardiac care department (ECC), during admission on a cardiology ward or at the cardiac outpatient clinic.

Diagnosing physician

GPs diagnosed AF 87 (33.7%) and cardiologists 122 (47.3%) times (figure 2). When the irregular heartbeat was detected in general practice, AF was most often diagnosed by the GP (78, 60.0%). Almost all diagnoses (242, 93.8%) were based on a 12-lead ECG, compared to 16 (6.2%) on ambulatory monitoring. All diagnoses made after a stroke were based on a 12-lead ECG.

Silent AF

Almost a third of the AF patients had silent AF (31.5%). We compared them with the AF patients in whom AF-targeted diagnostics were initiated because of symptoms or a stroke. Patients found incidentally were on average two years older than those found for another reason (79.0 vs. 77.0 years, p=0.033). The setting of irregular heartbeat detection and the physician diagnosing AF differed between patients with silent and symptomatic AF (both p<0.001) (table 3). In most patients with symptomatic AF, the irregular heartbeat was detected in general practice, whereas only a small part of patients with silent AF was detected there (61% vs. 27%, p<0.001). In symptomatic AF, the diagnosing physician was more often a GP than in silent AF (39.0% vs. 21.0%, p=0.008). During admission at the cardiology ward or ECC, no silent AF was found. Most patients detected by other physicians than GPs or cardiologists

were found incidentally (28, 57%). The diagnostic methods did not differ significantly between silent and symptomatic AF.

Discussion

Main findings

In this cohort study, we explored the diagnostic process leading to the detection of AF (n=258). More than half of the diagnoses were first suspected in primary care and a sixth in cardiology. In two out of three patients, symptoms were the trigger to diagnose AF. In only nine patients, AF detection was triggered by a stroke (3.5%). In almost a third of cases, AF was found incidentally ('silent AF'). The trigger leading to AF diagnosis did not differ for men and women. Overall, people aged ≥75 years less often presented with symptoms than younger patients. Compared to other physicians, GPs more often detected patients after a targeted search for AF – initiated due to symptoms or after a stroke – and less often incidentally. For cardiologists this difference was not significant. Other physicians found most of their cases incidentally. GPs independently diagnosed one-third of patients; cardiologists diagnosed almost half of all patients. The vast majority of diagnoses was based on a 12-lead ECG and only one out of 16 was based on ambulatory monitoring.

Trigger for AF detection

Palpitations and dyspnoea were more common symptoms than dizziness, syncope and chest pain; this matches findings of previous studies.[16, 17] In the study of Lip et al., women were more often symptomatic than men, whereas we found no gender-related differences.[16] In a study evaluating ECGs performed in Dutch primary care, half of all new AF diagnoses were based on routine ECGs for programmatic cardiovascular care.[18]

In previous studies among patients with known AF, the percentage of silent AF varied from 11% to 30%.[8, 17, 19, 20] In the study of Kerr et al, 21% of newly diagnosed AF was silent.[21] In our study, approximately a third of patients with AF was found incidentally. Only 3.5% of patients with AF was diagnosed after a stroke, compared to 4-14% in other studies.[5, 22, 23] Relatively many patients were found incidentally and few after a stroke, suggesting that AF is already detected in an early stage in everyday healthcare. This might explain why opportunistic screening yielded

insufficient new AF cases compared to usual care.[15] An alternative explanation is underdiagnosis of paroxysmal AF in post-stroke patients, due to the underuse of ambulatory monitoring.[24] However, ambulatory monitoring is also underused in symptomatic patients.[10, 11] Therefore, underdiagnosis cannot fully explain the low proportion of AF diagnosed after a stroke.

Setting irregular heartbeat detection

The irregular heartbeat was most often detected in general practice and less often in secondary care. This finding reflects the role of the GP as a gatekeeper in the Netherlands, in which a referral is needed for a specialist consultation.[25]

In a quarter of patients, the irregular heartbeat was detected during hospital admission or emergency room visit. Often an ECG is performed here or heart rate is monitored, creating opportunities to detect AF. Furthermore, other medical conditions – e.g. anaemia, myocardial infarction or fever – for which a hospital visit may be required, can trigger AF.[12]

Diagnostic method

Almost all AF diagnoses in our study were based on a 12-lead ECG. This finding is in accordance with the guidelines, which recommend a 12-lead ECG or rhythm strip of ≥30 seconds to diagnose AF.[12, 26] Ambulatory monitoring of variable duration, depending on symptom frequency, is recommended to detect paroxysmal AF.[12, 26] In this study, few diagnoses were based on ambulatory monitoring (6.2%), which is in accordance with previous research.[10, 11]

Strengths and limitations

To our knowledge, this is the first study exploring the way AF is detected in Dutch everyday healthcare. Our study has several strengths. First, we could prospectively include a substantial group of patients with newly discovered AF due to the large cohort. Second, the cohort consisted of patients without known AF and was established by taking a random sample, thus avoiding selection bias. Third, we did not merely rely on automated extraction of ICPC coding to confirm AF diagnosis. We manually reviewed electronic medical records and searched for related ICPC codes to account for incorrect registrations, increasing the validity of our data. Fourth, participating practices were distributed throughout the Netherlands, increasing generalisability.

Our study also has some limitations. We were dependent on the quality and completeness of the medical records. Based on these records we could not reliably distinguish paroxysmal, persistent and permanent AF. Furthermore, we were not able to access 27 medical files of patients with AF. The study cohort consisted of the control arm of a trial on AF detection. Participation in this trial may have influenced usual care due to a higher awareness of AF among the health care professionals. We aimed to reduce this influence by a blind and stratified randomisation, by prohibiting participation in other screening initiatives, by blinding practices for the selected patients and by opt-out instead of written informed consent.

Implications

It is vital that GPs, fulfilling the gatekeeper role, know what signals to look for and when to suspect AF, as they are often the first who encounter patients with new AF. Specialists other than the cardiologist also have to be vigilant, as silent AF represents a substantial portion of AF cases. Local working agreements and close cooperation between primary and secondary care and between specialists should facilitate the diagnostic process.

Conclusion

Diagnosing AF is a multidisciplinary process, involving not only cardiologists, but also GPs and other physicians. Whereas an irregular heartbeat was most often first noted in general practice, cardiologists most often diagnosed AF. One-third of patients had silent AF. Ambulatory monitoring is responsible for only a small proportion of diagnoses.

Declarations

Acknowledgements

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Competing interests

None declared.

Ethical approval

The medical ethical board of the Amsterdam University Medical Centers approved the current study in an amendment to the original study protocol, NL48215.018.14, registered at The Netherlands Trial Register, NL4776 (old NTR4914).

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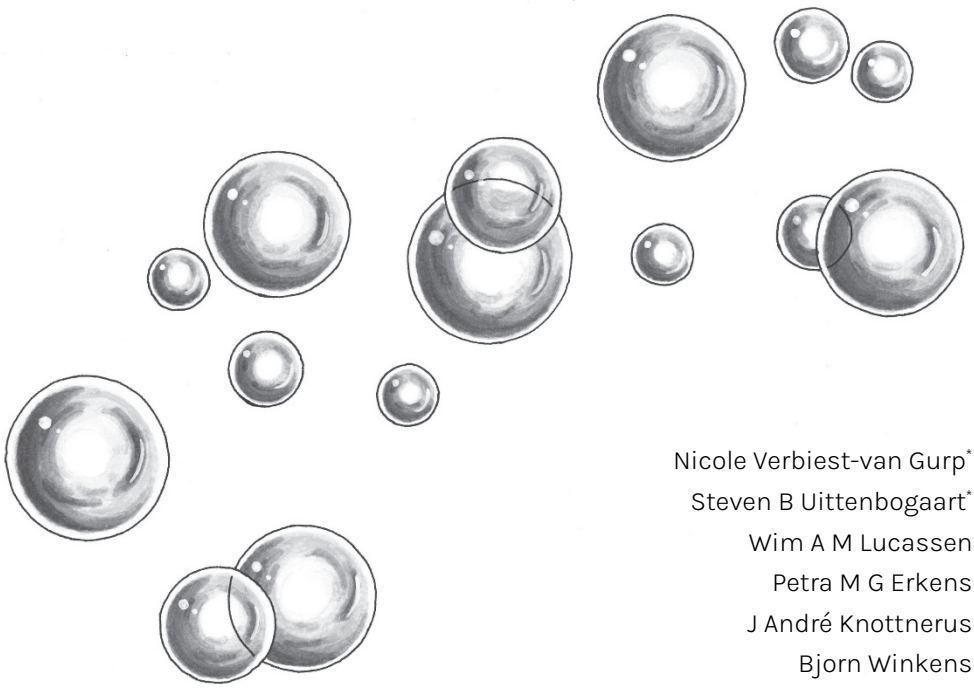
Appendix

Geographic distribution of the 49 general practices providing the cohort.

Chapter 6

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



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Abstract

Objective

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

Design

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

Setting

47 general practices participated between September 2015 and August 2018.

Participants

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

Outcomes

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

Results

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

Conclusion

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

Introduction

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

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

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

Methods

Design

We performed a diagnostic accuracy study, nested in the intention-to-screen arm of a cluster randomised controlled trial on opportunistic screening for AF in primary care, the D_2AF study.[8, 9]

Population

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

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

Index tests

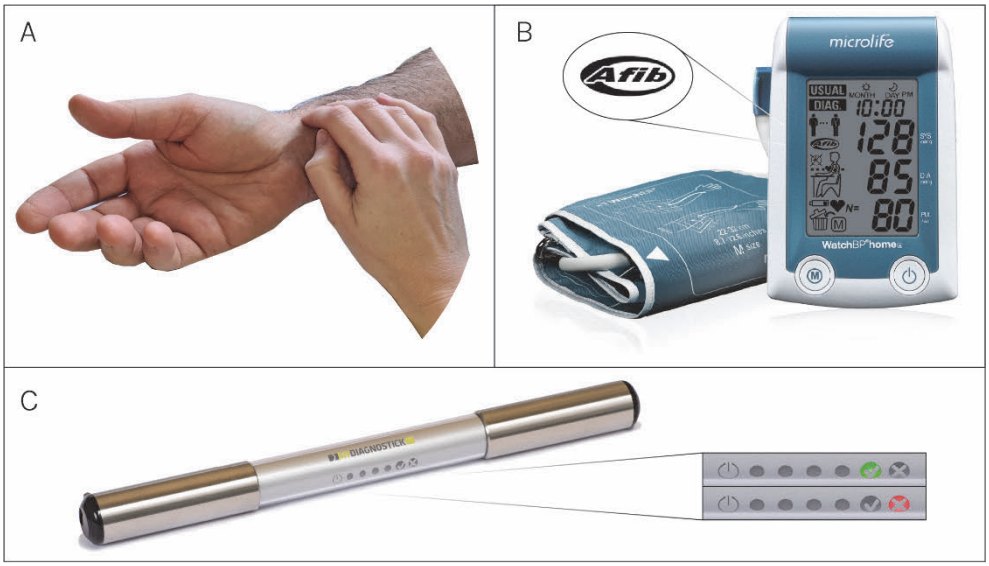
Three index tests were performed: radial pulse palpation, electronic blood pressure measurement (WatchBP Home A, Microlife, Widnau, Switzerland) and handheld ECG (MyDiagnostick, MyDiagnostick Medical B.V., Maastricht, The Netherlands), see figure 1.

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

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

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

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



Reference test

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

Study procedures

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

22 practices vice versa. Measurements were not to be repeated, in order to minimise expectancy bias.
All patients with at least one positive index test received a 12 lead ECG at shortest notice. For logistic and financial reasons a 12 lead ECG was not feasible in patients with three negative index tests, due to the expected large number.[11] To limit verification bias, a 12 lead ECG was also performed at shortest notice in a 10% random sample of patients with three negative index tests.
Finally, in the D_2AF screening trial, all patients in whom the 12 lead ECG did not show AF, were offered a two-week Holter registration (Multichannel Holter ECG recorder model H2, Fysiologic, Amsterdam, The Netherlands).

Data collection

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

Data analysis

We used IBM SPSS Statistics for Windows (version 25.0, Armonk, NY: IBM Corp.). For descriptive statistics, we report numbers and percentages (n, %) for categorical variables and means and standard deviations (M±SD) or medians with interquartile ranges (IQR) for numerical variables. To check for selection bias, we compared characteristics of participants and non-participants, and characteristics of patients with three negative index tests within versus outside of the sample receiving a 12 lead ECG. We used a Chi-square or Fisher's exact test where appropriate for categorical variables and an independent samples T-test for continuous variables. We considered a two-sided p-value ≤0.05 statistically significant.
We report our diagnostic accuracy study according to STARD.[12] To limit verification bias, we performed a 12 lead ECG in a 10% random sample of patients with three negative index tests.[9] To calculate the diagnostic parameters we applied multiple imputation (see text box), which is considered the best method to minimise

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

Multiple imputation

Multiple imputation (MI) is a statistical method that enables the analysis of incomplete data. MI consists of three steps: imputation, analysis and pooling. In the imputation step, the missing data are replaced with plausible values. The imputed values are based on all other available information of the patient whose data are missing and of the other patients. This process is repeated several times to create multiple datasets. In the next phase, each dataset is analysed separately, the same way as one would have analysed a complete dataset. Finally, the results are pooled, providing the mean results with a range.

Results

Study procedures

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

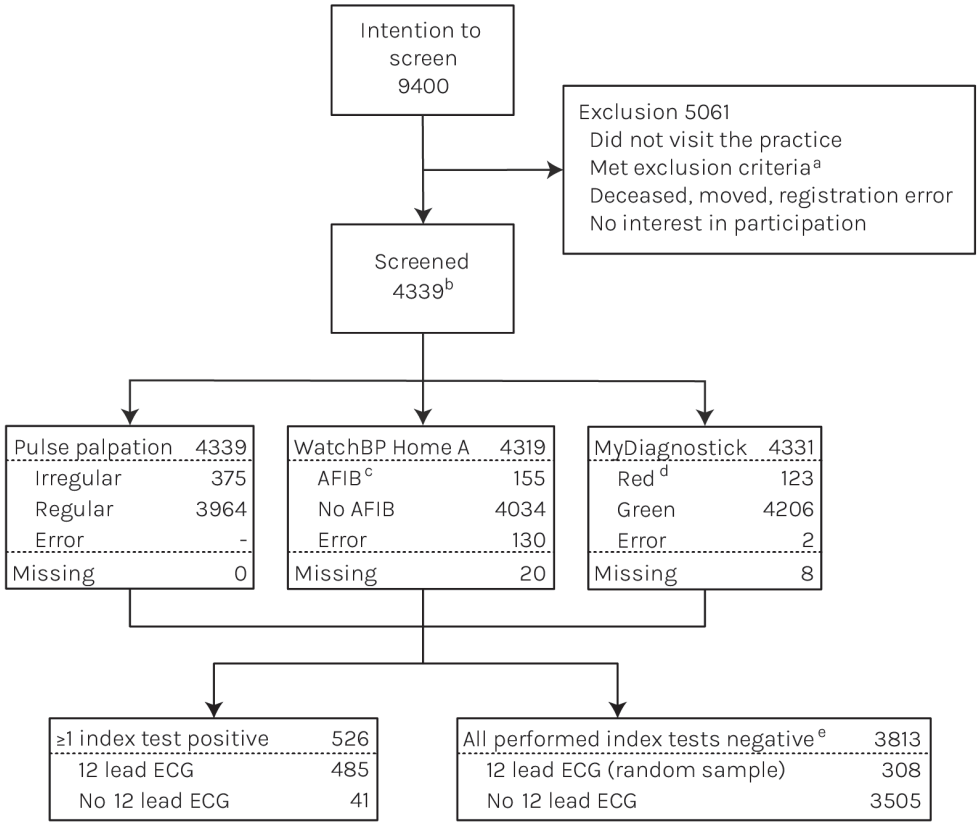
The median time between registration of the first index test and the 12 lead ECG was 25 minutes (IQR 18-44). The indicator light of the MyDiagnostick was registered for 4331 patients; for 3607 (83.3%) of them, we obtained the automatic interpretation from the local software. We corrected 17 manually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

Participants

Out of the 9400 patients whose medical file was marked, 4339 patients participated (figure 2), with a mean (±SD) of 92±23 per practice. On average, participants were younger and had less comorbidity than non-participants (appendix 1). Table 1 shows the participant characteristics and a comparison of patients with one or more positive index tests versus patients with three negative index tests. Within the

group of patients with three negative tests, a comparison of the random sample who received a 12 lead ECG (n=308) versus patients outside the sample (n=3505) revealed that patient characteristics were not significantly different, except for hypertension (p=0.013; see appendix 2).

Figure 2 Patients receiving index tests and their results.



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

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

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

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

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

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

Characteristic	All (n=4339)	≥1 positive index test[a] (n=526)	Three index tests negative (n=3813)	p-value
Female, n (%)	2336 (53.8)	248 (47.1)	2088 (54.8)	0.001
Age in years, M (SD)	73.5 (5.5)	74.8 (5.9)	73.4 (5.4)	<0.001
Ethnic origin[b]				0.052
White, n (%)	4173 (96.2)	513 (97.5)	3660 (96.0)	
Black, n (%)	77 (1.8)	10 (1.9)	67 (1.8)	
Other, n (%)[c]	84 (1.9)	3 (0.6)	81 (2.1)	
History[d]				
Hypertension, n (%)	2212 (51.1)	280 (53.2)	1932 (50.7)	0.251
Stroke/TIA, n (%)	329 (7.6)	37 (7.0)	292 (7.7)	0.621
Diabetes, n (%)	783 (18.1)	110 (20.9)	673 (17.7)	0.065
Heart failure, n (%)	80 (1.8)	18 (3.4)	62 (1.6)	0.004
Thromboembolism, n (%)	200 (4.6)	19 (3.6)	181 (4.7)	0.248
Vascular disease, n (%)	644 (14.8)	102 (19.4)	542 (14.2)	0.002
Symptoms[e]				
Palpitations, n (%)	735 (17.0)	102 (19.4)	633 (16.6)	0.108
Vertigo, n (%)	935 (21.6)	141 (26.8)	794 (20.8)	0.002
Syncope, n (%)	164 (3.8)	25 (4.8)	139 (3.6)	0.213
Dyspnea, n (%)	925 (21.3)	158 (30.0)	767 (20.1)	<0.001
Chest tightness, n (%)	426 (9.8)	64 (12.2)	362 (9.5)	0.054
Exercise intolerance, n (%)	962 (22.2)	153 (29.1)	809 (21.2)	<0.001
Any of the above, n (%)	2228 (51.3)	316 (60.1)	1912 (50.1)	<0.001
Signs				
Unequal pulse, n (%)	125 (4.9)	78 (14.8)	47 (1.2)	<0.001
Heart rate in bpm, M (SD)[f]				
Radial pulse palpation	71.2 (11.2)	68.8 (11.3)	71.5 (11.1)	<0.001
Watch BP Home A	72.1 (12.8)	71.7 (12.9)	72.1 (12.8)	0.512
MyDiagnostick	72.0 (11.9)	72.2 (14.1)	72.0 (11.6)	0.722
Systolic blood pressure[g], M (SD)	143.0 (18.7)	141.9 (18.9)	143.2 (18.8)	0.152
Diastolic blood pressure[g], M (SD)	78.7 (9.8)	78.7 (10.1)	78.7 (9.7)	0.865
AF on Holter[h], n (%)	4 (0.1)	0	4 (0.1)	0.029[i]

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

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

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

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

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

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

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

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

h) Holter results were available for 270 patients.

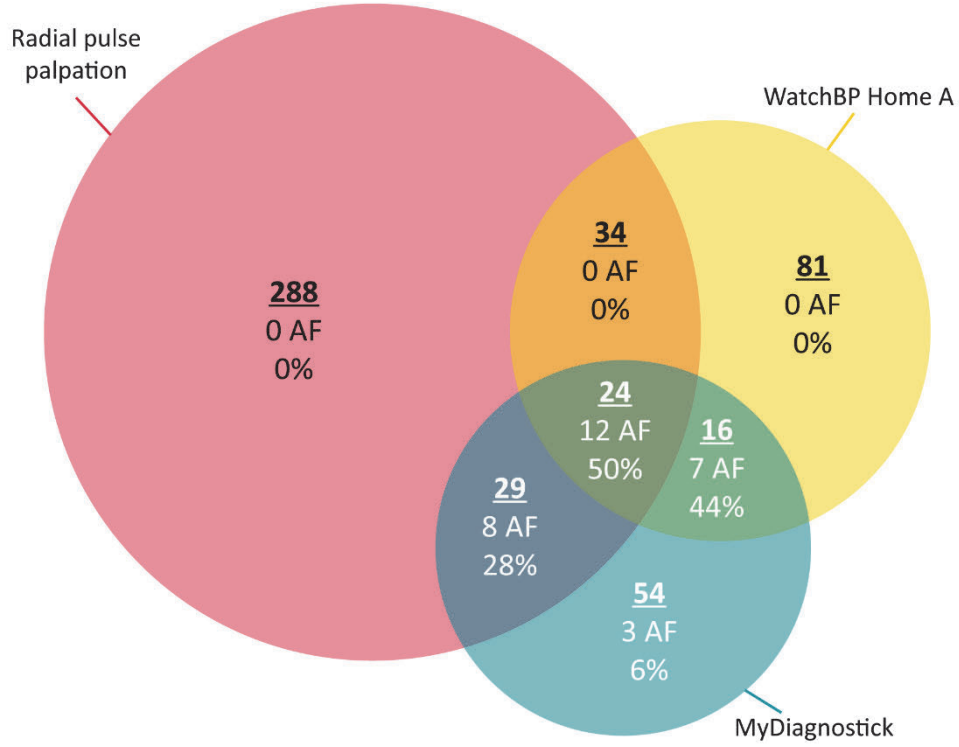
i) Fisher's exact test.

Observed cases and multiple imputation

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

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

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



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

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

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

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

Abbreviations: AF (atrial fibrillation)

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

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

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

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

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

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

Diagnostic accuracy

Table 3 displays the diagnostic test characteristics based on the pooled data. Both sensitivity and specificity of electronic blood pressure measurement (70.0% and 96.5%) and handheld ECG (90.1% and 97.9%) were higher than those of radial pulse palpation (62.8% and 91.8%). The sensitivity and specificity of the MyDiagnostick were significantly higher than those of the other two index tests in all 100 imputed datasets (all p-values were ≤0.039). The negative predictive values of all index tests were ≥99.7%. The positive predictive value of the handheld ECG was the highest (25.2% versus 13.8% and 5.8% for electronic blood pressure measurement and radial pulse palpation, respectively). The positive likelihood ratios of electronic blood pressure measurement (19.9) and handheld ECG (42.0) were high; the negative likelihood ratio of handheld ECG was 0.1. Additional analysis of five index test combinations did not reveal a superior combination (see appendix 5).

Discussion

Main findings

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

Strengths and weaknesses

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

Secondly, we minimised verification bias in the calculated diagnostic parameters. Rather than labelling patients with three negative index tests as ‘no AF’, we performed a 12 lead ECG in a random sample of these patients. A comparison of

patient characteristics within versus outside the sample showed that our sample was representative. In addition, we applied multiple imputation to compute all diagnostic accuracy parameters in a valid way.[13] Inverse probability weighting would have overestimated sensitivity and – to a lesser extent – the negative predictive value for the scenarios with the handheld ECG, due to zero false-negative results.[15]
Thirdly, we excluded patients with known AF, which increased the validity of our results for the diagnostic purpose of case finding. Clinical features of patients with known AF may differ from those with newly diagnosed and untreated AF, affecting test characteristics.[16] Moreover, including patients with known AF would artificially have raised AF frequency in the study population, affecting predictive values.[17]
A limitation of our study is that participants were slightly younger and had less comorbidity than non-participants. This may have reduced the yield of AF in our study and decreased positive predictive values.

Incidence of atrial fibrillation and positive predictive values

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

Radial pulse palpation

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

Electronic blood pressure measurement

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

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

Handheld electrocardiography

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

Implications for practice

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

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

Conclusion

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

Declarations

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Competing interests

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

Ethical approval

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

Availability of data and materials

Relevant anonymised patient level data are available on reasonable request.

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Appendix 1

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

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

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

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

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

Appendix 2

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

Characteristic	Patients with three negative index tests[a]			
	Total (n=3813)	ECG (random sample, n=308)	No ECG (n=3505)	p-value
Female, n (%)	2088 (54.8)	168 (54.5)	1920 (54.8)	0.937
Age in years, M (SD)	73.4 (5.4)	73.1 (5.3)	73.4 (5.5)	0.274
Ethnic origin[b]				0.495
White, n (%)	3360 (96.0)	293 (95.1)	3367 (96.2)	
Black, n (%)	67 (1.8)	8 (2.6)	59 (1.7)	
Other, n (%)[c]	81 (2.1)	7 (2.3)	74 (2.1)	
History[d]				
Hypertension, n (%)	1932 (50.7)	135 (44.0)	1797 (51.4)	0.013
Stroke/TIA, n (%)	292 (7.7)	17 (5.5)	275 (7.9)	0.143
Diabetes, n (%)	673 (17.7)	44 (14.3)	629 (18.0)	0.109
Heart failure, n (%)	62 (1.6)	5 (1.6)	57 (1.6)	1.000
Thromboembolism, n (%)	181 (4.7)	9 (2.9)	172 (4.9)	0.117
Vascular disease, n (%)	542 (14.2)	39 (12.7)	503 (14.4)	0.422
Symptoms[e]				
Palpitations, n (%)	633 (16.6)	51 (16.6)	582 (16.6)	0.976
Vertigo, n (%)	794 (20.8)	63 (20.5)	731 (20.9)	0.862
Syncope, n (%)	139 (3.6)	10 (3.2)	129 (3.7)	0.695
Dyspnea, n (%)	767 (20.1)	70 (22.7)	697 (19.9)	0.235
Chest tightness, n (%)	362 (9.5)	20 (6.5)	342 (9.8)	0.061
Exercise intolerance, n (%)	809 (21.2)	62 (20.1)	747 (21.3)	0.604
Any of the above, n (%)	1912 (50.1)	148 (48.1)	1764 (50.3)	0.444
Signs				
Unequal pulse, n (%)	47 (1.2)	2 (0.6)	45 (1.3)	0.585[k]
Heart rate in bpm, M (SD)[f]				
Radial pulse palpation	71.5 (11.1)	72.1 (11.0)	71.5 (11.2)	0.363
WatchBP Home A	72.1 (12.8)	72.1 (13.1)	72.1 (12.7)	0.953
MyDiagnostick	72.0 (11.6)	71.5 (10.5)	72.0 (11.7)	0.466
Systolic blood pressure[g], M (SD)	143.2 (18.8)	142.3 (19.7)	143.3 (18.6)	0.398
Diastolic blood pressure[g], M (SD)	78.7 (9.7)	79.0 (9.8)	78.7 (9.7)	0.671
AF on Holter[h], n (%)	4 (0.1)	4 (1.3)	0	1.000[i]

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

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

b) Mutually exclusive categories. For every patient, only one answering option could be filled in (exclusive categories). The ethnic origin did not differ significantly between patients with one or more positive tests and patients with three negative tests (p=0.495).
c) Patients in this category were mostly born outside the Netherlands (n=76); the four predominant countries of birth were Indonesia (n=35), Suriname (n=14), Morocco (n=8) and Turkey (n=5).
d) For seven patients, history was missing (n=3806).
e) Results were missing in four patients for palpitations (n=3809), three for vertigo (n=3810), three for syncope (n=3810), two for dyspnea (n=3811), one for chest tightness (n=3812) and 13 for exercise intolerance (n=3800).
f) There were 93 results missing for heart rate on WatchBP Home A (n=3720) and 638 for MyDiagnostick (n=3175).
g) If the WatchBP Home A failed, blood pressure was measured manually. Blood pressure was still missing for 53 patients (n=3781).
h) Holter results were available for 112 patients.
i) Fisher's exact test.

Appendix 3

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

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

Abbreviations: AF (atrial fibrillation).

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

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

Appendix 4

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

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

Abbreviations: AF (atrial fibrillation).

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

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

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

Appendix 5

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

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

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

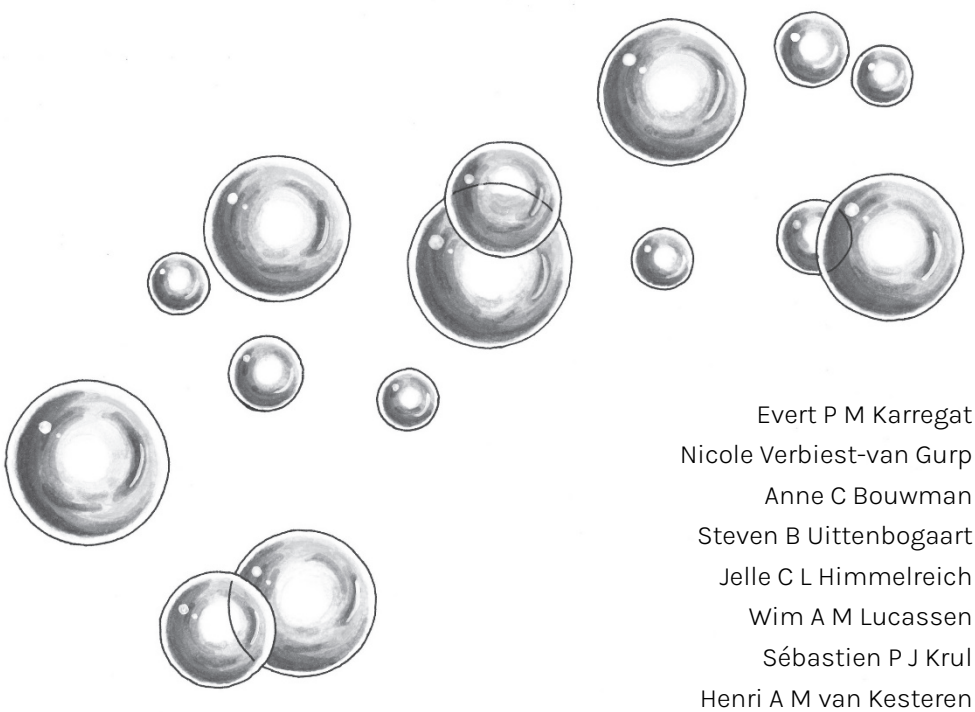
a) By protocol, to limit verification bias, we strived to perform the reference test (12 lead ECG) in a 10% random sample of patients with three negative index tests. In addition, to calculate all relevant diagnostic parameters, we used multiple imputation in the analysis (see main text). We report the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

b) Description of the index test combinations:

A. All three index tests, positive if at least one was positive.
B. Radial pulse palpation and handheld electrocardiography, positive if either test was positive.
C. Radial pulse palpation and electronic blood pressure measurement, positive if either test was positive.
D. Radial pulse palpation and handheld electrocardiography, positive if both tests were positive.
E. Radial pulse palpation and electronic blood pressure measurement, positive if both tests were positive.

Chapter 7

Screening for paroxysmal atrial fibrillation in primary care using Holter monitoring and intermittent, ambulatory single-lead electrocardiography



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Abstract

Background

Timely detection of atrial fibrillation (AF) is important because of its increased risk of thromboembolic events. Single time point screening interventions fall short in detection of paroxysmal AF, which requires prolonged electrocardiographic monitoring, usually using a Holter. However, traditional 24-48 h Holter monitoring is less appropriate for screening purposes because of its low diagnostic yield. Intermittent, ambulatory screening using a single-lead electrocardiogram (1 L-ECG) device can offer a more efficient alternative.

Methods

Primary care patients of ≥65 years participated in an opportunistic screening study for AF. We invited patients with a negative 12 L-ECG to wear a Holter monitor for two weeks and to use a MyDiagnostick 1 L-ECG device thrice daily. We report the yield of paroxysmal AF found by Holter monitoring and calculate the diagnostic accuracy of the 1 L-ECG device's built-in AF detection algorithm with the Holter monitor as reference standard.

Results

We included 270 patients, of whom four had AF in a median of 8.0 days of Holter monitoring, a diagnostic yield of 1.5% (95%-CI: 0.4–3.8%). In 205 patients we performed simultaneous 1 L-ECG screening. For diagnosing AF based on the 1 L-ECG device's AF detection algorithm, sensitivity was 66.7% (95%-CI: 9.4–99.2%), specificity 68.8% (95%-CI: 61.9–75.1%), positive predictive value 3.1% (95%-CI: 1.4–6.8%) and negative predictive value 99.3% (95%-CI: 96.6–99.9%).

Conclusion

We found a low diagnostic yield of paroxysmal AF using Holter monitoring in elderly primary care patients with a negative 12 L-ECG. The diagnostic accuracy of an intermittently, ambulatory used MyDiagnostick 1 L-ECG device as interpreted by its built-in AF detection algorithm is limited.

Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia and a major cause of stroke, heart failure and other cardiovascular morbidity.[1] Anticoagulant treatment of AF reduces the risk of thrombo-embolic events by more than 60%.[2-4] This is especially relevant in elderly patients, in whom both the prevalence of AF and the thrombo-embolic risk are increased.[5, 6] Therefore, it is of utmost importance to detect and treat AF.

AF can be paroxysmal by nature, limiting the diagnostic yield of single time point screening interventions.[7] To detect paroxysmal AF, prolonged continuous monitoring with electrocardiography (ECG), using for example a Holter monitor, is advocated.[1] Previously a prevalence of paroxysmal AF up to 6% was found with prolonged ECG monitoring, after a negative baseline ECG in high risk patients.[8] However, studies investigating community-based prevalence of paroxysmal AF in an elderly population, as determined with continuous Holter monitoring are scarce.[8, 9]

Screening for paroxysmal AF using traditional 24-48 h of Holter monitoring, is less appropriate for use in asymptomatic subjects, due to its low yield in arrhythmia detection and the high burden for patients.[10, 11] Intermittent use of a handheld single-lead (1 L-) ECG device at home may be a less burdensome alternative.[8, 12] Repeated ECG recordings improve the detection of paroxysmal AF up to four times compared to single time point screening interventions.[7, 12-14] However, the diagnostic accuracy of an intermittently used 1 L-ECG device for screening purposes to detect paroxysmal AF in comparison with a Holter monitor has not been studied so far.

The MyDiagnostick® (MyDiagnostick Medical B.V.®, Maastricht, The Netherlands) is such a handheld 1 L-ECG device (see figure 1). The algorithm of this device showed a good diagnostic accuracy in previous single time point screening studies, as compared to a 12-lead (12 L-)ECG (sensitivity 82%-100%; specificity 94-96%).[15, 16]

We determined the diagnostic yield of paroxysmal AF with two-week Holter monitoring in elderly patients, without a prior AF diagnosis and with a negative baseline 12 L-ECG during opportunistic screening.[17, 18] We subsequently calculated the diagnostic accuracy of the built-in AF detection algorithm of an intermittently and ambulatory used 1 L-ECG device (MyDiagnostick) with Holter monitoring as reference standard. Furthermore, from patients with at least one algorithm-positive 1 L-ECG recording, we investigated how often cardiologists were able to make an

accurate diagnosis of AF by visual assessment of the 1 L-ECG recordings with the Holter monitoring as reference standard.

Figure 1 The MyDiagnostick 1 L-ECG device

1 L-ECG, single-lead electrocardiogram. Photograph by MyDiagnostick Medical BV

Methods

This study is nested in the intention-to-screen arm of the D_2AF (Detection and Diagnosing of Atrial Fibrillation) study: a cluster randomized controlled trial comparing opportunistic screening of AF with usual care in primary care patients aged 65 years or older. The study protocol is described elsewhere.[17] We report our findings according to the Standards for Reporting Diagnostic Accuracy (STARD) 2015 statement.[19]

Study procedure

In 47 general practices across the Netherlands, allocated to the intervention arm of the D_2AF study, patients of 65 years or older, not previously diagnosed with AF were eligible.[18] The D_2AF study screened patients using three screening tests: radial pulse palpation, and measurements with two devices with AF detection algorithm, i.e. an electronic sphygmomanometer (WatchBP Home A) and a handheld 1 L-ECG device (MyDiagnostick). The D_2AF investigators obtained a 12 L-ECG in patients with at least one positive screening test and in a random sample of 10% of patients with three negative tests. We asked patients in whom no AF was diagnosed on the 12 L-ECG, to participate in this second part of the D_2AF study. We performed two additional tests to detect paroxysmal AF. For two weeks, we applied Holter monitoring and asked

patients to simultaneously use a 1 L-ECG device (MyDiagnostick) at home thrice daily.

Index test

The MyDiagnostick is a bar, with electrodes at both ends, which a patient needs to grasp for one minute to provide a 1 L-ECG (right-left arm, corresponding with lead I on a standard 12 L-ECG). We instructed participants to use the MyDiagnostick three times a day for two weeks. Ideally this would result in (14 x 3 =) 42 1 L-ECG recordings per patient. During recording, we asked patients to sit relaxedly, not to talk and not to squeeze the electrodes. The built-in AF detection algorithm assesses every recording, resulting in a red (possible AF) or green (no AF) indicator light. However, this indicator light was turned off for study purposes, so patients were not aware of the algorithm results. The obtained recordings and corresponding results of the built-in AF detection algorithm, are stored in a PDF format in the device until uploaded onto the general practice's computer.

The 1 L-ECGs were assessed for AF in two ways:

- Firstly, using the previously mentioned built-in AF detection algorithm.
- Secondly, all 1 L-ECG recordings of patients with at least one algorithm-positive recording (possible AF) were visually assessed by two cardiologists (SK and HvK). A third cardiologist-electrophysiologist (JL) served as referee in case of disagreement. Assessors were blinded for the result of the reference test. Since previous research showed a very high negative predictive value (95-100%) of the MyDiagnostick's AF detection algorithm, 1 L-ECG recordings of patients with only negative algorithm results (no AF) were not visually assessed (15, 16).

Reference test

The Holter monitoring device (Multichannel Holter ECG recorder model H2, Fysiologic®, Amsterdam, The Netherlands) is wired with four patches obtaining leads V1 and V5. Patients used a small disposable shoulder bag to wear the device. Patients received several spare sets of patches and were instructed to change them at least every three days and after showering or bathing. The complete two-week Holter recording was first automatically analysed by a validated software algorithm. This algorithm analysed the RR intervals to detect and categorize possible arrhythmias. Subsequently, an experienced assessor, supervised by a cardiologist, visually investigated suspected ECG recordings for the presence of AF. A second

cardiologist checked all positive results. Assessors were blinded for the result of the index test.
AF was defined according to the European Society of Cardiology guideline: an ECG showing irregular RR intervals and lacking distinct P waves.[20]

Outcome measures

The first primary outcome was the diagnostic yield of paroxysmal AF in patients of 65 years and older after negative opportunistic screening with a 12 L-ECG, as found by the two-week Holter monitor.
The second primary outcome was the diagnostic accuracy, expressed as the sensitivity, specificity, positive and negative predictive value (PPV and NPV, respectively) of the two-week, intermittently used 1 L-ECG device as interpreted by its built-in AF detection algorithm, compared to a simultaneously performed Holter monitor as reference standard.
As secondary outcome, we reported results of the cardiologists' visual assessment of 1 L-ECG recordings from patients with at least one algorithm-positive 1 L-ECG recording. We reported A) the total number of patients classified by the cardiologists with AF, and B) the number of false-positive AF diagnoses by the cardiologist panel with the Holter monitor as reference standard, with the subsequent PPV of their assessment.
Furthermore, to investigate a possible effect of our selection procedure, we performed a stratified analysis based on results of the three baseline screening tests as performed during the D_2AF study, prior to receiving the Holter and 1 L-ECG device for home recordings. We compared diagnostic accuracy of the MyDiagnostick's built-in AF detection algorithm in terms of sensitivity and specificity for patients who had at least one positive baseline screening test (indicated population) with that of patients who had three negative baseline screening tests (random sample).

Data analysis

For calculation of paroxysmal AF-yield we included all patients who received Holter monitoring, regardless of the duration of Holter monitoring. For diagnostic accuracy calculations, if no Holter recording was available at the time of an algorithm-positive 1 L-ECG recording, we removed the paired results from analysis.
We analysed results at patient-level, as that is clinically more relevant than analysis on recording level. We regarded one or more algorithm-positive 1 L-ECG recording(s)

as a positive index test result. Furthermore, we instructed cardiologists to regard a patient as having AF if at least one of all 1 L-ECG recordings showed AF.

Statistical analysis

We present continuous variables depending on their distribution as means with standard deviation or median with interquartile range (IQR). We present discrete variables as numbers and percentages. Continuous data were compared using the students *t*-test. Proportions were compared using the chi-square test. We present sensitivity, specificity, PPV and NPV as percentage and 95% confidence interval (95%-CI). Statistical significance was assessed at 0.05 level. Analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp) and MedCalc Statistical Software version 19.3.1 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020).

Results

Study population characteristics

In total, 763 patients had a negative baseline 12 L-ECG (see appendix 1). Of these, 486 (64%) did not participate in this study. Reasons for not participating are listed in appendix 1.

Apart from 277 eligible patients with a negative 12 L-ECG recording, 14 additional patients of whom the 12 L-ECG results were missing did perform home recordings. Because in none of those 14 patients (paroxysmal) AF was diagnosed on the Holter monitor, we assumed they did not have AF on the 12 L-ECG either, thus we included them in this analysis.

Of the 291 patients with home recordings, 270 had Holter data available. Of these patients, mean age was 73.4 years and 50.0% was female (see table 1). Patients having performed Holter recordings were on average one year younger compared to eligible patients not having performed Holter recordings (P=0.021). For the diagnostic accuracy calculations, we included 205 patients with at least one simultaneous Holter and 1 L-ECG recording for analysis (see table 1). Reasons for missing simultaneous recordings were either signal failure of the Holter monitor during recording, premature ending of the Holter recording as decided by the patient, or erroneous preparation of the recorder resulting in Holter recordings shorter than two weeks. None of the baseline characteristics of the patients with

simultaneous 1 L-ECG and Holter recordings reached statistical significance compared to eligible patients without home recordings.

Table 1 Baseline characteristics of included patients with Holter monitoring results versus eligible patients without home recordings

	Patients with Holter monitoring result, included for paroxysmal AF-yield calculation (n=270)	Patients with simultaneous ambulatory 1 L-ECG and Holter recordings, included for diagnostic accuracy calculations (n=205)	Eligible patients without ambulatory recordings (n=486)*
Female, n (%)	135 (50.0)	109 (53.2)	250 (51.4)
Age in years, mean (SD)	73.4 (5.2)	73.6 (5.1)	74.4 (5.9)
Hypertension, n (%)	145 (53.7)	110 (53.7)	238 (49.3)
Stroke/TIA, n (%)	15 (5.6)	10 (4.9)	37 (7.7)
Diabetes, n (%)	52 (19.3)	38 (18.5)	90 (18.6)
Heart failure, n (%)	7 (2.6)	5 (2.4)	12 (2.5)
Thromboembolism	11 (4.1)	10 (4.9)	14 (2.9)
CHA_2DS_2-VASc score, n (%)			
Score 1	27 (10.0)	17 (8.3)	47 (9.7)
Score 2	78 (28.9)	60 (29.3)	135 (28.0)
Score 3	73 (27.0)	57 (27.8)	155 (32.1)
Score 4	58 (21.5)	44 (21.5)	91 (18.8)
Score 5	25 (9.3)	20 (9.8)	38 (7.9)
Score ≥6	9 (3.3)	7 (3.4)	17 (3.5)

1 L-ECG, single-lead electrocardiogram; AF, atrial fibrillation; SD, Standard Deviation; TIA, transient ischemic attack; CHA_2DS_2-VASc score, this score is used for thromboembolic risk prediction in atrial fibrillation. Short for: Congestive heart failure (1 point), Hypertension (1 point), Age (≥75 = 2 points), Diabetes (1 point), previous Stroke, transient ischemic attack or thromboembolism (2 points); Vascular disease (peripheral artery disease, myocardial infarction or aortic plaque, 1 point), Age (65-74 = 1 point) and Sex category (female gender = 1 point).

We used International Classification of Primary Care (ICPC)-codes. For hypertension we used K86 and/or K87, for stroke/TIA K89 and/or K90, for diabetes T90, for heart failure K77, for thromboembolism K93 and/or K94.

* Of three eligible patients without home recordings baseline ICPC codes were missing.

Diagnostic yield

Holter monitoring detected four cases of paroxysmal AF in 270 patients (1.5%; 95%-CI: 0.4 – 3.8%). Of these 270 patients receiving Holter monitoring, 91 (34%) wore the device for the entire two-week period. Of the remaining 179 patients, often no rationale was available for discontinuation (44%) and whenever provided, participants mostly found the Holter monitor too burdensome (29%) (see appendix 1). The median recording time of the Holter monitor was 8.0 days (IQR: 5.5 – 13.5) in these 270 patients.

Table 2 Intermittently and ambulatory obtained 1 L-ECG recordings as assessed by the built-in AF detection algorithm (n=205) vs Holter monitoring at home in detecting paroxysmal AF.

		Holter	
1 L-ECGs' algorithm	AF	No AF	Total
Possible AF	2	63	65
No AF	1	139	140
Total	3	202	205

1 L-ECG, single-lead electrocardiogram; AF, atrial fibrillation.

Table 3 Assessment of the 1 L-ECG recordings by cardiologists of patients with algorithm-positive recordings (possible AF, n=65) vs Holter monitoring at home in detecting paroxysmal AF.

		Holter	
Cardiologists' assessment of patients with algorithm-positive 1 L-ECG recordings	AF	No AF	Total
AF	1	6	7
No AF	0	34	34
Not interpretable	1	23	24
Total	2	63	65

1 L-ECG, single-lead electrocardiogram; AF, atrial fibrillation.

Diagnostic accuracy AF detection algorithm

Two hundred and five patients performed simultaneous 1 L-ECG and Holter recordings. The Holter monitor detected three cases of paroxysmal AF among those 205 patients. A median of 22 (IQR: 16 - 38) simultaneous 1 L-ECG recordings per patient were obtained. In 65 of these 205 patients, the 1 L-ECG's algorithm was positive in at least one recording with a median number of four.

Sensitivity and specificity of detecting a patient with paroxysmal AF using the 1 L-ECG's algorithm were 66.7% (95%-CI: 9.4 – 99.2%) and 68.8% (95%-CI: 61.9 – 75.1%), respectively. The PPV and NPV were 3.1% (95%-CI: 1.4 – 6.8%) and 99.3% (95%-CI: 96.6 – 99.9%), respectively (see table 2).

Efficacy of cardiologists' assessment of algorithm-positive 1 L-ECG recordings
Cardiologists classified seven out of the 65 patients with at least one algorithm-positive 1 L-ECG recording, as AF (see table 3). Six of them were false-positive based on the simultaneous Holter monitor. The PPV of the cardiologists' assessment was 14.3% (95%-CI: 7.4 – 25.8%). Furthermore, in 24 patients the cardiologists could not assess the 1 L-ECG recordings due to insufficient quality.

Diagnostic accuracy stratified by results of the baseline screening tests
In patients with three negative baseline screening tests, specificity of the 1 L-ECG's algorithm was 85.9% (95%-CI: 76.2 – 92.7%), compared to 58.1% (95%-CI: 48.9 – 66.9%) in patients with one or more positive baseline screening test(s) (see appendix 2). We could not calculate the sensitivity of the 1 L-ECG's algorithm in patients with one or more positive baseline test(s) because none of those patients were diagnosed with AF on the Holter recording.

Discussion

We detected four cases of paroxysmal AF by Holter monitoring in 270 patients of 65 years or older after negative opportunistic screening with a 12 L-ECG. Intermittent, ambulatory screening with a MyDiagnostick 1 L-ECG device to detect paroxysmal AF in elderly people, had a limited diagnostic accuracy, in particular a low PPV (3.1%), when using the built-in AF detection algorithm. Cardiologists' assessment of 1 L-ECG recordings of patients with algorithm-positive results, did not sufficiently improve the positive predictive value (14.3%) to make a reliable diagnosis. Furthermore, the 1 L-ECG recordings of one third of all patients with algorithm-positive 1 L-ECG recordings were classified as uninterpretable by the cardiologists.

Previous work
Previous population-based screening studies among patients without a previous AF diagnosis and with a negative baseline ECG using Holter monitoring or intermittent 1 L-ECG recordings to screen for paroxysmal AF, found higher diagnostic yields (2.8% - 7.4%) than we did.[7-9, 12, 13, 21] This may be because their screening period was longer and because they targeted a high-risk population, based on higher age, $CHA_{(2)}DS_2$(-VASc)-score or NT-pro-BNP, whereas we targeted patients of 65 years and older. Furthermore, prevalence of AF is already relatively

high in Dutch primary care practices compared to other countries; this may be due to well-organized preventive cardiovascular disease programs in Dutch primary care. This may limit diagnostic yield of screening interventions.[18]

There have been multiple studies on the diagnostic accuracy of the MyDiagnostick 1 L-ECG device as a single time point screening tool for AF.[15, 16, 22] To our knowledge, we are the first to investigate the diagnostic accuracy of an intermittently used 1 L-ECG device in screening for paroxysmal AF in patients at home, with simultaneous Holter monitoring as reference standard in patients with a negative baseline 12 L-ECG. The sensitivity and specificity of the MyDiagnostick in this study differs greatly from those in previous studies because we screened for paroxysmal instead of persistent or permanent AF. Furthermore, we analysed results at patient-level, which means that a single false-positive 1 L-ECG recording immediately diminished specificity. Finally, because our reference standard was a continuous Holter recording rather than a single time point reference standard as used in previous single time point analyses, paroxysmal AF could still have occurred in between the intermittent 1 L-ECG recordings, thereby limiting sensitivity.[8] Furthermore, patients used the MyDiagnostick in our study in an unsupervised ambulatory setting, while in previous validation studies this was supervised by a health care professional.

Recently, Fredriksson et al. evaluated the diagnostic yield of intermittent screening for paroxysmal AF with another 1 L-ECG device (Zenicor II), interpreted manually, compared to an event recorder with automatic triggering.[8] Intermittent screening using the Zenicor II detected one third of paroxysmal AF cases, and did not result in false-positives. However, because not all recordings of the reference test (event recorder) were stored, as in our study, no direct comparison of ECG signals was possible. It is notable that Fredriksson et al. found no uninterpretable 1 L-ECG recordings. In contrast, we found 1 L-ECG recordings of 37% (n=24) of patients to be uninterpretable by our panel of cardiologists in the subset of patients with algorithm-positive 1 L-ECG recordings (n=65). The explanation of this finding is unclear.

Strengths and limitations

Our study has a number of strengths. Firstly, we used a continuous two-week Holter monitor, ensuring maximal ECG hearth rhythm recording, minimizing the chance of missing an episode of paroxysmal AF. This also enabled a direct comparison between ECG signals using either method (Holter monitor and 1 L-ECG device) in the same time frame, resulting in a fair assessment of the 1 L-ECG's diagnostic

accuracy. Secondly, we reported results at patient-level rather than at test level. Reporting results at patient-level best resembles daily clinical practice where any number of algorithm-positive 1 L-ECGs would render a patient potentially positive for paroxysmal AF, until visual assessment of the algorithm-positive 1 L-ECG's. As the MyDiagnostick 1 L-ECG device's built-in AF detection algorithm has a very high NPV but al low PPV (especially in low prevalence populations) our panel of cardiologists only assessed algorithm-positive 1 L-ECG recordings.[16, 22] Thirdly, we used cardiologists for outcome assessment of algorithm-positive 1 L-ECG recordings. We prioritized this 'best clinical practice' over optimally resembling a primary care setting in which GPs are the first to interpret the 1 L-ECG recordings. Finally, as the difference between the number of AF diagnosis as detected with Holter monitoring and the number of patients with algorithm-positive 1 L-ECGs was striking, we performed rigorous "post hoc" verification of the Holter monitoring results. Fragments of the Holter monitor's recordings were visually re-assessed within the time frames at which there were algorithm-positive 1 L-ECG recordings. No false-negative Holter monitoring results were found, confirming the robustness of the reference standard.

A number of limitations should also be mentioned. First, we included a selected population based on the results of the three baseline screening tests in the first part of the D_2AF study, followed by a relatively low proportion of patients who performed home recordings. Of the patients in our diagnostic accuracy analysis, 60% (124/205) had one or more positive baseline screening tests, as opposed to 12% (488/4106) in the total D_2AF population.[18] Our secondary outcome showed that specificity of the 1 L-ECG's algorithm was higher in patients with three negative baseline screening tests (85.9%), compared to patients with one or more positive baseline screening tests (58.1%), suggesting this may have led to an overestimation of the 1 L-ECG's false-positive rate. A second limitation is the low number of patients receiving a Holter monitor (n=270) compared to the number of eligible patients (n=777). Unfortunately we did not systematically evaluate the reason for not participating. We suppose this is partly because patients were simply not asked, otherwise it might be reasonable to suggest it seems patients experienced a threshold for participation. This may be because of the relatively high burden participation took for patients, being subjected to two interventions (Holter monitoring and 1 L-ECG recordings thrice daily for two weeks). This may also partially explain the relatively short duration of Holter monitoring (8.0 days), compared to the intended duration (14 days). A third limitation is that one might argue about the fact

that we used a two-lead Holter as reference standard. However, the two-lead Holter device we used is currently used for routine continuous cardiac rhythm monitoring at the department of cardiology at the Amsterdam University Medical Center. Moreover, the "post hoc" verification of our Holter monitoring results, in which fragments of the Holter monitor's recordings were visually re-assessed within the time frames at which there were algorithm-positive 1 L-ECG recordings, contained no false-negative Holter results at algorithm-positive 1 L-ECG recording's time-frames. A final limitation is that only three patients with simultaneous home recordings had AF on the Holter, resulting in large confidence intervals for our sensitivity calculation.

Clinical relevance

Population based single time point screening interventions for AF, in well-organized health care systems previously proved ineffective.[18, 23] The diagnostic yield of screening interventions for paroxysmal AF is scarcely investigated, whilst stroke risk of paroxysmal AF appears to be lower compared to persistent or permanent AF.[8, 24] Furthermore, screening for (paroxysmal) AF may well cause harm due to misdiagnosis and additional testing.[25] In this study we found a low prevalence of paroxysmal AF with prolonged ECG monitoring using a continuous Holter monitor among primary care patients, 65 years or older, with a negative baseline ECG during opportunistic single time point screening in the Netherlands. These results question to whether there is any added value of screening for paroxysmal AF in this population situated in a well-organized health care system.

This study also showed that intermittent screening with a MyDiagnostick 1 L-ECG device resulted in a high number of false-positives, even after visual assessment by cardiologists. Furthermore, the MyDiagnostick 1 L-ECG recordings of patients with algorithm-positive results were frequently considered uninterpretable by cardiologists (n=24/65). We therefore conclude the MyDiagnostick 1 L-ECG device is not useful for intermittent, ambulatory screening for paroxysmal AF in this population.

Future work

It might be possible that other 1 L-ECG devices lead to other results. Therefore, it is unclear to what extent our outcomes are limited by the strategy (intermittent screening) or by the device used (MyDiagnostick). Therefore, other 1 L-ECG devices and/or algorithms may show different diagnostic accuracy of an intermittent

screening strategy for paroxysmal AF. Topic for future investigation can be whether the presence of direct visual feedback of the 1 L-ECG signal, that some 1 L-ECG devices provide, enables users to improve signal quality and thereby interpretability. Validity, usability and efficiency of other non-invasive rhythm monitoring devices, like for example ECG patches, should also be explored. New screening studies using better risk stratification methods to pre-select patients at high risk not merely based on age, may help to increase the diagnostic yield of screening interventions using prolonged rhythm recordings.

Conclusion

Screening for paroxysmal AF using Holter monitoring in Dutch elderly primary care patients with a negative 12 L-ECG resulted in a low diagnostic yield. We do not recommend screening for paroxysmal AF in this population. The diagnostic accuracy of an intermittently used MyDiagnostick 1 L-ECG device was limited, with a high false-positive rate. The MyDiagnostick 1 L-ECG device is not useful for intermittent, ambulatory screening for paroxysmal AF in this population.

Declarations

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Competing interests

None of the authors report a conflict of interest. The authors had full autonomy in study design, conduct and reporting of the manuscript.

Ethical approval

The D_2AF study – this study being part of — was performed in accordance with the declaration of Helsinki and received approval by the medical ethical board of the Amsterdam UMC, location AMC (number NL48215.018.14). All patients gave written informed consent.

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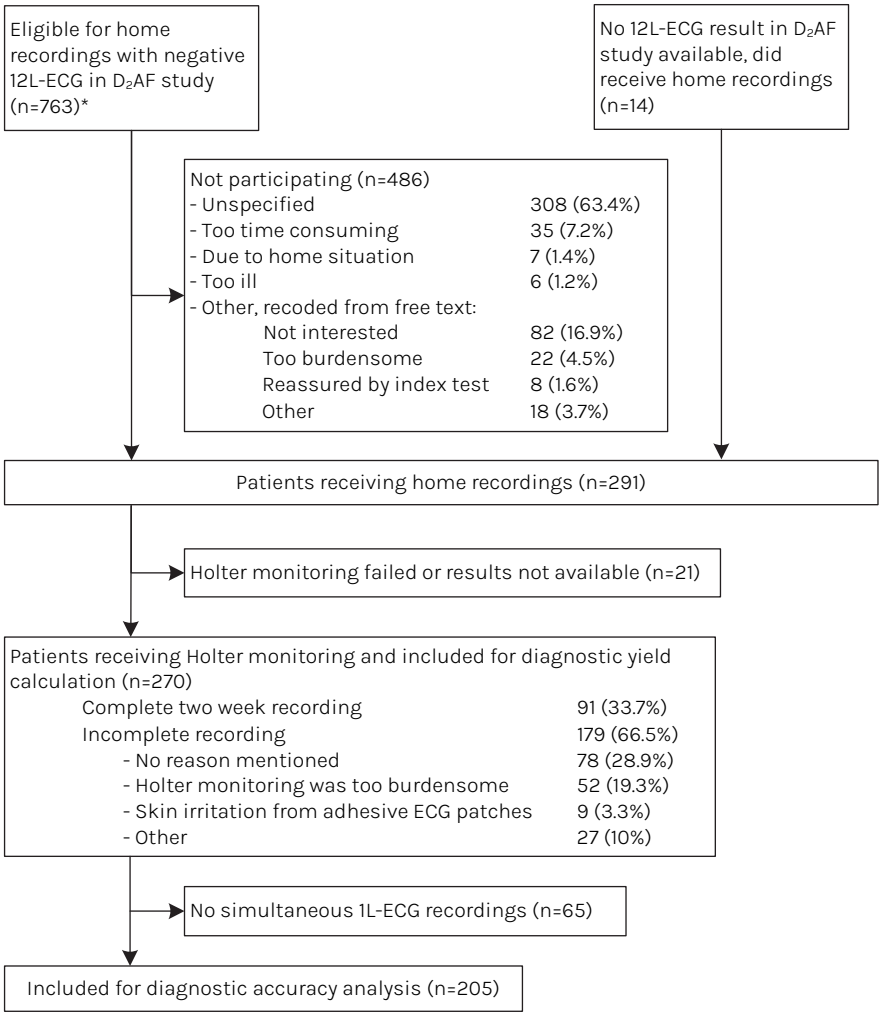
Appendix 1

Participants eligible for home recordings included in the current analysis



1L-ECG, single-lead electrocardiogram.

* In our previous work we presented the results of the randomised controlled trial, comparing the AF-detection rate of opportunistic screening with usual care (D_2AF study, Uittenbogaart et al. BMJ 2020). In that study, 716 patients had no AF on the 12L-ECG. In this study, we included an additional 61 patients (n=777). This is because 47 patients received home recordings >3 months after study completion and were therefore excluded from the previous analysis in the D_2AF study, while for this analysis, they were included. Furthermore, of 14 patients who received home recordings we could not retrieve a baseline 12L-ECG recording. Because none had (paroxysmal) AF on the Holter monitor, we assume they did not have AF on the 12L-ECG either, and we included them in this analysis.

Appendix 2

Intermittent 1L-ECG recordings as assessed by the built-in AF detection algorithm vs Holter monitoring at home to detect paroxysmal AF, stratified by baseline screening test results in the first part of the D_2AF study.

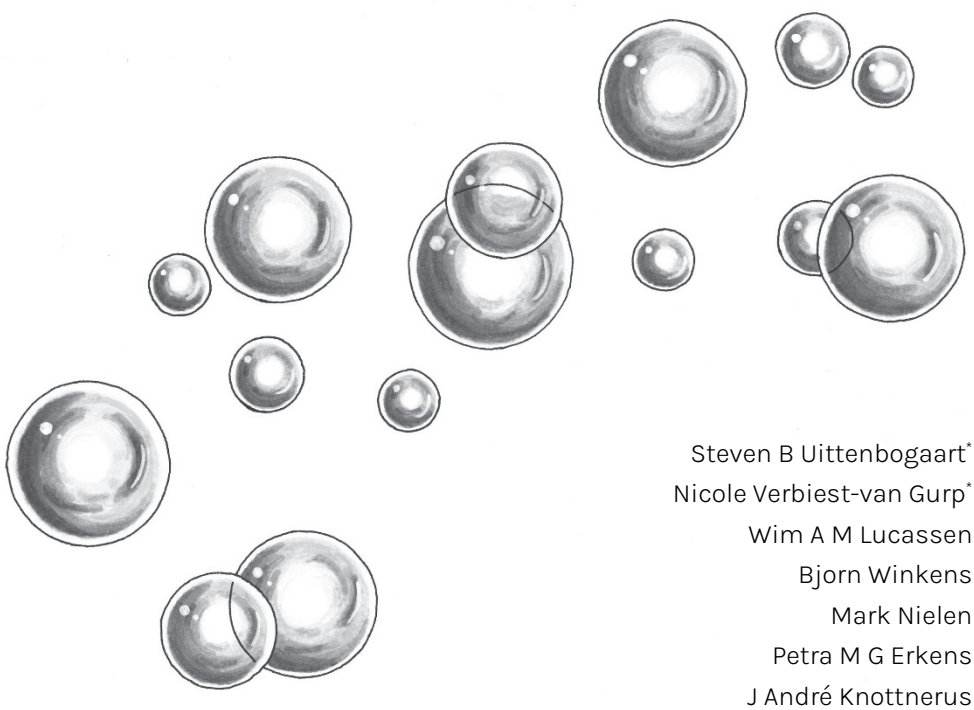
		Holter	
	1L-ECGs' algorithm	AF	No AF
Three negative baseline tests	AF	2	11
	No AF	1	67
One or more positive baseline tests	AF	0	52
	No AF	0	72

1L-ECG, single-lead electrocardiogram; AF, atrial fibrillation; D_2AF study: Detecting and Diagnosing Atrial Fibrillation study.

Baseline tests as performed in the D_2AF study: pulse palpation, electronic sphygmomanometer with built-in AF detection algorithm, and a 1L-ECG device with built-in AF detection algorithm.

Chapter 8

Opportunistic screening versus usual care for detection of atrial fibrillation in primary care: cluster randomised controlled trial



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Abstract

Objective

To investigate whether opportunistic screening in primary care increases the detection of atrial fibrillation compared with usual care.

Design

Cluster randomised controlled trial.

Setting

47 intention-to-screen and 49 usual care primary care practices in the Netherlands, not blinded for allocation; the study was carried out from September 2015 to August 2018.

Participants

In each practice, a fixed sample of 200 eligible patients, aged 65 or older, with no known history of atrial fibrillation in the electronic medical record system, were randomly selected. In the intention-to-screen group, 9218 patients eligible for screening were included, 55.0% women, mean age 75.2 years. In the usual care group, 9526 patients were eligible for screening, 54.3% women, mean age 75.0 years.

Interventions

Opportunistic screening (that is, screening in patients visiting their general practice) consisted of three index tests: pulse palpation, electronic blood pressure measurement with an atrial fibrillation algorithm, and electrocardiography (ECG) with a handheld single lead electrocardiographic device. The reference standard was 12 lead ECG, performed in patients with at least one positive index test and in a sample of patients (10%) with three negative tests. If 12 lead ECG showed no atrial fibrillation, patients were invited for more screening by continuous monitoring with a Holter electrocardiograph for two weeks.

Main outcome measures

Difference in the detection rate of newly diagnosed atrial fibrillation over one year in intention-to-screen versus usual care practices.

Results

Follow-up was complete for 8874 patients in the intention-to-screen practices and for 9102 patients in the usual care practices. 144 (1.62%) new diagnoses of atrial fibrillation in the intention-to-screen group versus 139 (1.53%) in the usual care group were found (adjusted odds ratio 1.06 (95% confidence interval 0.84 to 1.35)). Of 9218 eligible patients in the intention-to-screen group, 4106 (44.5%) participated in the screening protocol. In these patients, 12 lead ECG detected newly diagnosed atrial fibrillation in 26 patients (0.63%). In the 266 patients who continued with Holter monitoring, four more diagnoses of atrial fibrillation were found.

Conclusions

Opportunistic screening for atrial fibrillation in primary care patients, aged 65 and over, did not increase the detection rate of atrial fibrillation, which implies that opportunistic screening for atrial fibrillation is not useful in this setting.

What is already known on this topic

- In 2007, the SAFE study showed that opportunistic screening for atrial fibrillation over a year detected more new diagnoses than usual care
- Randomised trials replicating the effectiveness of screening are lacking
- The effectiveness of prolonged screening on clinical endpoints, such as stroke and death, is not known

What this study adds

- In primary care, opportunistic screening in patients aged 65 and over did not lead to a higher detection rate of atrial fibrillation compared with usual care

Introduction

Atrial fibrillation is a common cardiac arrhythmia and a major cause of stroke, heart failure, and other cardiovascular diseases.[1] The prevalence of atrial fibrillation increases with age, and with the ageing population, the burden of atrial fibrillation is growing rapidly.[2, 3] Treatment with oral anticoagulant drugs reduces the risk of stroke by 60%. In 25% of patients who have had a stroke, however, atrial fibrillation is not diagnosed until after the stroke.[4]

Patients with atrial fibrillation might present with symptoms such as palpitations, shortness of breath, light headedness, or dizziness. Physicians can detect an irregular heart rhythm by physical examination and can confirm atrial fibrillation with 12 lead electrocardiography (ECG).[5] But the possible paroxysmal character of atrial fibrillation and the occasional asymptomatic course of the condition can hamper detection.[6]

Screening for atrial fibrillation could increase early detection and subsequent treatment of atrial fibrillation, and prevent strokes, but community screening for atrial fibrillation is still controversial.[7, 8] Randomised trials comparing the results of screening with usual care are lacking. Trials evaluating the effect of treating atrial fibrillation detected by screening with oral anticoagulant agents are pending. The Screening for Atrial Fibrillation in the Elderly (SAFE) study is the only randomised controlled trial that has compared screening, by pulse palpation, with usual care, in a primary care population.[9] Both systematic (inviting the whole target population) and opportunistic (only screening patients who visited the practice) screening detected more new diagnoses than usual care (yearly incidence of atrial fibrillation

1.62% and 1.64% v 1.04%, respectively). The investigators preferred opportunistic screening because of the more labour intensive, costly, and intrusive approach of systematic screening.

Since the publication of the SAFE study in 2007, numerous devices have been developed to screen for atrial fibrillation (eg, electronic blood pressure monitors with an atrial fibrillation detection function and handheld single lead electrocardiographic devices).[10] We performed the Detecting and Diagnosing Atrial Fibrillation (D_2AF) study to investigate whether opportunistic screening in primary care patients increased the detection of atrial fibrillation compared with usual care.[11] Three methods were used to detect atrial fibrillation: pulse palpation, electronic blood pressure measurement with an atrial fibrillation algorithm, and ECG with a handheld single lead electrocardiographic device. Also, we explored the added value of continuous Holter monitoring for two weeks.

Methods

Trial design

We performed a cluster randomised controlled trial comparing opportunistic screening of atrial fibrillation with usual care. The study was carried out for one year in each practice, after which we compared the number of new diagnoses of atrial fibrillation in the intention-to-screen with the usual care practices. We published the study protocol previously.[11]

Practices and randomisation

We recruited primary care practices, located throughout the Netherlands, within the networks of the two participating universities and the Dutch Nivel Primary Care Database.[12] We used computerised randomisation in permuted blocks of random sizes (four, six, and eight). We stratified on region (north or south) and the pre-existing prevalence of atrial fibrillation in all patients in the practice aged 65 and over (the cut-off was 8.05%, based on the prevalence of atrial fibrillation in 2015 in a group of primary care practices associated with the two universities conducting this study). We used the pre-existing prevalence of atrial fibrillation as a marker of the risk of atrial fibrillation in the practice population and the awareness of the general practitioner in detecting atrial fibrillation. Practices were not blinded for allocation.

Selected patients

In each practice, we randomly selected and marked a fixed sample of 200 patients eligible for opportunistic screening, aged 65 or older, with no known history of atrial fibrillation in the electronic medical record system. We used the International Classification of Primary Care codes to exclude patients with a history of atrial fibrillation (K78) and to determine baseline information on relevant morbidities.[13]

Intention-to-screen practices

We provided practices with an electronic blood pressure monitor with an atrial fibrillation detection function (WatchBP Home A, Microlife, Widnau, Switzerland), two handheld single lead electrocardiographic devices (MyDiagnostick, MyDiagnostick Medical, Maastricht, Netherlands), and ECG and Holter equipment (multichannel Holter electrocardiograph recorder model H2, Fysiologic, Amsterdam, Netherlands). The secondary investigators (practice nurse, practice assistant, general practitioner) were trained on the use of the study software and equipment and given instructions on pulse palpation. We instructed practices to ask eligible patients to participate in the study when they visited the practice in the study year. When the physician (or other practice staff) opened the electronic medical record of a marked patient, a notification on their computer screen alerted them that the patient was selected for screening for atrial fibrillation. Patients were not eligible if they had a pacemaker or an implantable cardioverter defibrillator, could not provide informed consent, had a terminal illness, or could not visit the practice.

After obtaining written consent, the secondary investigator collected information (at that visit or at a later visit) on symptoms related to atrial fibrillation and performed the three index tests: palpation of the radial pulse was always performed first, followed by an electronic blood pressure monitor with an atrial fibrillation detection function, and ECG with the handheld device, in a preset alternating order. We instructed the secondary investigators to palpate the radial pulse for a minimum of 15 seconds; any irregularity was regarded as a positive test. For both electronic devices, we used the automated algorithm for detection of atrial fibrillation: a blinking AFIB icon on the electronic blood pressure monitor and a red indicator light on the device.

Patients with at least one positive index test, and a random sample of patients (10%; generated by the study software) with three negative index tests underwent 12 lead ECG as the reference standard for atrial fibrillation. We instructed the investigators to perform 12 lead ECG immediately after the index tests. The results of the ECG were

transferred digitally and evaluated by an experienced assessor, supervised by a cardiologist. A second cardiologist re-evaluated all electrocardiograms. In the event of disagreement, a third cardiologist decided on the diagnosis. The general practitioner's office received the electrocardiogram and a report of the assessment by the cardiologist.
We invited patients in whom 12 lead ECG showed no atrial fibrillation to undergo continuous Holter recording for two weeks.

Usual care practices
In the usual care practices, the secondary investigators and patients were unaware of which 200 patient records were selected. During recruitment, we informed all practices about the aim of the study but did not provide equipment or training. During the study year, the practice could not participate in other screening activities related to atrial fibrillation.

Usual care in the Netherlands
The guideline for atrial fibrillation from the Dutch College of General Practitioners recommends assessing heart rhythm in every patient with shortness of breath, reduced ability to exercise, palpitations, dizziness, light headedness, syncope, chest pain, and transient ischaemic attack or stroke, as part of the usual diagnostic work-up. Further recommendations are to assess the heart rhythm in each patient when measuring blood pressure.[14] Systematic screening is not recommended. In the past few years, structured disease management programmes were introduced in Dutch general practice. Patients with a cardiovascular disease, diabetes, or chronic respiratory disease, or with a risk factor for these diseases, could participate in the programmes and visit the practice at least once a year. During these visits, the heart rhythm was assessed with pulse palpation or sometimes with an electrocardiograph.[15]

Diagnosis of atrial fibrillation
Three months after the end of the study year, in the intention-to-screen and usual care practices, we extracted the International Classification of Primary Care codes for atrial fibrillation and related diagnoses (that is, palpitations, irregular pulse, paroxysmal tachycardia, extrasystoles, transient ischaemic attack, and stroke) from the electronic medical records of the marked patients. We accepted a diagnosis of atrial fibrillation if it was confirmed by ECG, in primary or secondary

care. We also accepted a description of the diagnosis of atrial fibrillation in a hospital letter. We only included diagnoses within the study year. If a diagnosis preceded the start of the study, we excluded these patients from the analyses (eg, if the diagnosis of atrial fibrillation was miscoded in the electronic medical record or if a hospital letter with a diagnosis of atrial fibrillation preceding the start of the study arrived late). Follow-up was incomplete if the patient died, or if they unregistered or moved away from the practice during the study year.

Outcome and sample size

Our primary outcome was the difference in the number of patients with newly diagnosed atrial fibrillation during the study year between the intention-to-screen and usual care practices. We based our sample size on a yearly incidence of new atrial fibrillation of 1.3%,[16] a minimum detectable odds ratio of 1.8 of identifying new atrial fibrillation by opportunistic screening versus usual care, and 80% power at a significance level of 5%.[9, 17, 18] Given a calculated design effect of 2.99 based on fixed cluster sizes of 200 patients and an intracluster correlation coefficient of 0.01,[19, 20] a minimum of 8076 patients in each study arm was required. We corrected for a loss to follow-up of 15%. Thus 96 clusters of 200 patients were required, a total of 19 200 patients.

Statistical methods

We assessed the difference in detection rate of atrial fibrillation with logistic mixed effects models with a random intercept on general practice to account for clustering of patients within a practice. For the intention-to-screen analysis, the fixed part of the model consisted of group (intention to screen v usual care) and stratification variables (that is, prevalence of atrial fibrillation and region). For the sensitivity analysis, we performed multiple imputation of missing outcome data where the missing outcome was imputed with group, age, sex, and stratification variables. After the creation of five complete datasets by multiple imputation with 20 iterations, we compared the pooled results with the original analysis.

In an ad hoc per protocol analysis, we compared patients who were screened with patients who received usual care. We performed similar analyses but we also corrected for potential confounders: age (in years), sex (male or female), and history of hypertension, diabetes mellitus, stroke (transient ischaemic attack and stroke), thromboembolism, and heart failure. Also, we assessed whether atrial fibrillation was detected earlier in the intention-to-screen group than in the usual care group,

by performing a survival analysis (Kaplan-Meier curves, log rank tests, and Cox regression analysis with the same fixed variables). In this sensitivity analysis, (censored) time to atrial fibrillation was defined as the difference between inclusion date and date of detection of atrial fibrillation, death, lost to follow-up, or end of the study year, whichever occurred first.

Continuous variables are reported as mean (standard deviation), and categorical variables as numbers and percentages. A two sided P value of 0.05 or less was considered statistically significant. We used IBM SPSS Statistics for Windows (version 25.0, IBM, Armonk, NY) for all analyses, except for the logistic mixed effects models, which we assessed with the glmer package with RStudio (version 1.2.5019, RStudio, Boston, MA).

Patient and public involvement

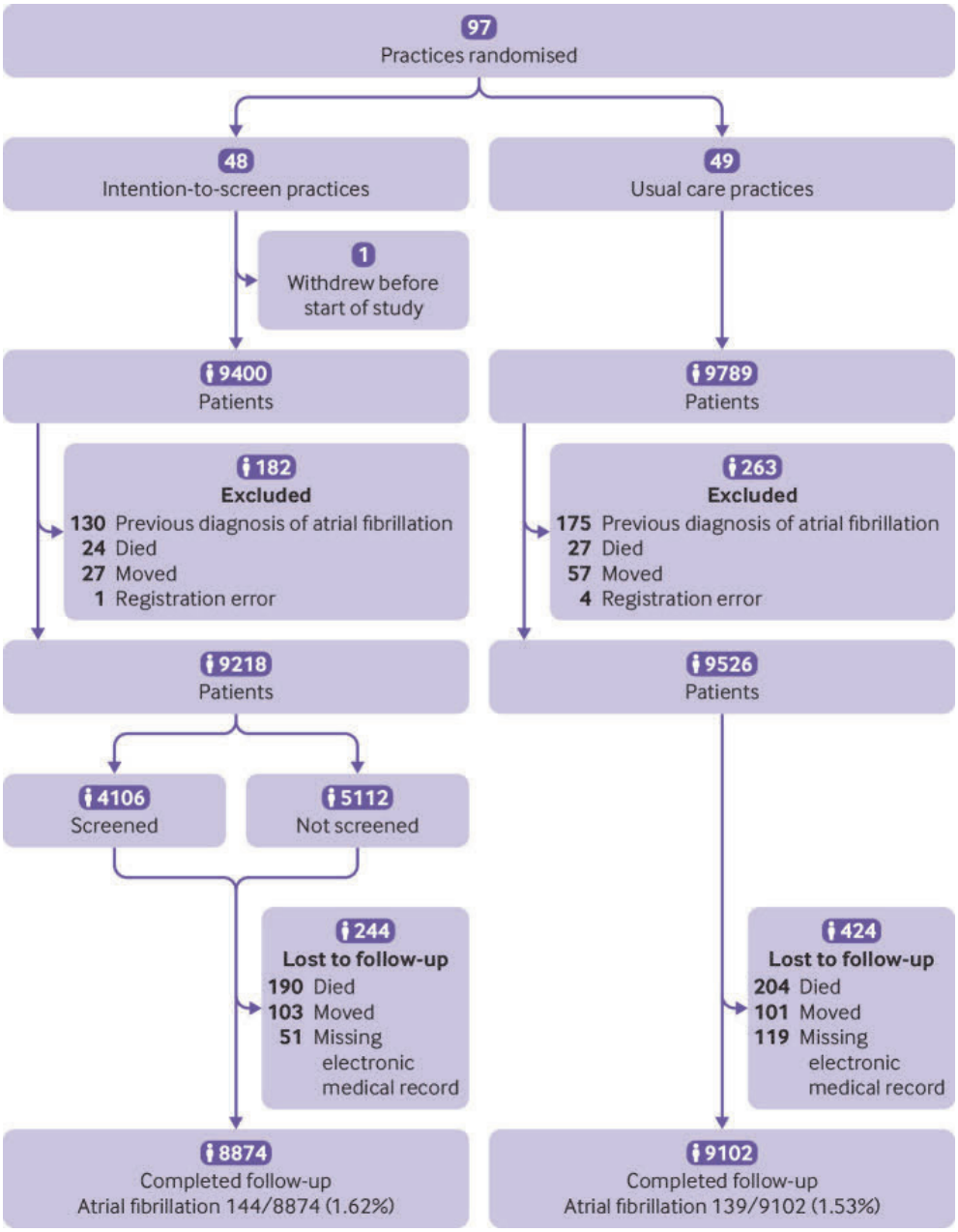
Patient influence on research design, methodology, and execution: none. At the time of the study design, the funding organisation did not request explicit public or patient involvement in clinical studies in general practice. But patient representatives participated in scientific committees that judged eligibility for funding.

Results

Initially, we recruited 97 general practices in the Netherlands, and randomisation resulted in 48 intention-to-screen and 49 usual care practices. One intention-to-screen practice withdrew directly after randomisation. Thus 96 primary care practices participated in the study. In one small practice, only 189 patients were potentially eligible, resulting in 19 189 patients.

The study was carried out between September 2015 and August 2018. After data collection had ended, we detected 130 and 175 patients with a diagnosis of atrial fibrillation preceding the start of the study year that was not known at the time of selection in the intention-to-screen and usual care practices, respectively. We excluded these patients from the analyses. Thus 9218 and 9526 eligible patients in the intention-to-screen and usual care groups, respectively, were included in the analyses (figure 1).

Figure 1 Flowchart of enrolment of primary care practices (clusters) and patients in the study



Baseline characteristics

Baseline prevalence of atrial fibrillation in patients aged 65 or older was comparable in the intention-to-screen and usual care practices (10.1% and 10.0%, respectively). The mean baseline prevalence of atrial fibrillation was higher than the stratification threshold of 8.05%; in 83 of 96 practices, the prevalence was greater than 8.05%. At baseline, mean age was 75.2 (standard deviation 6.8) years in the intention-to-screen group and 75.0 (6.9) years in the usual care, and most patients were women (55.0% and 54.3%, respectively). Comorbidities were equally distributed across the groups (table 1). In the intention-to-screen group, the screened population was younger than those not screened (73.5 (5.5) years v 76.6 (7.3) years, P<0.001), and the screened population had fewer comorbidities, including stroke and transient ischaemic attack (7.7% v 11.3%, P<0.001) and heart failure (1.8% v 5.4%, P<0.001). Only hypertension was more frequent in the screened population (51.2% v 48.3%, P=0.006).

Table 1 Baseline characteristics of patients included in the Detecting and Diagnosing Atrial Fibrillation (D_2AF) study

	Usual care	Intention to screen			
		Total	Screened	Not screened	P value*
No	9526	9218	4106	5112	—
Age (mean (SD))	75.0 (6.9)	75.2 (6.8)	73.5 (5.5)	76.6 (7.3)	<0.001†
Women (No (%))	5177 (54.3)	5071 (55.0)	2196 (53.5)	2875 (56.2)	0.008‡
Hypertension (No (%))	4579 (48.7)	4540 (49.6)	2098 (51.2)	2442 (48.3)	0.006‡
Stroke or transient ischaemic attack (No (%))	911 (9.7)	886 (9.7)	315 (7.7)	571 (11.3)	<0.001‡
Diabetes (No (%))	1750 (18.6)	1768 (19.3)	732 (17.9)	1036 (20.5)	0.002‡
Heart failure (No (%))	362 (3.9)	348 (3.8)	75 (1.8)	273 (5.4)	<0.001‡
Thromboembolism (No (%))	431 (4.6)	460 (5.0)	191 (4.7)	269 (5.3)	0.15‡

SD=standard deviation. International Classification of Primary Care codes were used: for hypertension K86 or K87, or both; for stroke K90; for transient ischaemic attack K89; for diabetes T90; for heart failure K77; and for thromboembolism K93 or K94, or both. For intention to screen and usual care, 62 patients (0.7%) and 127 (1.3%) had missing values for all comorbidities.

* Screened versus not screened in the intention-to-screen group.

† Independent sample t test.

‡ Pearson $\chi 2$ test.

Table 2 Intention to screen versus usual care primary outcome and post hoc analyses

Analysis	Group	Intention to screen (newly diagnosed atrial fibrillation/all patients (No))	Usual care (newly diagnosed atrial fibrillation/all patients (No))	Odds ratio or hazard ratio (95% CI)	P value
Primary analysis	Intention to screen	144/8874	139/9102	1.06* (0.84 to 1.35)	0.60
Primary analysis	Per protocol	48/4085	139/9102	0.86* (0.61 to 1.20)	0.36
Multiple imputation	Intention to screen	N/A	N/A	1.04* (0.82 to 1.31)	0.75
Multiple imputation	Per protocol	N/A	N/A	0.86* (0.61 to 1.20)	0.37
Cox regression (time to atrial fibrillation)	Intention to screen	144/8874	139/9102	1.06† (0.84 to 1.34)	0.61
Cox regression (time to atrial fibrillation)	Per protocol	48/4085	139/9102	0.86† (0.62 to 1.20)	0.38

N/A=not available. Intention-to-screen analyses were adjusted for stratification variables (prevalence of atrial fibrillation and region). Per protocol analyses were also adjusted for age (in years), sex (male or female), and history of hypertension, diabetes mellitus, stroke (transient ischaemic attack or stroke), thromboembolism, and heart failure. Although a random intercept was included to adjust for clustering of patients in a care practice, the estimated intraclass correlation was 0. For multiple imputation, we imputed the outcome with group, age, sex, and stratification variables.
* Odds ratio. †Hazard ratio.

Intention to screen versus usual care

Complete follow-up data were available for 8874 patients (96.3%) in the intention-to-screen group and for 9102 patients (95.5%) in the usual care group (figure 1). After one year, we found 144 (1.62%) patients with newly diagnosed atrial fibrillation in the intention-to-screen group and 139 (1.53%) in the usual care group (odds ratio 1.06, 95% confidence interval 0.84 to 1.35, corrected for clustering and stratification variables) (figure 1). In the per protocol group, (that is, those who were screened with the intervention protocol), we found 48 new diagnoses of atrial fibrillation, 26 detected by opportunistic screening, four by Holter monitoring, and 18 during usual care. We found an incidence of 1.18% in the per protocol group versus 1.53% in the usual care group (adjusted odds ratio 0.86, 95% confidence interval 0.61 to 1.20). The results before and

after multiple imputation were similar, and the Cox regression analysis showed no significant difference in time to detection of atrial fibrillation for the intention-to-screen and per protocol analyses (table 2).

Atrial fibrillation detected with the screening protocol

In the intention-to-screen group, 4106 of 9218 patients (44.5%) participated in the screening protocol. The percentage of screened patients varied between practices, ranging from 6.7% to 65.8%. Two practices discontinued screening during the study year because of organisational issues; both were included in the analysis.

Of 488 patients with at least one positive index test, 12 lead ECG was performed in 448 patients (figure 2). The median time between the first index test and 12 lead ECG

Figure 2 Flowchart of the results of the screening intervention (n=4106). In 488 patients, electrocardiography (ECG) was required according to the protocol because the patient had at least one positive index test. An electrocardiogram was missing in 40 patients because of technical or organisational difficulties, or refusal of the patient. Of 3618 patients with three negative index tests, 294 were randomised to 12 lead ECG. Of 294 (with three negative index tests) and 422 (with at least one positive index test) patients who had a negative electrocardiogram, 266 continued with Holter monitoring for two weeks

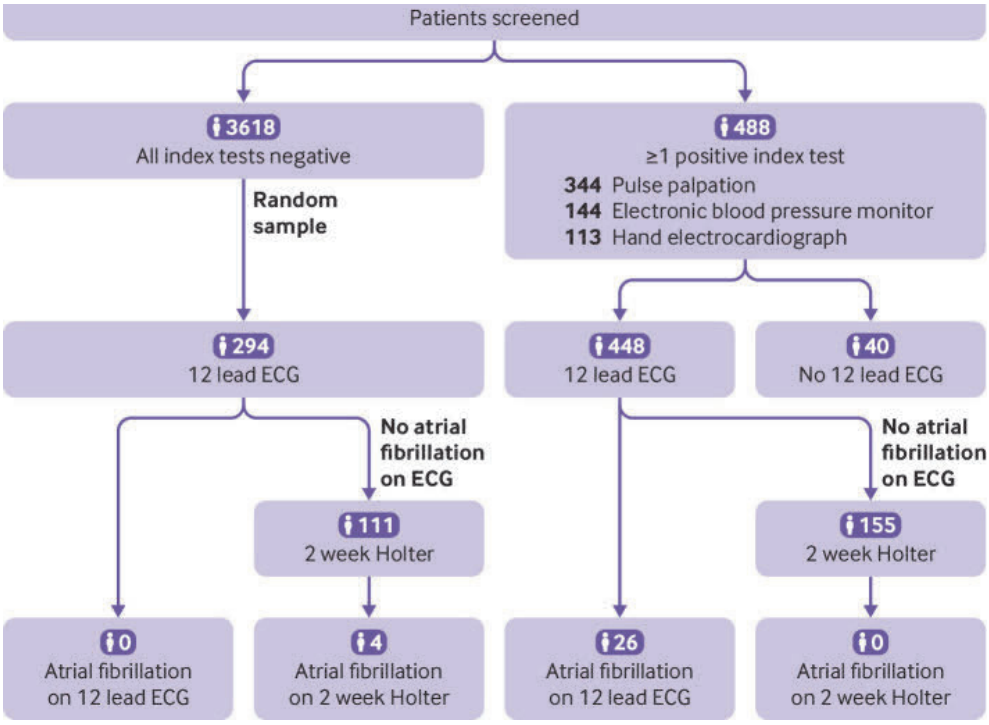


Table 3 Characteristics of patients with newly diagnosed atrial fibrillation

	Intention to screen		Usual care		Detected by one time point screening	
	Female	Male	Female	Male	Female	Male
No	67	77	68	71	9	17
Age (mean (SD))	79.8 (7.8)	76.2 (6.8)	78.3 (7.4)	76.6 (7.1)	75.6 (5.6)	73.5 (5.2)
65-75 (No (%))	23 (34.3)	36 (46.8)	27 (39.7)	31 (43.7)	5 (55.6)	10 (58.8)
75-85 (No (%))	22 (32.8)	34 (44.2)	25 (36.8)	30 (42.3)	3 (33.3)	7 (41.2)
>85 (No (%))	22 (32.8)	7 (9.1)	16 (23.5)	10 (14.1)	1 (11.1)	0
Hypertension (No (%))	49 (73.1)	40 (51.9)	47 (69.1)	31 (43.7)	6 (66.7)	8 (47.1)
Stroke or transient ischaemic attack (No (%))	9 (13.4)	11 (14.3)	15 (22.1)	7 (9.9)	0	0
Diabetes (No (%))	15 (22.4)	20 (26.0)	21 (30.9)	16 (22.5)	1 (11.1)	2 (11.8)
Heart failure (No (%))	7 (10.4)	5 (6.5)	9 (13.2)	7 (9.9)	1 (11.1)	1 (5.9)
Thromboembolism (No (%))	4 (6.0)	5 (6.5)	5 (7.4)	2 (2.8)	0	0
CHA_2DS_2-VASc score (No (%))*						
Score 1	0	10 (13.0)	0	5 (7.0)	0	6 (35.3)
Score 2	4 (6.0)	18 (23.4)	11 (16.2)	22 (31.0)	2 (22.2)	3 (17.6)
Score 3	21 (31.3)	21 (27.3)	13 (19.1)	21 (29.6)	2 (22.2)	5 (29.4)
Score 4	22 (32.8)	16 (20.8)	15 (22.1)	9 (12.7)	4 (44.4)	3 (17.6)
Score 5	8 (11.9)	6 (7.8)	15 (22.1)	10 (14.1)	0	0
Score ≥6	12 (17.9)	6 (7.8)	14 (20.5)	4 (5.6)	1 (11.1)	0

SD=standard deviation. International Classification of Primary Care codes were used.

* The CHA_2DS_2-VASc score is used to predict thromboembolic risk in atrial fibrillation. CHA_2DS_2 = Congestive heart failure, Hypertension, Age (>65=1 point, >75=2 points), Diabetes, previous Stroke, or transient ischemic attack (2 points); VASc = vascular disease (peripheral arterial disease, previous myocardial infarction, aortic atheroma), and sex category (female gender) is also included in the scoring system. CHA_2DS_2-VASc score was determined at the time of diagnosis.

was 26 minutes. In 40 patients, no electrocardiogram was obtained because of technical or organisational issues, or refusal of the patient. Also, ECG was performed in 294 (8.1%) of 3616 patients with three negative index tests. Of 4106 patients screened, we found 26 patients with atrial fibrillation diagnosed by 12 lead ECG (0.63%), all of whom had at least one positive index test. For patients with a negative electrocardiogram, 266 patients (37.2% (266/716)) continued with Holter monitoring

for two weeks; four more new diagnoses of atrial fibrillation were detected (1.50% (4/266)).
Most patients with atrial fibrillation detected by screening were men. Six men had a CHA_2DS_2-VASc score of one (table 3). All other patients had a score of two or more. Patients with atrial fibrillation detected by screening were younger than those found during usual care in both the intention-to-screen and usual care practices (table 3).

Discussion

In this cluster randomised controlled trial, opportunistic screening in primary care patients, aged 65 and over, did not increase the detection of previously unknown atrial fibrillation.

Comparison with the literature

Our results differed from the SAFE study where more diagnoses of atrial fibrillation were detected by screening than usual care (1.63% v 1.04%, difference=0.59%, 95% confidence interval 0.20 to 0.98).[9] Our results are in line with the Improving Detection of Atrial Fibrillation in Primary Care with the MyDiagnostick (IDEAL-MD) trial, also conducted in the Netherlands, which did not detect more new diagnoses of atrial fibrillation by opportunistic screening than usual care (1.43% v 1.37%, P=0.73).[21]
Why did we not detect more new diagnoses of atrial fibrillation with our extensive and sensitive screening protocol? One reason might be the younger age of the screened patients because the detection rate is dependent on the age of the population.[22] Also, the baseline prevalence of atrial fibrillation in the participating centres (10.1%) was higher than in the Rotterdam study (8.1%) and the SAFE study (6.9-7.9%), and much higher than the prevalence reported in a systematic review (4.4%).[2, 9, 23] The high baseline prevalence of atrial fibrillation in our study strongly suggests that detection of atrial fibrillation is already high in usual care in the Netherlands. The high incidence of atrial fibrillation in the usual care practices (1.53% v 1.04% in the SAFE study) supports this view[9] and might be explained by several reasons. Firstly, the introduction of the new oral anticoagulant agents in the past decade has raised awareness of the importance of timely detection of unknown atrial fibrillation. Secondly, most primary care practices in the Netherlands have introduced cardiovascular disease management programmes

where the heart rhythm of patients is checked during visits. Thirdly, participating general practitioners might have had more interest in cardiovascular care than their non-participating colleagues. Finally, awareness of atrial fibrillation could have been raised by participating in a study about atrial fibrillation, the so-called Hawthorne effect.[24] We tried to minimise this effect by blinding usual care practices to the selected patients in the practice.

Holter monitoring for two weeks detected a further 1.5% of new diagnoses of atrial fibrillation. Our findings showed that one time point screening missed silent and paroxysmal atrial fibrillation. Our results are in line with the Mass Screening for Untreated Atrial Fibrillation (STROKESTOP) and Akershus Cardiac Examination 1950 (ACE 1950) studies, which screened patients aged 75 and 65, respectively, with twice daily intermittent ECG for two weeks.[25, 26] In both studies, the detection rate at the index visit was 0.5%. After two weeks of screening, a further 2.5% (in the STROKESTOP study) and 0.9% (in the ACE 1950 study) new diagnoses were detected. In the mHealth Screening to Prevent Strokes (mSToPS) trial (mean age 73.5), a two week monitoring period with a Holter patch without an index visit detected new atrial fibrillation in 4.7% of patients (43/906).[27]

Strengths and weaknesses

The intervention practices screened only 45% of eligible patients. This inclusion rate was higher than in the ThermoCool SmartTouch Catheter for the Treatment of Symptomatic Paroxysmal Atrial Fibrillation (AF-SMART) and IDEAL-MD studies, but lower than in the SAFE study.[9, 21, 28] We believe that the low inclusion rate was more likely because of organisational issues rather than patients not willing to participate. Despite our efforts to facilitate the study procedures, the study protocol was time consuming (three measurements, followed by ECG) and was executed during clinical hours in primary care practices with a high workload. We did not design the screening protocol with three index tests to implement in its entirety in primary care, however, but for maximum sensitivity and to establish the test characteristics of the new technologies. Future studies on screening procedures should aim to minimise the extra burden caused by the study design. Also, we selected a random sample of primary care patients, with no pre-selection by the physician, which increased the generalisability of our findings to the whole population, but also meant that a proportion of the selected patients were not eligible for screening because they could not visit the practice (eg, because they were frail) or for other reasons (eg, they had a pacemaker). The patients that

participated in opportunistic screening were younger and had fewer comorbidities (so-called worried well) than patients who were not screened. Because the prevalence of atrial fibrillation increases with age, this might have led to an underestimation of the potential for screening when looking at the primary care population as a whole.

Although the percentage of screened patients was relatively low, the follow-up of a positive index test with 12 lead ECG was high compared with the follow-up in the SAFE study (92% v 66%). In 40 patients with at least one positive index test, the required 12 lead ECG was missing. Visual inspection of the 40 single lead electrocardiogram recordings (after the end of the study and not part of the reference standard) did not suggest additional diagnoses of atrial fibrillation.

Unfortunately, only a small number of patients were willing to undergo Holter monitoring, possibly because of the inconvenience of wearing a device for two weeks. Our study was powered to evaluate opportunistic screening of patients visiting their general practitioner and the added diagnostic power of continuous screening was not taken into account in our power calculation.

Implications and future research

The results of our study are likely applicable to other well organised primary care populations outside of the Netherlands. In areas where a larger percentage of unknown atrial fibrillation is likely to be prevalent, opportunistic screening of atrial fibrillation might still be effective. Nevertheless, doctors' awareness of the importance of timely detection of atrial fibrillation is necessary. Future research on screening for atrial fibrillation should focus on the selection of patients with the highest risk of having or developing undetected atrial fibrillation and the role of repeated or prolonged monitoring. The uptake of continuous rhythm monitoring as a means of screening for atrial fibrillation might be more effective with new and wireless technologies, such as smart watches or wireless patches.[29]

Conclusion

An extensive opportunistic screening protocol did not increase the detection of atrial fibrillation compared with usual care in patients aged 65 and over.

Declarations

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: support from the Netherlands Organisation for Health Research and Development and Amsterdam Universities Medical Centres for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Data sharing

Relevant anonymised patient level data are available on reasonable request.

Ethical approval

The medical research ethics committee of the Amsterdam University Medical Centre (Amsterdam UMC), Amsterdam, approved the trial (14 November 2014, No NL48215.018.14). The D_2AF study is registered at the Netherlands Trial Register (NTR reference No NL4776 (old NTR4914)).

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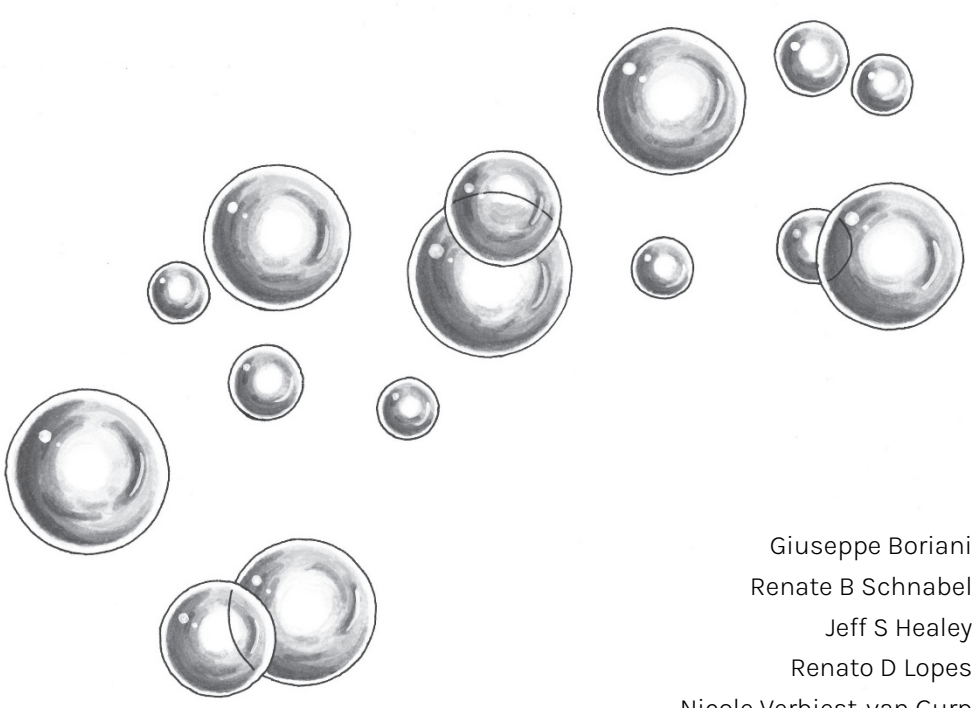
Chapter 9

Consumer-led screening for atrial fibrillation using consumer-facing wearables, devices and apps: A survey of health care professionals by AF-SCREEN international collaboration



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Abstract

Aim

A variety of consumer-facing wearables, devices and apps are marketed directly to consumers to detect atrial fibrillation (AF). However, their management is not defined. Our aim was to explore their role for AF screening via a survey.

Methods and Results

An anonymous web-based survey was undertaken by 588 health care professionals (HCPs) (response rate 23.7%). Overall, 57% HCPs currently advise wearables/apps for AF detection in their patients: this was much higher for electrophysiologists and nurses/allied health professionals (74–75%) than cardiologists (57%) or other physicians (34–38%). Approximately 46% recommended handheld (portable) single-lead dedicated ECG devices, or, less frequently, wristband ECG monitors with similar differentials between HCPs. Only 10–15% HCPs advised photoplethysmographic wristband monitors or smartphone apps. In over half of the HCP consultations for AF detected by wearables/apps, the decision to screen was entirely the patient's. About 45% of HCPs perceive a potential role for AF screening in people aged >65 years or in those with risk factors. Almost 70% of HCPs believed we are not yet ready for mass consumer-initiated screening for AF using wearable devices/apps, with patient anxiety, risk of false positives and negatives, and risk of anticoagulant-related bleeding perceived as potential disadvantages, and perceived need for appropriate management pathways.

Conclusions

There is a great potential for appropriate use of consumer-facing wearables/apps for AF screening. However, it appears that there is a need to better define suitable individuals for screening and an appropriate mechanism for managing positive results before they can be recommended by HCPs.

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia diagnosed in clinical practice, with an incidence that increases in the elderly[1, 2] and a prevalence of diagnosed AF that is progressively increasing and is expected to further expand in the next decades in view of progressive aging of the population and exposure to risk factors and facilitating factors.[3, 4]

AF is associated with significant morbidity and mortality and is an important risk factor for ischemic stroke, particularly in the elderly.[5] AF is frequently asymptomatic, particularly in the elderly,[6] and asymptomatic AF is associated with a worse outcome as compared to symptomatic AF, both in terms of risk of stroke and mortality.[6, 7]

Since nearly one in five AF-related ischemic strokes may occur without a diagnosis of AF prior to the stroke event[8] there is growing interest in the identification of patients with unrecognized, unknown asymptomatic AF through screening initiatives[9, 10] with consequent institution of oral anticoagulants in patients at risk. It is well known that in AF, oral anticoagulation (OAC) is able to reduce the risk of stroke by more than 60%.[11]

Pulse palpation has been the first and simplest method proposed for AF screening, followed by automatic blood pressure devices with dedicated algorithms for detecting AF, but more recently several new methods and tools have been proposed, with an impressive variety of technologies based on plethysmography or single-lead ECG, also implemented in wearables (smartphones, watches etc.).[12-14] In 2017 it was reported that more than 100,000 mobile Health apps and K400 wearable activity monitors were available for cardiac rhythm check or monitoring and that more than 60% of owners of a smartphone use their phone for information and education about their health.[15]

The wide debate focused on benefits, efficacy and limitations of screening initiatives[16-19] prompted us to propose an on-line survey to explore current views, current practice and related organizational issues on AF screening using the most advanced technologies implemented in watches, smartphones and other devices, usually named “wearables”.[20]

Questions in the survey were designed to elucidate how health care professionals perceive the significance of AF screening through wearables, in what settings it may be considered as appropriate and useful, what is the current status of referral and what are the potential developments in the field.

Methods

The survey was distributed in two steps. First the invitation to participate in this anonymous, web-based survey was sent in December 2019 by email to all 177 members of the AF-SCREEN International Collaboration, a group created in 2016 to promote discussion and research about screening for unknown or under-treated atrial fibrillation as a way to reduce stroke and death (http://www.afscreen.org/).[12, 21, 22] In January and February 2020, the same invitation was distributed through e-mails, in two rounds, by AF-SCREEN members to a "convenience sample" of colleague health care professionals (HCPs), physicians, nurses or allied health professionals involved in care of patients with arrhythmias or stroke, including cardiologists, electrophysiologists, neurologists, internal medicine physicians or geriatricians, primary care physicians/general practitioners (PCP/GPs), nurses, pharmacists or other allied health professionals, as shown in Table 1. The analysis of the survey was managed in an anonymous way. Despite anonymity, the question on field of work was answered by 475 respondents: of the 113 respondents who did not answer this question, 23 were members, and 90 were non-members. In this report we will present numbers and percentages for answers to each of the survey questions.

Table 1 Survey respondent field of work (N = 475).

	Whole Group (N = 475)	AF SCREEN Members (N = 96)	Non Members (N = 379)
Category	%	%	%
Electrophysiologist	37.1	38.6	36.7
General cardiologist	17.7	28.1	15.0
Neurologist/stroke physician	4.0	12.5	1.8
Primary care physician/general practitioner	24.0	10.4	27.5
Internal medicine physician/geriatrician	2.9	5.2	2.4
Nurse/allied health professional	11.4	4.2	13.2
Other	2.9	1	3.4

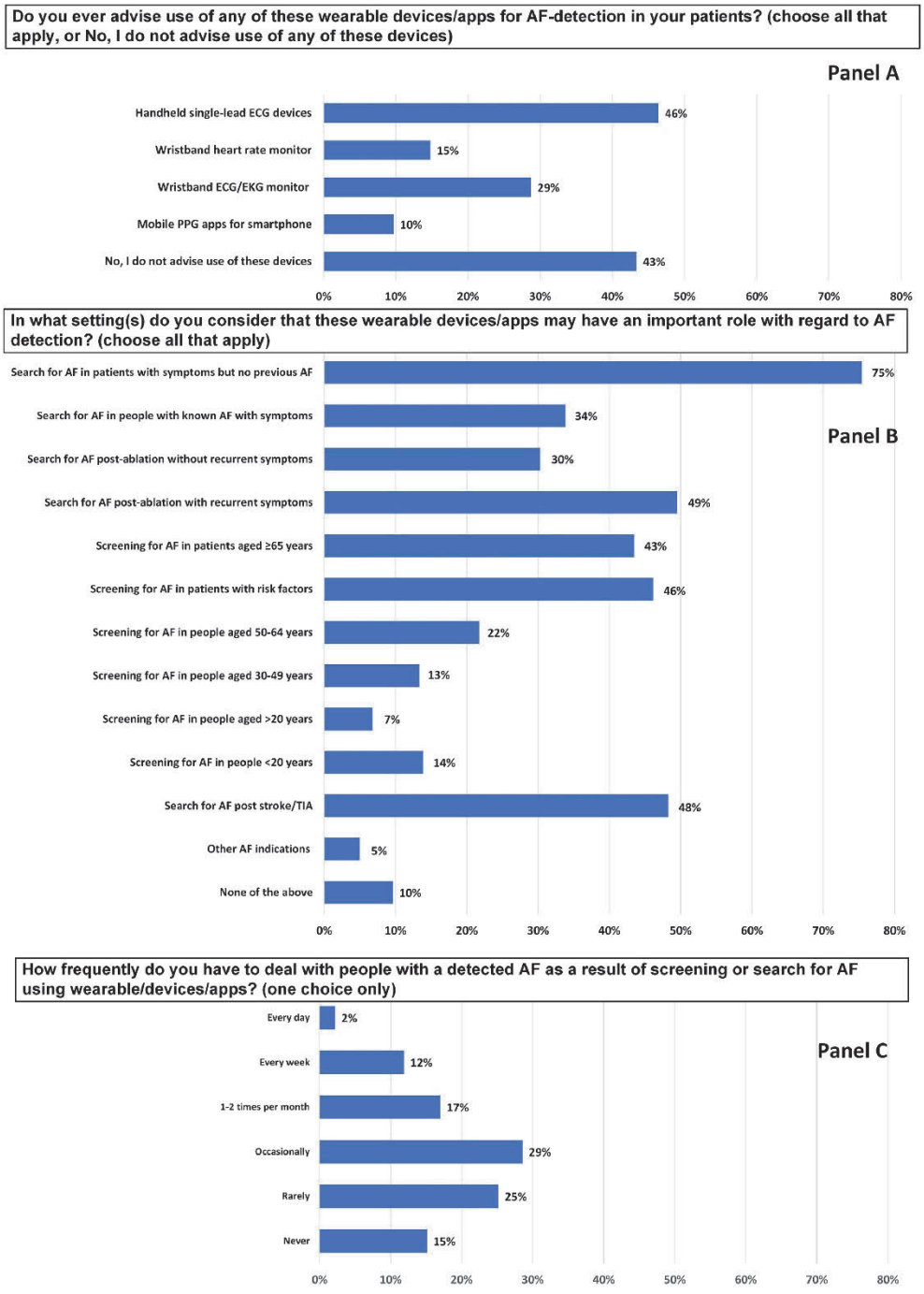
Results

Overall, 2481 invitations were sent by email and 588 HCPs completed the survey anonymously (119 AF-SCREEN members and 469 non-members, response rate 23.7%). The geographical region of respondents was reported in 482 replies, and was Europe in 373 (77.4%), Asia/Oceania in 66 (13.7%) and North or South America in 40 (8.3%), with 3 (0.6%) in other regions. Survey respondent characteristics are shown in Table 1.

The first question of the survey analysed if health care professionals ever advise use by patients of any of the available wearable devices/apps for AF-detection. The results shown in figure 1, panel A indicate that these devices are never suggested by 43% of respondents, while 57% of respondents at least sometimes advice their use: handheld (portable) single-lead dedicated ECG devices in 46% and wristband ECG/EKG monitors (e.g., Apple Watch 4, Kardia, Huawei, Verily, etc.) in 29%, with a lower relative percentage of suggestions addressed to wristband heart rate monitor (e.g., Apple Watch 3, Fitbit, Garmin, Biostrap, etc.) (15%) or to mobile PPG apps for smartphone camera flash downloaded from Apple or Google Play stores (10%). There were distinct differences between groups of health professionals in these responses. Between 62–67% of PCP/GPs, neurologists and other specialist physicians never advised use of these devices for AF detection compared to 43% of general cardiologists, and only 25% of electrophysiologists. The figure was 26% for allied health professionals and nurses, presumably with an interest in AF screening, and 27% for AF-SCREEN members compared to 44% for non-members. Similar differentials between HCP categories were seen for handheld ECGs, and wristband ECGs, with 45% of electrophysiologists sometimes advising wristband ECGs, compared to only 10–20% of other specialists and PCP/GPs.

The second question focused on the scenario(s) where these devices may have an important role with regard to AF detection (figure 1, panel B) and the answers stress the role of wearables, devices and apps to search for AF in patients with palpitations or other symptoms but no previous detected AF (supported by 75% of respondents), as well as for search of AF post stroke/TIA and post AF ablation with recurrent symptoms (supported by 48–50% of respondents). Electrophysiologists were the most likely to advise use of the devices in patients with symptoms (86%). With regard to the potential use for screening, according to 44–46% of respondents there is an important role of this technology for subjects aged > 65 years or in patients with risk factors (hypertension, diabetes, etc.). Conversely, screening in less

Figure 1 Questions and answers of the survey on use of wearable devices/apps for AF detection.



selected subjects, with lower age, is considered to be meaningful by only a minority of respondents. Only 10% of HCPs stated there was no value of any of the potential indications for search of AF or AF screening.

The answers to the question on how frequently HCPs currently have to deal with subjects with AF detected through wearable devices/apps reveals that this happens only rarely or occasionally (less than 1–2 times per month) for 25–29% of respondents (figure 1, Panel C). Only a small minority of respondents report to be frequently involved in this activity, while for 15% no involvement was reported. PCP/GPs were least likely to have to deal with AF detected this way at least 1–2 times per month (12%) compared to 30–44% for other physicians and general cardiologists or electrophysiologists.

The use of wearables or devices for AF search/screening may be related to a choice taken by the patient or by a physician. According to respondents to this survey, the use of these devices for AF search was the patient's personal decision in just over half of cases leading to a consultation with the HCP, while it was advised by a physician in the remainder.

The referral to physicians of patients for clinical evaluation after AF detection through wearable devices/apps in more than 50% of cases was related to patient self-referral or was prompted by a primary care physicians or, less frequently by other physicians (figure 2, panel A). Only rarely was the referral prompted by pharmacists or patient associations/groups.

The age of subjects referred to physicians for a clinical evaluation after AF detection through wearables/apps (figure 2, panel B) was in the majority 65 or older although around 30% were between 55 and 65 and around 36% below 55.

The organization of referral for clinical evaluation after AF detection is an important issue and more than half of the respondents considered as appropriate a referral through general practitioners with the support of predefined pathways, or through dedicated physicians/nurses, while conventional contacts were advisable for around 29% of respondents (figure 2, panel C). Referral from call centres/websites or through pharmacists had a low rate of preferences.

The potential disadvantages of mass community screening using wearable devices/apps were reported as related to anxiety in people with a positive test by around 65% of respondents, but were also related to false reassurance in case of a negative test by 41% of respondents (figure 3, panel A). Moreover, for 39% of respondents the risk of bleeding due to anticoagulant prescriptions after a positive test, in light of a still unproven benefit for AF detected this way, actually represents

Figure 2 Questions and answers of the survey on referral of patients after AF detection through wearable devices/apps.

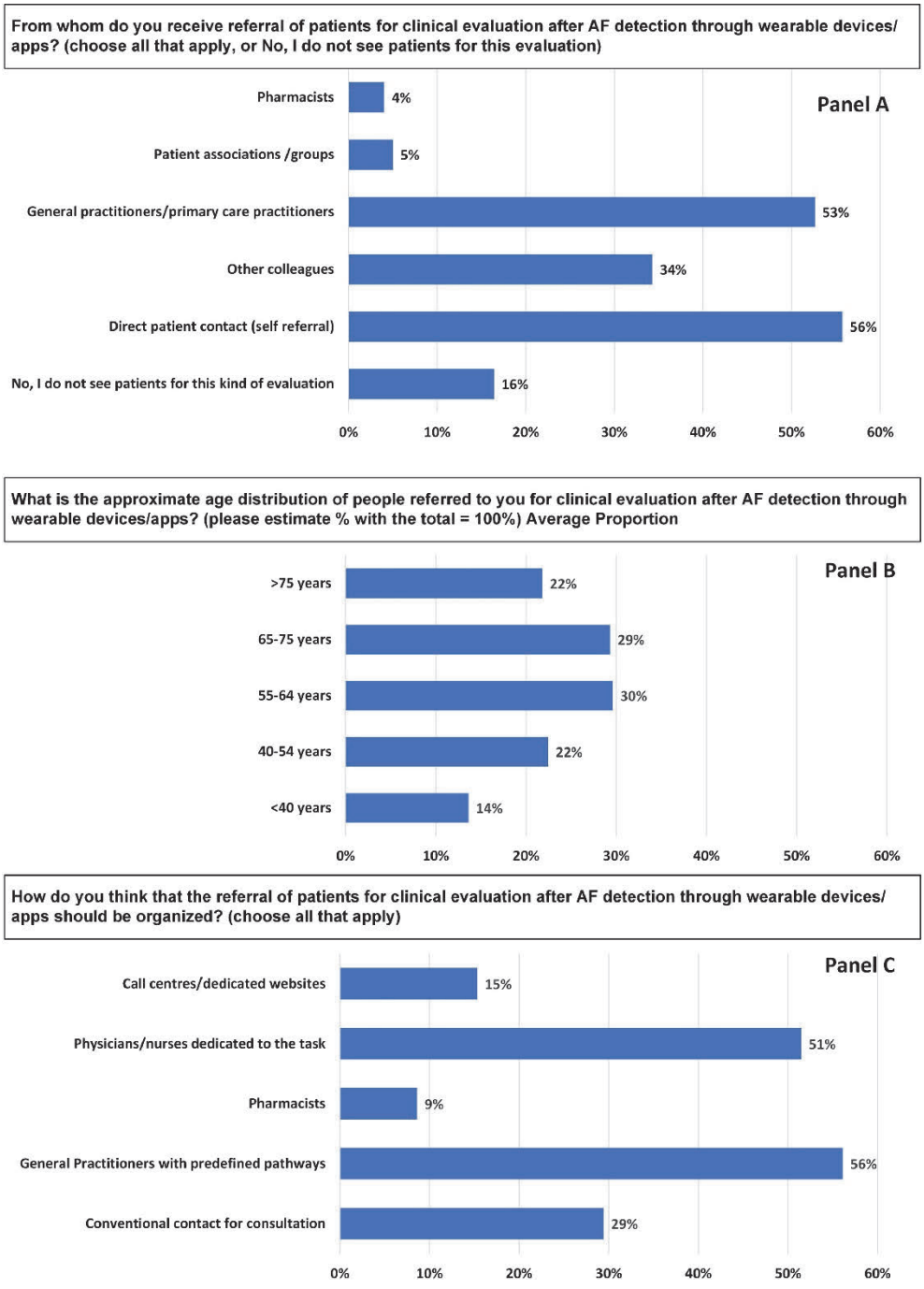
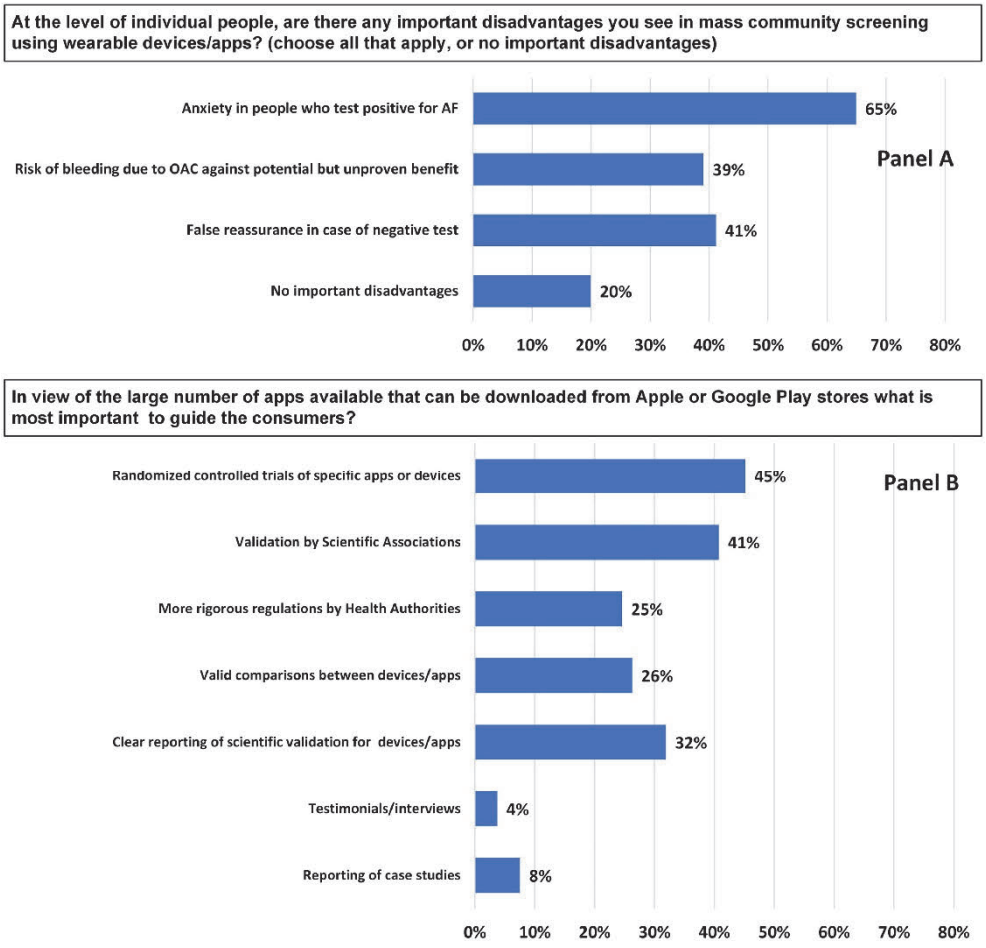


Figure 3 Questions and answers of the survey on AF screening using wearable devices/apps.



a disadvantage of screening. Conversely, for around 20% of respondents no important disadvantages for mass community screening are currently perceived at the level of individual people.

As there are now many Apps currently available for download from Apple or Google Play stores, between 30 and 45% of respondent considered in order to appropriately guide the consumers it would be important to obtain validation through randomized controlled trials, reports based on scientific data, or recommendations from Scientific Associations. About 25% believed there should be more rigorous regulation from Health Authorities and/or valid comparisons between devices or apps (figure 3, panel B).

The final question of the survey explored respondents' thoughts on whether we are actually ready to commence mass community screening for AF using wearable devices/apps now: the answer was no for almost 70% of respondents. There were no important differences amongst the different HCPs.

Discussion

Wearables now allow non-invasive monitoring of a range of human body vital signs and could facilitate user-initiated disclosure of many diseases.[23] The field of mobile technology has in recent years been characterized by an impressive growth which has the potential for changing clinical practice as a disruptive transformation. Moreover, the use of wearables to diagnose AF is being promoted widely to the general public by manufacturers as a health benefit of their products. However, apart from the need for specific regulations, also taking into account the legal implications of mode and time of physician's reaction to detection of a suspected AF,[24, 25] our survey respondents did convey a number of caveats on the use of wearables and Apps. Finally, the majority indicated that these devices were not yet ready for commencing mass screening for AF.

In general, screening for an arrhythmia like AF using devices and apps marketed to the general community should be well organized, with a specific and appropriate design of screening initiatives, as well as defined pathways involving health care professionals and individuals engaged in the screening process with effective feedback loops.[26] For AF, the wide diffusion of devices that can provide information on cardiac rhythm carries the risk that the coordination, in terms of appropriate targeting and management of screening activities, may no longer be in the hands of clinicians and HCPs, but will by default become an uncontrolled activity, with unknown risks and consequences.[20, 27, 28]

Our survey focused on wearables and apps[25] in the setting of screening and search for AF, and highlights that in a sample of almost 600 HCPs, involving mostly electrophysiologists, cardiologists and general practitioners, the use of these devices is currently advised by around half of them. Unsurprisingly, electrophysiologists and to a lesser degree general cardiologists, were more likely to advise their use that other specialist physicians and PCP/GPs. The nurses and allied health professionals who took our survey were also high users of this technology, as might be expected for groups of these HCPs with an interest in AF

screening who were recruited to this survey. Overall, there was a preference for handheld (portable) single-lead dedicated ECG devices and to a slightly lesser degree for wristband ECG monitors, but a much lower degree of preference for apps based on photo-plethysmography using a wristband or the camera flash of smartphones. This may be interpreted as a higher degree of confidence, from the perspective of physicians, on tools detecting AF by direct recording of an electrocardiographic signal.

Most of the consumer-facing devices and apps are registered as a medical device.[29-34] Many studies have validated the novel devices and tools, with variable sensitivity and specificity. However, the same rigorous validation does not necessarily apply to many apps proposed to consumers without availability of valid scientific data,[15] nor to the outcome of screen-detected AF in the mostly younger people who choose to buy and use wearable devices and apps in this way. In the literature, a great debate has developed in recent years on the significance and effectiveness of initiatives targeting AF search/screening in specific target populations. Moreover, many wearable products are marketed as direct-to consumer so it is probable that they will be largely used by subjects with healthier profiles and lifestyle,[35] as seen in both the Apple Heart Study and Huawei Heart Study where the mean age was 41 and 35, respectively.[33, 34] These individuals have a low pre-test probability of AF with a questionable significance of screening for AF.[12] In fact, the "possible AF" notification rate in the 52% of participants aged <40 in the Apple Heart Study was only 0.16%.[34] As a matter of fact, age- and literacy-related disparities in the use of mobile technologies were reported both in Germany[36] and the United States,[37] with a discrepancy between the epidemiology of AF, more common and more dangerous among older people with multiple chronic diseases, and the low penetration in this population of wearable devices.[38]

Our survey suggests that there is a consensus on recommending wearables/apps for searching for AF in symptomatic patients or post stroke/TIA, two settings where wearables may constitute an alternative to Holter monitoring (24-h or longer durations), external continuous or loop recorders or, even to implantable loop recorders. The place of AF screening itself, whether this is case finding, or opportunistic or systematic screening is still a debated topic.[12, 16, 17, 39-44] Thus, it is not surprising that the use of wearables/Apps for this purpose remains even more controversial. What emerges from the current referral of subjects following AF detection by wearables and apps marketed directly to consumers is a true asymmetry between the current buyers and users of wearables, and the appropriate

target. Buyers and wearers are mostly people younger than 50 years, and not those who would represent the most appropriate age group to target with AF screening programmes according to detection rates and number needed to screen to detect one person requiring thromboprophylaxis for stroke,[10] as recommended in guidelines and consensus documents (i.e. subjects above 65–75 years).[12-14, 45-47]

At present, despite the availability of many wearables for monitoring cardiac rhythm and detecting AF, it is apparent from our survey, that the evaluation by physicians of patients with AF detected through a wearable device is not common, and that there are no specifically-defined care pathways for referral, despite general recommendations.[12-14, 45, 46]

According to around 65% of the respondents, the potential anxiety of people who tested positive at AF screening constitutes a major limitation to the use of wearables, and this concern, including also the risks of false positives, and of prescribing anticoagulation to those who may not benefit but are exposed only to the risks, similar to any disease screening initiative, is in line with the comments by US Preventive Services Task Force and other experts in the field.[16, 17, 40] However, appropriate targeting with screening addressed to subjects at a higher risk of stroke if AF is detected, coupled with detailed information to screening candidates on the significance and the implications (in terms of anticoagulant treatment) of undergoing screening, could help to minimize anxiety, as in any screening program. Importantly, perceived disadvantages also included the risks of falsely reassuring those with AF that may be missed by the various wearable systems that rely on intermittent-monitoring PPG algorithms to initiate a warning. The heterogeneous opinions on the current value and significance of AF screening through wearables is highlighted by the opposite position of 20% of respondents, who actually indicated that nowadays there are no important disadvantages at the individual level for promoting mass community screening activities.

Ongoing randomized studies, already started or in a planning phase[12, 14, 41] will be an important step for defining the net benefit of AF screening in specific populations, with regard to stroke prevention and long-term survival, against adverse bleeding events related to OAC.[48, 49] As compared to other screening initiatives, AF screening through wearables certainly has potential, provided there is appropriate population targeting, for a favourable cost-effectiveness profile, a key element in evaluation of health care interventions.[50] The collection of data on population screening, in specific target populations, can help to estimate the benefits of screening interventions, as done in Sweden where the 5-year follow up of a systematic

screening performed in patients aged 75 showed a lower incidence of ischemic stroke in the intervention region, as compared with a control region, in parallel with an 88% rate of screening-detected AF treatment with oral anticoagulants and excellent long term adherence to therapy.[51]

For some wearables, the diagnostic value of the specific technology has been tested in terms of sensitivity and specificity (Huawei, Apple watch, Kardia, etc.) in specific settings, with some limitations given the ultimately small numbers used in the direct comparisons. However, as highlighted by respondents, there is absolute need to make clear to consumers what devices or Apps are validated. In the rapidly growing market of mobile health technology (more than 100,000 mobile Health apps and ≥400 wearable activity monitors available),[15] no clinical validation is available for many of these devices and therefore caution is needed in their use for clinical reasons. Given this perspective, scientific associations, patient associations and regulatory agencies should provide some guidance on how to organize initiatives on AF screening and in whom it is reasonable to address a search for AF, as well as propose pathways for appropriate evaluation of subjects who test positive, independently of commercial interests. Even if there is a general tendency in the market to directly approach consumers and to promote use of wearables and Apps without the traditional control of physicians, the need for appropriate targeting, provision of information, and evaluation of individuals tested positive, indicate that physicians should be involved in these activities. This is required to magnify the potential value of these new diagnostic resources that may actually change the process of care, and minimize the harms of inappropriate use. Despite general recognition of the potential, it is noteworthy that according to around 70% of HCPs we surveyed, we are actually not ready to apply the technology of wearable devices/apps for mass community AF screening.

In our society the media share important responsibilities in addressing the general use of wearables in a proper and rational way, with need for a clear distinction with regard to lifestyle and wellness, the fields where wearables are widely promoted.[27] Scientific Associations, patient groups and associations, general practitioners, specialist physicians, and researchers in the field, as well as the industry, other health care providers and regulators should have a greater dialog and collaboration in the field of AF screening to increase the value for the health care process through appropriate use of these new diagnostic resources, in a context where physicians responsibilities still need to be well defined.

Our survey has some limitations, first of all related to a response rate of 24%. Response rates to physician surveys have declined over the past several decades, and paradoxically web surveys were found to result in lower response rates compared to other more traditional data collection modalities.[52,53] As reported in the literature, conducting surveys among physicians and medical personnel is more difficult than in other fields, and response rates are actually lower than response rates of surveys conducted within the general population.[52-54]

Moreover, as for any anonymous survey based on voluntary participation, we can presume that willingness to participate may per se identify health care professionals with a specific interest on the topic of AF screening and with specific knowledge on most recent technologies for cardiac rhythm monitoring. On the one hand this may limit the possibility to extrapolate the findings to other health care professionals with a lower degree of knowledge or confidence with wearables, but on the other hand it increases the relevance of the caution in promoting mass screening for AF using wearables that this survey highlights.

Conclusion

There is a great potential for appropriate use of consumer-facing wearables/apps for AF screening, but the current consumer-led use following direct marketing suggests the need for identification of appropriate targets, organization of referral and appropriate patient information on the purpose and implications of AF detection. Greater dialog between stakeholders is required to ensure there is value for the health care process through appropriate use of these new diagnostic resources. The final gestalt of the majority of the 588 respondents to our survey was that these apps and devices which are directly marketed to consumers are not yet ready for mass screening for AF.

Declarations

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Competing interests

GB reported speaker's fees of small amount from Bayer, Boehringer, Boston, Biotronik and Medtronic.

RBS has received lecture fees and advisory board fees from BMS/Pfizer outside this work.

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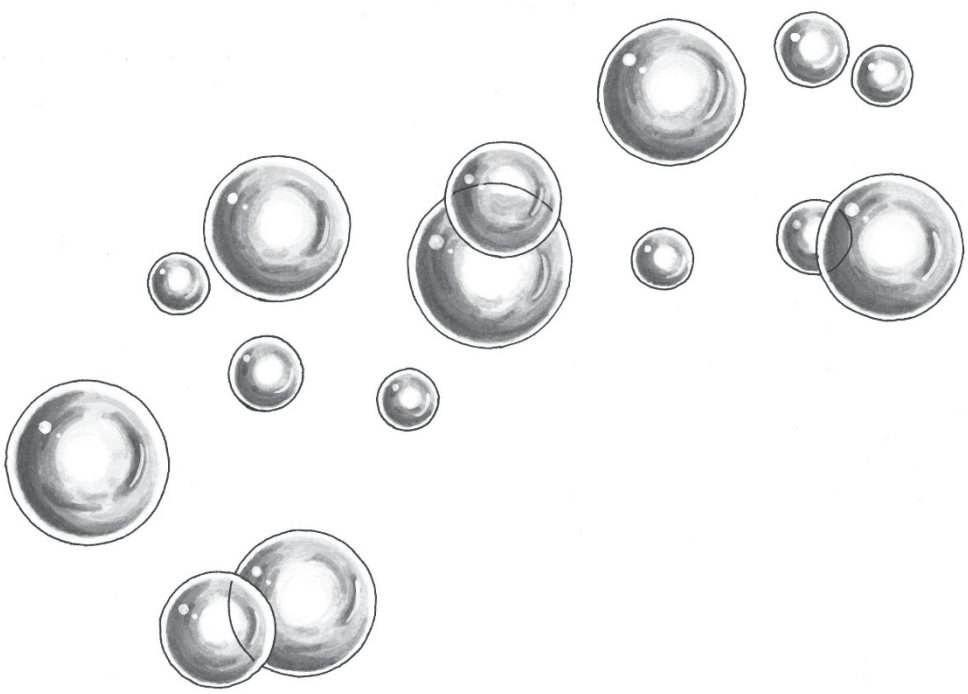
Chapter 10

General discussion



General discussion

The purpose of this thesis was to find ways to enhance the detection of atrial fibrillation (AF). Here we discuss our main findings, methodological and practical considerations and implications for practice and future research.

Main findings

To find ways to improve AF detection, we first evaluated current practice. We explored diagnostic choices of both general practitioners (GPs) and cardiologists in two case vignette studies. Cardiologists indicated to apply ambulatory monitoring in cases with non-frequent symptoms suggestive for AF. The monitoring duration was shorter than recommended by the National Institute for Health and Care Excellence (NICE).[1] Our case vignette study among GPs showed that they tended to use shorter monitoring than recommended in these cases as well.

After the analysis of these fictive vignettes, we evaluated current practice in everyday health care. We assessed the diagnostic pathways in consecutive patients with newly diagnosed AF. A third of patients had silent AF, an irregular heartbeat was most often first noted in general practice, and cardiologists most often diagnosed AF. Various disciplines were involved in diagnosing AF.

Following the evaluation of current practice, we conducted a diagnostic accuracy study, embedded in a cluster randomised controlled trial (RCT). We determined test characteristics of three methods for AF detection in primary care: radial pulse palpation and measurements with two devices with an AF detection algorithm, namely an electronic blood pressure monitor ('eBPM') and a handheld single-lead electrocardiography device ('handheld ECG'). Characteristics of both the handheld ECG and eBPM surpassed those of radial pulse palpation. The handheld ECG had the most favourable diagnostic characteristics, with a high sensitivity (90.1%) and specificity (97.9%). Combining the tests had no clear advantage.

We also evaluated the diagnostic accuracy and yield of home monitoring. Performing a two-week Holter among patients with a negative 12-lead electrocardiogram (ECG) yielded four (1.5%) extra cases. The trice daily measurements these patients performed with a handheld ECG at home gave too many false-positive results to be considered for implementation in daily practice.

In a cluster RCT among 17976 patients of ≥65 years in general practice, we investigated the effectiveness of opportunistic screening compared to usual care.

Opportunistic screening did not result in a significantly higher AF detection rate than usual care in the Netherlands (1.62% vs. 1.53%, respectively).
Finally, we performed a survey to address the rapidly developing consumer market regarding AF detection methods. In an international survey we gauged the opinion of health care professionals on apps and devices directly marketed to consumers. They judged that these apps and devices are not yet ready for mass screening for AF.

Methodological and practical considerations

In the execution of the 'Detecting and Diagnosing Atrial Fibrillation' (D_2AF) study, we faced multiple challenges. Here we discuss the requirements of our overarching design with nested studies, the hurdles that were taken in patient selection and participation, the choice to change our analysis method to multiple imputation, the use of case vignettes and how we combined a GP traineeship with a PhD trajectory. With each challenge we had to weigh factors as validity, reliability, reproducibility, simplicity, generalisability, feasibility, time, and costs and decide what benefited the research the most.

Nested studies

The size and setting of the RCT offered the opportunity to increase scientific gain by embedding other studies. Several studies were nested in the cluster RCT, i.e. two diagnostic accuracy studies and a cohort study. The studies each had their own requirements and sometimes they conflicted, for instance regarding the required sample size. A large population was necessary for the RCT and the cohort study, but less patients would have sufficed for diagnostic validation and would have enabled performance of a 12-lead ECG in all participants. Another example is the head-to-head comparison of the three index tests. This augmented the diagnostic accuracy study but complicated the opportunistic screening protocol of the RCT and perhaps decreased participation. Sometimes the different study requirements fit together easily, for example regarding the study period. Time was restricted to one year for the RCT, after which this study ended. Nevertheless, the cohort study in the control arm of the RCT carried on, with a mean follow-up of more than two years. Furthermore, patients who were screened after the study year of the RCT could still be included in the diagnostic study.
The combination of our studies offered not only challenges, but also valuable opportunities. It enabled us to determine test characteristics in a population

without known AF – for whom the index tests are intended – and therefore provide reliable predictive values. Furthermore, the combination of two diagnostic accuracy studies applying the handheld ECG in two settings, resulted in an important insight; whereas the handheld ECG performed well in single-timepoint screening in office, it did poorly in multiple-timepoint screening at home.

Patient selection

Initially, we intended to develop software which could interact with the electronic medical records, to select the study population. When a patient would visit an intention-to-screen practice, the software would check the medical record for eligibility ($CHA_2DS_2VASc \geq 2$). If eligible, a message would pop-up in screen, alerting the health care professional to invite the patient to participate. The 96 GPs in our trial used GP information systems ('HIS') of seven different providers: Medicom, MicroHIS, Mira, OmniHIS, TetraHIS, Zorgdossier and Promedico. It was not possible to develop software that would fit all systems. Even if one HIS would have supported our software, we would have had to restrict recruitment of the 96 practices to those using that system, compromising feasibility and generalisability. Therefore, we abandoned the idea of implementing software in the HIS. Instead, we decided to select patients at the start of the study and mark them manually in the HIS. This way, the practice workers were still notified if an eligible patient visited the practice. As all women and most men of ≥65 years have a CHA_2DS_2VASc score of ≥2, we simplified the selection criteria to an age of ≥65 years. As most of the other screening studies also select patients based on this criterium, it would be easier to compare the results, thus increasing generalisability. Besides that, it increases the reproducibility. Furthermore, risk scores such as the CHA_2DS_2VASc are subject to change, as it was $CHADS_2$ before, it may change again. By extracting patient characteristics, we were still able to determine the CHA_2DS_2VASc score afterwards.
We were able to work around the inability to implement software in the HIS. However, our manual procedure was time consuming, in a project in which time was already scarce. A nationwide, uniform HIS with an integrated standard research module to be adapted by researchers, would provide a solution to many researchers. For now, however, that is still a utopia.

Patient participation

We took several measures to optimise patient participation. We limited the number of patients to 200 per practice to keep the study-related work-load manageable. Our electronic trial management system allowed us to monitor the number of patients included per practice. If inclusion stagnated, we acted by calling or paying the practice a visit. Furthermore, our online case report form also functioned as a script, describing the study procedures. We provided a paper manual as well and trained the practice workers on how to perform the study tasks. Moreover, we distributed newsletters and videos, to keep them posted of the study's progress and to invoke a joint sense of responsibility for the progress of the study. We offered payment in the form of small financial incentives and equipment. We developed a study logo (figure 1) to increase recognisability.

Figure 1 The Detecting and Diagnosing Atrial Fibrillation study logo

Whereas follow-up – i.e. whether or not the patient had AF at the end of the study year – was complete for the majority of patients, participation of patients in our opportunistic screening protocol was lower than expected. In the RCT, 4106 out of 9218 patients were screened. An additional group of 233 patients was screened after conclusion of the study year, who could still be included in the diagnostic accuracy study (n=4339). So despite our efforts, we were not able to escape Lasagna's law.[2] The lower than expected participation in our opportunistic screening protocol may be attributable to organisational issues. Our protocol was designed for scientific purposes – maximising sensitivity and allowing a direct comparison between the index tests – and not for implementation in usual care as such. Performing the research procedures took time and came on top of the daily routine. In future research, we recommend facilitating research procedures as much as possible and to keep the protocol simple. It could be worthwhile to assess support for the planned study procedures among general practitioners and potential participants, and – if resources allow it – to perform a pilot study.

Multiple imputation

Ideally, in a diagnostic validation study all participating patients perform both the index tests and the reference standard (12-lead ECG). However, due to the large

population needed for the RCT, we could not offer all patients a 12-lead ECG. It would have required too much time and too many resources from general practices, to perform 200 ECGs per practice in a year. Therefore, we chose to perform the reference standard in a subset of patients: all patients with one or more positive index tests and a random sample of 10% of patients with three negative index tests. However, this meant we could not fill the contingency table of the diagnostic accuracy study with the observed data.

Table 1 Contingency table in diagnostic accuracy studies

	Reference standard positive	Reference standard negative	Total
Index test positive	A	B	A+B
Index test negative	C	D	C+D
Total	A+C	B+D	A+B+C+D

A complete case analysis, i.e. only using complete observed records to calculate diagnostic test characteristics, would have resulted in a verification bias. However, simply regarding the patients with three negative index tests without a 12-lead ECG as negative, would also have created a bias. False negative results would have been underestimated (table 1, box C), while overestimating sensitivity and negative predictive value (NPV).

Originally, we planned to perform inverse probability weighting (IPW). However, IPW did not fit our data for two reasons. Firstly, a condition for applying IPW, is that data is missing at random (MAR). In our study, our data was indeed missing by design as we took a random sample (MAR), but also due to drop-out, which may be related to health status and the chance of having AF (missing not at random, MNAR). As IPW does not take patient characteristics into account, results would be subject to bias. Secondly, IPW would overestimate sensitivity and – to a lesser extent – negative predictive values for the scenarios with the handheld ECG, as none of 793 complete cases for the handheld ECG had a false negative result. In IPW, the missing values in the contingency table are multiplied by weight to reach the total of 4339. However, as zero remains zero when multiplied, IPW would result in an unlikely sensitivity and negative predictive value of exactly 100%.[3, 4] Especially sensitivity would be biased, as the numbers in the sensitivity equation are smaller than in the NPV equation, and thus more susceptible to changes. Due to the large risk of bias arising from using IPW, we chose not to rely on this analysis.

Instead of IPW, we used multiple imputation (MI), which was better suited to analyse our data.[5, 6] Conditions for MI were favourable; apart from the results for 12-lead ECG

and Holter, very few missing values occurred in the variables included in the analysis. Rather than using a weighted multiplication factor, with MI we could lend information from these variables and construe a more reliable model. We did perform IPW as a sensitivity analysis. Both IPW and MI resulted in a higher sensitivity and specificity of the devices than of radial pulse palpation, whereas sensitivity and specificity of the handheld ECG remained the highest. Overall, the main conclusion would have been the same.

Online case vignette studies

Two chapters in this thesis describe a case vignette study, an online questionnaire to examine judgement and decision-making. This type of research does not describe real behaviour in everyday healthcare, but provides a prediction of how the subjects would behave under the provided circumstances.[7] Hypothetical choices may evoke a different reaction than actual choices in real life, for instance due to – sometimes unpredictable – circumstantial factors. However, previous research showed that choices of health care professionals in a vignette study were made similarly in comparable cases in everyday health care.[8, 9] In our two studies the case vignettes were the same, for a good comparison between cardiologists' and GPs' diagnostic choices. Being aware of the drawbacks of vignette studies, we also examined the diagnostic pathway to AF diagnosis in a cohort study.

Combined clinical and scientific training

Two PhD students (Steven Uittenbogaart and I) were part of the D_2AF study team. Both of us were an 'AIOTHO', a Dutch acronym for 'Arts In Opleiding Tot Huisarts en Onderzoeker', which is a physician in training to become both a GP and a scientist.[10, 11] Periods of research alternated with periods of clinical traineeships, and sometimes they were intertwined.

The AIOTHO-construction had both positive and negative consequences. Performing a trial such as the D_2AF study within the usual four years of a PhD trajectory, would have been very challenging. Due to the combination with the GP training, it was not four, but six years. However, given the total time available for the combined PhD trajectory and the GP training, there was much time pressure on the PhD researchers to achieve the complete study as planned. We aimed to alternate the presence of the researchers on the project in an overlapping construction. During the crucial periods of the study – such as the recruitment of practices – we aimed to have at least one PhD researcher 'on the project'. After most practices had started

their study year, we had to rely on the help of our team, in particular of the research assistants.
Whereas the AIOTHO-construction had some important disadvantages, the D_2AF study would not have fitted within the timespan of a regular PhD-trajectory. Future AIOTHO-projects should arrange sufficient budget to compensate the absence of the PhD researcher with research assistants or other supporting scientific staff.

Implications for general practice and future research
Our results imply that AF detection is already performed effectively in the Dutch health care system. With the opportunistic screening we carried out, we did not accomplish a higher yield of AF compared to usual care. However, based on our research we still have recommendations to improve current practice and can provide inspiration for future research.

Devices for AF-detection
In the D_2AF study measurements were performed in general practice by health care professionals and at home by patients themselves. We showed that radial pulse palpation was inferior to the eBPM and the handheld ECG for in-office opportunistic screening; the handheld ECG had the highest accuracy. The superiority of a handheld ECG device over radial pulse palpation in screening for AF was recently confirmed in the STROKESTOP II study.[12] We recommend using the handheld ECG for AF detection. The eBPM can also be used, but diagnostic accuracy was inferior to that of the handheld ECG. However, for GPs who do not possess these devices radial pulse palpation is still a reasonable alternative to exclude AF, given the high negative predictive value.
All patients with a negative 12-lead ECG should, according to our protocol, have performed two-week Holter measurements and held the handheld ECG trice daily. However, we experienced a large dropout in this part of the study; whereas 763 patients had a negative 12-lead ECG, we have Holter data of only 270 patients. Furthermore, the mean recording time was eight instead of 14 days. Reasons for a shorter monitoring duration were the burden of wearing the device, irritation from the patches and technical issues with the device. The shorter monitoring duration in the trial matches the findings of the vignette studies; a substantial part of GPs and cardiologists chose a shorter monitoring duration than the guidelines recommend. It is also reflected in our analysis of the usual care practices; only 16

out of 258 AF diagnoses were based on ambulatory monitoring. A more user-friendly device is needed for long-term arrhythmia monitoring.

Our survey among cardiologists showed that newer tools such as single-lead ECG devices were not embedded into everyday health care. However, our survey was performed from 2014 to 2015, meanwhile this may already have changed. Industry and technology are developing incredibly fast.[13] The field of Mobile Health (mHealth), i.e. the use of ambulatory devices or technologies in healthcare, rapidly increases.[14] There are several possible alternatives for ambulatory monitoring, for example ECG-patches.[15-17] They are better tolerated than conventional ambulatory monitoring.[18] Diagnostic accuracy seems promising, with a sensitivity of 93.1% and specificity of 93.4%.[19] Another option for ambulatory monitoring, is the intermittent use of easily accessible devices. Many devices, such as sphygmomanometers, smartphones, or single-lead ECG devices, could be used for this purpose.[20-22] We tested the trice daily use of a handheld ECG device. It had a limited diagnostic accuracy; sensitivity was 66.7% and specificity 68.8%. Interestingly, this was much lower than for the single measurement performed in general practice (sensitivity 90.1%, specificity 97.9%). Furthermore, cardiologists judged the quality of the rhythm strips of home measurements to be poor. Besides that, in intermittent measurements episodes of paroxysmal AF can be missed.[23] Therefore, we do not advise using the handheld ECG trice daily for screening at home. We cannot extend this conclusion to intermittent measurements with other devices, as the internal algorithm on which AF detection is based differs per device.

Another easily accessible monitoring tool is a watch or wrist band.[24] These devices can record continuously and are not burdensome. They detect arrhythmias based on a photoplethysmogram (PPG) – a technique to register pulse rhythm optically by means of a light-emitting diode (LED) – and not on electrocardiography. A definite diagnosis cannot be made based on PPG, so any arrhythmia needs confirmation with a 12-lead ECG. However it can still be a useful screening tool as it can also detect asymptomatic arrhythmias. Two studies show a high sensitivity (94-98%) and specificity (97-98%) of these PPG devices.[25, 26] One smartwatch can record a single-lead ECG by touching the digital crown (button) with the other hand.[27] The smartwatch can also be paired with a wrist band with electrodes, which enables making an ECG when touching the band.[28, 29]

Promising as the new mobile arrhythmia detection devices are, they are not yet ready to be used for mass screening purposes. More research is needed to validate the devices and determine their place in everyday health care. However, most

diagnostic accuracy studies and RCTs take many years. By the time the results are made public, the device may already be obsolete. Case-control diagnostic accuracy studies in smaller populations with a higher percentage of known AF can be performed more swiftly. However, this study type comes with a greater risk of bias than, for instance, a cross-sectional design. Before using a new device in everyday practice, one should check if validation studies have been performed.

To screen, or not to screen?

Should we screen for atrial fibrillation? With our opportunistic screening protocol, we did not detect more patients with AF than in usual care (1.62% vs. 1.53%, respectively). This is in contrast with the results of the 'Screening For AF in the Elderly' (SAFE) study, the only available RCT at the start of D_2AF comparing screening for AF with usual care. The AF detection rate in the screening arm of the SAFE study was significantly higher than in the control group (1.63% vs. 1.04%, respectively). In 2017 the 'Assessment of REmote HEArt Rhythm Sampling using the AliveCor heart monitor to scrEen for Atrial Fibrillation' (REHEARSE-AF) was performed.[30] In this RCT opportunistic screening consisted of twice weekly measurements with a handheld ECG for one year, this yielded more AF than usual care (3.8% vs. 1.0%, respectively). However, two more recent RCTs show results similar to ours. In 2020 the 'Improving DEtection of Atrial fibriLlation in Primary Care With the MyDiagnostick' (IDEAL-MD) study also showed no improvement of AF detection rate in screening compared to usual care (1.43% vs. 1.37%, respectively).[31] In 2021 the results of the VITAL-AF study were presented; screening did not improve AF detection rate significantly compared to usual care (1.72% vs. 1.59%, respectively).[32-34] Interestingly, the AF detection rates in the control arms differed. The yield of AF in the control groups of the negative trials, i.e. VITAL-AF, IDEAL-MD, and D_2AF, was higher than in the positive trials, i.e. SAFE and REHEARSE-AF.[35] In areas with a low yield of AF in usual care, a larger percentage of unknown AF can be expected and the chance of a significant effect of screening increases. In such areas opportunistic screening of AF might still be effective. In areas with a high yield of AF in usual care, as in the D_2AF study, screening is less likely to be effective. The results of D_2AF probably also apply to other well organised primary care populations elsewhere. Future research on screening for AF should focus on the selection of patients at higher risk of having AF. This could be done by only screening patients aged ≥65 years in areas with a low yearly incidence of AF, arbitrarily <1.25%. Another option is to select patients with certain risk factors for AF, such as heart failure or hypertension.

The high quality of usual care in the Netherlands regarding AF detection, is further illustrated by other findings of our research. For instance, the AF prevalence in participating practices among patients aged ≥65 years was already high before the start of the D_2AF study (10.1%). Furthermore, in the usual care group, we found that as much as a third of patients with newly diagnosed AF, had silent AF, whereas in other studies the percentage of silent AF is between 11-30%.[36-40] Only few (3.5%) were diagnosed after a stroke, compared to 4-14% in other studies.[41-43] Together, these findings suggest that patients were diagnosed in an early stage – before the occurrence of stroke – in usual care, which diminished the chance of a positive effect of screening.

The Dutch College of General Practitioners recommends to assess the heart rhythm when measuring blood pressure.[44] Other forms of screening are not recommended. The European Society of Cardiology advises to perform opportunistic screening in hypertensive patients, and in patients ≥65 years of age.[45] Cardiologists in our vignette study seemed divided in whether or not to screen patients with only cardiovascular risk factors. This ambivalence reflects reality, because it was (and is still) debatable whether screening for AF is useful and if so, in what setting. If proven effective, most GPs in our survey would support opportunistic screening for AF.

Based on our research, we would not recommend the Dutch College of General Practitioners to change their advice regarding screening for AF. Opportunistic screening among patients aged 65 years and above should not be implemented in Dutch healthcare.

Treating screen-detected AF

AF needs to be treated to prevent strokes, heart failure and death. With anticoagulants, 60% of strokes can be prevented.[46] Treatment with anticoagulants prevents thrombo-embolic events but is also associated with a higher bleeding risk. The risks and benefits of treatment need to be weighed in each patient. For this we use the CHA_2DS_2VASc score; treatment with anticoagulants is recommended when a patient scores two or higher. However, these findings are based on treatment of patients who were not detected by means of screening. Is it right to assume that treatment of screen-detected AF, gives the same results as in routinely detected AF? The question is whether screen-detected AF differs from otherwise detected AF. For if it does not differ, we might assume that treatment will have the same effect. AF can present in different ways. Patients may or may not experience symptoms (symptomatic versus silent AF). Furthermore, symptoms may be typical or atypical

(palpitations versus other symptoms). Previous research showed that the presentation of AF may be associated with the prognosis. Siontis et al. found that the CHA_2DS_2VASc scores of patients presenting with asymptomatic or atypical AF are higher than of those with typical AF.[47] However, the 'RAte Control versus Electrical cardioversion for persistent atrial fibrillation' (RACE) study showed that asymptomatic patients had a better prognosis than symptomatic patients.[48] Zink et al. screened for known and new AF in pharmacies.[49] They found that patients with screen-detected AF had a higher mortality risk and risk for hospitalisation within one year, than patients with a normal rhythm. However, they did not compare patients with screen-detected AF to patients with otherwise detected AF. Furthermore, including known AF in the screening group may have distorted the results.

Do patients with screen-detected AF have common characteristics regarding prognosis and reaction to therapy? Perhaps it is merely the detection pathway that they share. Which patients are detected by means of screening depends on many aspects, such as the patient selection criteria, the setting in which they are screened, and the tools that are used. Also, the organisation of everyday health care in the screening area may be of influence. If in current care the awareness of AF is already high, many patients may already have been discovered. Consequently, the yield of screening may be low. In other areas, health care may be less focussed on AF-detection and the yield may be higher, possibly detecting patients with other characteristics. Research comparing screen-detected and otherwise detected AF needs to be interpreted with care, considering the method, population and setting of screening.

Recently the LOOP study was published.[50] This RCT compared an implantable loop recorder with usual care in patients aged 70-90 years with at least one additional stroke risk factor. AF detection increased threefold, and anticoagulation was initiated. However, the risk of stroke or systemic arterial embolism was not reduced, implying that not all screen-detected AF needs to be treated with anticoagulation. The data suggested that patients with dysregulated hypertension could possibly benefit from screening for AF and subsequent anticoagulation, but this requires further research.

Screen-detected AF may have other characteristics than AF not detected by screening. Treatment of AF detected by an implantable loop recorder did not result in a reduction of strokes or embolisms. Further research is needed to evaluate the prognosis and the effect of treatment in screen-detected AF, preferably using hard

endpoints such as stroke and death. Meanwhile we should treat screen-detected AF according to current protocols for AF.

Future research

More RCTs evaluating the effect of screening for AF are needed, preferably with hard endpoints (stroke and death). A meta-analysis, combining the data of RCTs to evaluate the effect of screening may give more insight. In other settings than ours – i.e. usual care in the Netherlands – screening may still be worthwhile, for instance in settings with less attention for AF detection and a higher expected prevalence of undetected AF. Narrowing down the population to those more at risk of having AF, might also increase the yield of screening.

Ambulatory monitoring seems to be used less often than recommended in the guidelines. In the home monitoring part of our trial, we experienced a large dropout of patients, due to reluctance to use it. Easily applicable rhythm monitoring devices should be evaluated further, regarding diagnostic properties and the yield of newly diagnosed AF when used for screening purposes.

Future research is needed to evaluate screen-detected AF. Characteristics, prognosis, and effect of treatment should be clarified, as this information is crucial when considering implementing screening. Preferably this should be done in different settings, for instance primary and secondary care, and geographic areas. The characteristics, prognosis and effect of treatment may also depend on these situational factors and should be clarified.

Conclusion

This thesis contributes to the worldwide discussion on the detection of AF and how to enhance it. In opportunistic screening in general practice, the handheld ECG had better diagnostic characteristics than radial pulse palpation and eBPM. We do not recommend to screen for AF by means of radial pulse palpation, as the devices outmatch it. Intermittent measurements of the handheld ECG at home for opportunistic screening purposes are not accurate enough and should not be performed. Detection of AF in the Netherlands is already of a high standard. Opportunistic screening in this setting, among patients aged ≥65 years, is not useful. However, in other settings and with different monitoring devices, screening for AF may still prove worthwhile. Further research is needed to identify high risk groups in which screening is effective.

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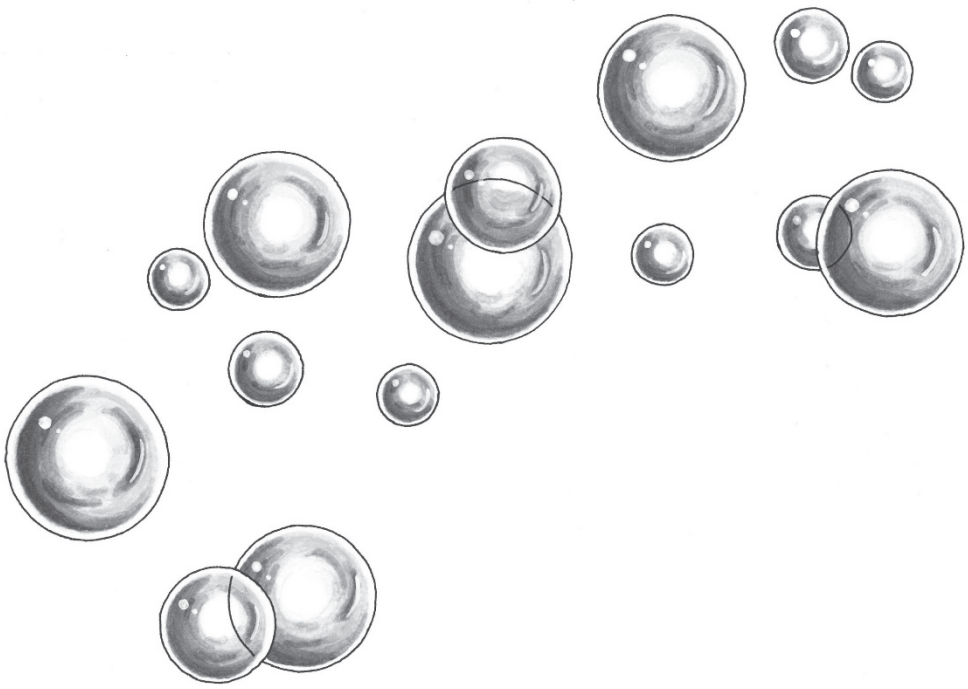
Chapter 11

Impact



Impact

Research is driven by the urge to improve the world around us. It is usually inspired by a problem in daily life. The problem we addressed, was the occurrence of serious medical events such as a stroke, heart failure and death, as a consequence of undetected atrial fibrillation (AF). Our aim was to detect AF in an early stage, to prevent these severe consequences. We gathered knowledge by performing research, to find ways to solve the issue. Now, years after the start of our studies, when the research is finished, it is very important to look back to the problem in daily life that inspired us in the first place. How should the results be interpreted? In this chapter we reflect on how our research can influence daily life (societal impact) and science (scientific impact).

Societal impact

Research can impact society on different levels, such as climate, culture, and economy. The societal impact of this thesis can best be described in terms of policy making, industry and health. We also put our results in an international perspective.

Policy making

We initiated our trial with the intention to improve AF detection. Against our expectations, we did not pave the way for opportunistic screening. On the contrary: our results make us question dearly whether it should be done at all. Therefore, we do not recommend incorporating screening for AF in the Dutch 'NHG-standaarden', even though international guidelines already advise screening.[1-5]

In the usual care group, we found that diagnosis of AF was generally the result of an interdisciplinary process. General practitioners (GPs) most often detected the irregular pulse, whereas the cardiologists usually diagnosed it. A smooth cooperation between these physicians is therefore very important. We recommend making local working agreements to facilitate this process. These could comprise easy referral options, a possibility to share electrocardiography (ECG) recordings with a cardiologist for specialist advise, and/or protocolised care pathways.

Industry

In our diagnostic accuracy study (chapter 6) we used three AF detection methods for opportunistic screening: radial pulse palpation and measurements with two devices with built-in AF detection algorithm – an electronic blood pressure monitor

('eBPM', WatchBP Home A) and a single-lead ECG device ('handheld ECG', MyDiagnostick). The eBPM and the handheld ECG were both suitable for opportunistic screening purposes. The handheld ECG device had the best diagnostic accuracy. Being able to measure blood pressure with the eBPM can be an advantage. However, the ability to extract a rhythm strip from the handheld ECG might even be more convenient, especially if the quality is sufficient for diagnosing AF.[6] We assessed the rhythm strips of the intermittent home measurements described in chapter 7; sensitivity and specificity were lower than for single measurements in general practice. Furthermore, cardiologists judged the quality to be poor for the measurements at home. However, another study showed that AF can safely be ruled out using the rhythm strips of the same device, when the measurements are not performed at home but supervised by a GP.[7] The setting, performer, and number of measurements seem to influence both the accuracy and the quality of the recording. Ensuring a good quality of the rhythm strips under different circumstances is important when developing single-lead ECG devices. Direct feedback by means of a screen with a visible rhythm strip could facilitate this.

Ambulatory monitoring by means of a Holter or event recorder does not seem to be a popular method among professionals and patients. Performing ambulatory monitoring can be burdensome for patients; they must temporarily disconnect the device while bathing or showering, and it can be a nuisance when going to sleep. In our vignette studies in chapter 2 and 3, GPs and cardiologists chose long-term monitoring less often than recommended by the guidelines. Furthermore, in our trial we experienced a large dropout of patients before and during the two-week Holter and intermittent single-lead ECG measurements. The yield of new cases in asymptomatic patients of ≥65 years with a negative 12-lead ECG was low. This might be due to a selection bias; those that did perform the measurements at home were younger and had less comorbidity. However, consistently applying ambulatory monitoring in patients with intermittent signs or symptoms, as recommended by the guidelines, might still enhance AF detection.

Industry has already reacted to the reluctance to perform ambulatory monitoring, with the development of innovative and less obtrusive methods. Examples of these new methods are ECG patches, smartwatches, and smartphones.[8, 9] However, many of these devices still require validation. In the survey in chapter 9 we explored consumer-facing wearables, devices and apps for AF detection. Currently health care professionals around the world believe we are not ready to implement them to

screen for AF. We first need to better define suitable individuals for screening and an appropriate mechanism for managing positive results.
The results of our research can impact the development of devices. We advise to focus on the development of continuously instead of intermittently measuring devices. The challenge is to develop valid, reliable, and patient friendly devices for long-term monitoring.

Health care
The proposed opportunistic screening strategy in the Detecting and Diagnosing Atrial Fibrillation (D_2AF) study, described in chapter 4 to 8, was ineffective and cannot, as such, be implemented in everyday health care. We showed that usual care is equally effective in detecting AF, therefore, patients will not be screened for AF. We spare patients from having to undergo unnecessary testing. However, the ineffectiveness of opportunistic screening in our setting, does not mean that the investigated devices are useless. When the blood pressure needs to be taken, one might as well use a device with AF-detection function. This is in line with the advice of the Dutch College of General Practitioners to assess heart rhythm when measuring blood pressure.[1]
It is tempting to use the handheld ECG as a diagnostic tool in other situations, for instance in patients with symptoms suggestive of AF, or in home dwelling patients who cannot visit the practice for a 12-lead ECG. However, our results cannot be extended to these patient groups and previous research on the MyDiagnostick also focussed on screening settings, so we still advise caution when applying the device in other situations.[10-12] Furthermore, the AF detection algorithm of other handheld ECG and eBPM devices may differ from the devices that we used. Therefore, diagnostic accuracy can be different. As such, our results are not automatically applicable to other devices.

International collaboration
Different guidelines from various countries give advice on diagnostic procedures for AF.[1-5] International guidelines advise screening, while the Dutch guideline does not. Studies from varying countries gave contradictory results regarding the effect of screening.[13-17] It is important to look at these international differences, to uncover which factors attribute to success and which to a lack of effect. An international research agenda could facilitate the process and create cohesion.

The publication of the D_2AF study protocol aroused the interest of the AF-SCREEN international collaboration, a group promoting discussion and research about screening for AF. Steven Uittenbogaart and I were invited to attended an AF-SCREEN meeting in Rome in 2016.[18] During this gathering, we took part in a consensus procedure on recommendations on screening for AF, resulting from a Delphi process. The two of us and the 49 other attendents voted and proposed changes, which were worked out further in a smaller group the next day. This resulted in the publication of a white paper.[19] With our vote we were able to have an impact on these international recommendations.

In 2019 the members of the collaboration distributed a survey among their colleagues, on the use of wearables and devices.[20] The results were presented in chapter 9. It is because of the collaboration, that the survey could be distributed widely, reaching different kinds of health care professionals internationally.

In the future, the collaboration may be used to perform larger international studies, or facilitate the exchange of data. However, as scientists devoted to screening for AF, we must ensure not to develop tunnel vision. Keeping an open mind is important, because – as we showed in our trial – screening for AF is not always effective.

Scientific impact

We now have a look at how our results impact science. However, what defines scientific impact? To clarify that, we go back to the first randomised controlled trial (RCT), conducted by Bradford Hill.[21] He laid the foundations for modern medical research in 1948, when he successfully showed that streptomycin was more effective than only bedrest in treating tuberculosis. Ever since, RCTs represent a high methodological quality in evidence-based medicine, with great scientific impact.

Trials with a significant positive effect, such as the trial of Bradfort Hill, usually get the most attention.[22] They lead to new treatments or diagnostic strategies and provide a clear path to improve current practice. In contrast, negative trials are often regarded as failures. They were (and still are) underrepresented; it is more difficult to get the results published, they have a lower citation index, are less often presented at conferences, and get less attention in the media than positive trials.[23] Measuring scientific impact by the attention a study gets, however, is unjust. The importance of negative trials – if they are not underpowered – is underrated. The results show us what *not* to do and can lead to valuable hypotheses for new research. Furthermore, highlighting positive trials at the expense of negative trials

can create a distorted view of reality, especially when results of trials are bundled in systematic reviews or meta-analyses.

Screening for AF

Let us focus on our research field. In 2007 Fitzmaurice et al. published the 'Screening For AF in the Elderly' (SAFE) study. This RCT on screening for AF showed a positive effect of screening.[13] After this, AF detection became a hot topic. In the past two decades, many studies were performed in different settings, looking at various aspects of screening. Which device should be used?[24-26] In which setting and which population should we screen?[27-31] The European Society of Cardiology (ESC) recommended opportunistic screening in the updated guideline on management of AF in 2016.[32] In 2017 Halcox et al. confirmed the positive effect of screening in the 'Assessment of REmote HEArt Rhythm Sampling using the AliveCor heart monitor to scrEen for Atrial Fibrillation' (REHEARSE-AF) trial.[14] Small systematic reviews on screening for AF were performed in 2018 and 2019, favouring screening.[33, 34] But then, in 2020, two Dutch RCTs, our own D_2AF study (chapter 8) and the 'Improving DEtection of Atrial fibriLlation in Primary Care With the MyDiagnostick' (IDEAL-MD) study, showed no effect of screening for AF.[15] While we all thought screening for AF was effective, now doubt arose. Even though our trial was negative, it was ever so important: it made us question the benefit of screening, which was previously assumed to be certain.

The conflicting results on the effect of screening for AF could inspire other scientists. In future systematic reviews on the effect of screening for AF, the inclusion of our study might shift the balance. Future research could focus on screening in populations with a low incidence of AF or select patients based on risk factors for development of AF, for instance heart failure and hypertension. More research is needed to uncover which factors lead to an effective intervention.

Conclusion

We demonstrated that opportunistic screening for AF is not effective in Dutch patients ≥65 years of age. We show that a change of course is necessary in research on AF detection. Hopefully our research will impact the direction of future research, like a pebble in the pond.

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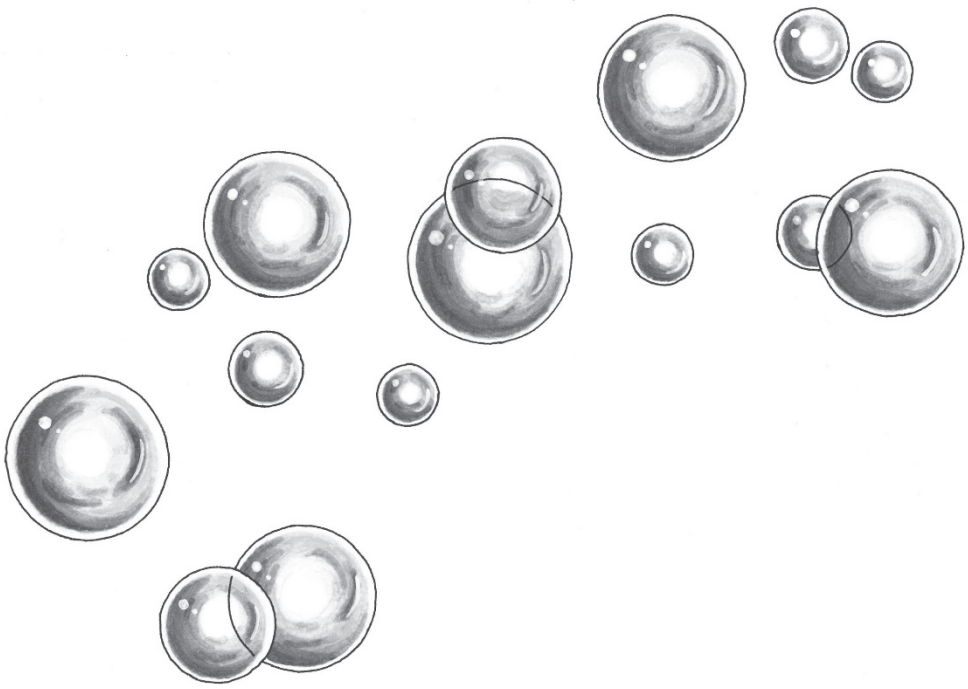
Summary



Summary

Atrial fibrillation (AF) is a common arrhythmia, especially among the elderly. However, patients may remain undetected, as it can be asymptomatic (silent AF) or occur intermittently (paroxysmal AF). Due to possible serious consequences such as a stroke, it is important to find patients with AF in an early stage. The detection of undiagnosed AF is the topic of this dissertation.

Chapter 1 gives a general introduction into the subject. It describes the pathophysiology of AF, the importance of early diagnosis, and the difficulties health care workers face in the detection.

Clarifying current practice could give more insight in how to improve AF detection. Both general practitioners (GPs) and cardiologists are key players in the detection of AF. They can diagnose and treat patients with AF independently or collaborate in the process. In chapter 2 we focus on the diagnostic choices of cardiologists. We developed an online survey with six case vignettes, which is a concise way of presenting a situation to evoke judgement. One case vignette covered a patient without signs or symptoms of AF, but with cardiovascular risk factors from the CHA_2DS_2VASc score. Performing diagnostic tests if no signs or symptoms are present, is called (opportunistic) screening. Nearly half of the cardiologists answered that they would perform diagnostic tests in this case. The other five case vignettes covered patients with various signs and symptoms of different frequencies. All but one cardiologist would perform tests in these cases. However, monitoring duration was shorter then recommended in patients with symptoms less than once daily. Following the case vignettes, we inquired after the availability of diagnostic tools; cardiologists had many different ambulatory monitoring tools at their disposal, but only 10% of them had access to a single-lead electrocardiography (ECG) device.

After exploring cardiologists' choices regarding AF detection, we focus on GPs in chapter 3. We modified the survey to fit the situation of GPs but retained the core of the six case vignettes. One out of three GPs would perform diagnostic tests in the patient without signs and symptoms of AF but with cardiovascular risk factors, in contrast to nearly half of the cardiologists. This reflects the lower prior probability of pathology in primary care compared to secondary care. All GPs would perform

diagnostic tests in the other case vignettes, which is consistent with the actions of cardiologists. GPs showed the same tendency as cardiologists to perform shorter monitoring than recommended in the guidelines. As GPs might not have the same confidence as cardiologists in performing the diagnostic work-up of AF, we inquired after their own perceived competence. Nearly all GPs declared they had enough knowledge and experience to diagnose AF. Almost all GPs could order a 12-lead ECG without the interference of a cardiologist. Four out of five GPs would support screening for AF, should it prove to be effective.

After the fictional patients of the case vignettes, we lay the foundation for our screening study in **chapter 4**. We describe the protocol of the Detecting and Diagnosing Atrial Fibrillation (D_2AF) study, a cluster randomised controlled trial (RCT) on opportunistic screening – or case finding – for AF among patients of 65 years and over in primary care. We used three screening methods (index tests): radial pulse palpation and measurements with two devices with a built-in AF detection algorithm, namely an electronic blood pressure monitor ('eBPM') and a single-lead ECG device ('handheld ECG'). Patients with at least one positive index test received a 12-lead ECG, just as a random sample of patients with three negative index tests. All patients without AF on the 12-lead ECG were eligible for home measurements for two weeks, with the handheld ECG and a Holter device.

Three other studies in this dissertation were embedded in the RCT. In the 'usual care' (control) arm of the RCT we performed a cohort study, to explore in what way patients with new AF were found in everyday health care. In the 'intention-to-screen' (intervention) arm we carried out a diagnostic accuracy study to determine and compare test characteristics of the three screening methods. A second study in this arm explored the yield of AF from home measurements and the test characteristics of repeated handheld ECG measurements at home.

In chapter 2 and 3 we explored current practice by means of case vignettes. In **chapter 5** we describe the way real-life patients with new AF were found in everyday health care. In the control practices of the D_2AF study, we found 285 patients with new AF after a mean follow-up of more than two years. Of 258 of them, we reviewed the electronic medical files. The irregular pulse was most often first noted in general practice, but cardiologists most often diagnosed AF. Although AF diagnosis was largely triggered by symptoms, one third of patients had silent AF and was

discovered incidentally. Only nine patients were detected after a stroke. Diagnosis was based on a 12-lead ECG in most cases. This cohort study showed that diagnosing AF is a multidisciplinary process, in which GPs, cardiologists and other physicians are involved in various combinations.

A 12-lead ECG is too time-consuming for opportunistic screening for AF in general practice. Different simple tests – some more innovative than others – can be performed instead. Chapter 6 presents the diagnostic properties of the three index tests we used for opportunistic screening of AF in the intervention arm of the RCT. A total of 4339 patients was screened with the index tests. If one or more of these tests indicated AF, a 12-lead ECG was performed. A random sample of 10% of patients with three negative index tests also got a 12-lead ECG. Sensitivity, specificity, and predictive values were highest for the handheld ECG (MyDiagnostick), followed by the eBPM (WatchBP Home A) and radial pulse palpation. Both devices were more accurate screening tools than radial pulse palpation. Different combinations of these tests did not improve diagnostic characteristics.

Apart from measurements at the general practice, patients also performed diagnostic tests at home. In chapter 7 we describe the results of this study. After a negative 12-lead ECG, we asked patients to take home a Holter device and to hold the handheld ECG trice daily for two weeks. In total, 291 patients performed home measurements, of 205 of them we had simultaneous measurements with both devices. We diagnosed new paroxysmal AF with the Holter device in four patients (prevalence 1.5%). Diagnostic accuracy of the intermittently used handheld ECG device was limited with a high false-positive rate. Quality of the rhythm strips was poor.

In chapter 8 we present the results of the cluster RCT on opportunistic screening of AF. We recruited 96 general practices, 47 were randomised to opportunistic screening and 49 to usual care. In each practice we randomly selected 200 patients of 65 years or older, without known AF. When patients in the screening arm visited the practice for any reason, they were asked to participate in the trial. Radial pulse palpation was performed first, followed by measurements with the eBPM and handheld ECG in a pre-set order per practice.
Follow-up was complete for 8874 patients in the intention-to-screen group and 9102 in the usual care group. Within the study year, 4106 patients were screened, 30 of

whom had new AF. After the study year we compared the percentage of new AF in both groups, on an intention-to-screen basis. Unexpectedly, we found no significant difference between the two groups; the opportunistic screening arm yielded 1.6% (n=144) new AF, compared to 1.5% (n=139) in the usual care arm.

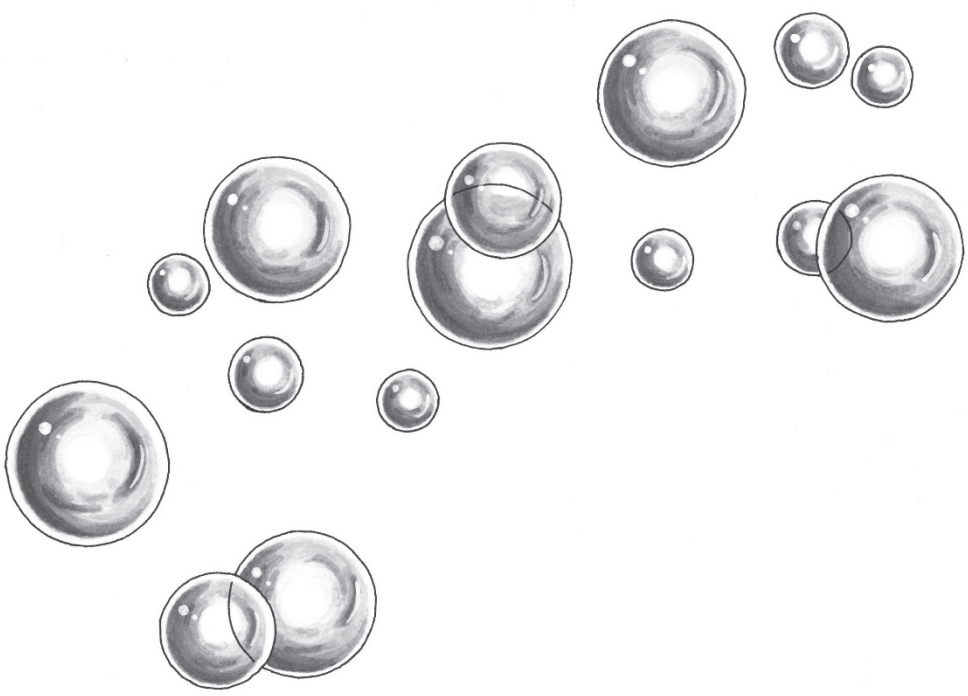
The opportunistic screening we performed did not yield enough new AF for implementation in daily practice. However, other methods dan ours can still be considered. In chapter 9 we investigate what might be the future of AF detection. On the consumer market, there are devices and apps to detect AF in abundance. To clarify their role in screening, the AF-SCREEN international collaboration (a group promoting discussion and research about screening for AF) conducted a survey among health care professionals. The survey was distributed by the AF-SCREEN members to 2481 health care professionals, 588 of whom completed it. Fifty-seven percent of the respondents indicated to advise devices or apps at least sometimes. Almost 70% of respondents believed we are not yet ready for mass consumer-initiated screening for AF using devices and/or apps. It might cause patient anxiety, false positives and negatives, and anticoagulant-related bleeding. Also, there is a need for appropriate management pathways before implementation.

The general discussion of this thesis is presented in chapter 10. Here we give an overview of our findings and put them in a broader perspective. It handles the methodological and practical considerations of our research. A characteristic trait of the study was the combination of four sub-studies in one overarching design. This design came with practical challenges, concerning for instance the study period and population. However, it also enabled us to determine diagnostic test characteristics in a large population without known AF. Moreover, we were able to test the MyDiagnostick in different settings; it turned out to perform well in the consultation room, but not when handled by patients at home.
Next we reflect on the implications for general practice and future research. The many devices for AF detection that are currently on the market, are not yet ready for mass screening. More research is needed to validate them. We found no effect of opportunistic screening, therefore we do not recommend implementing it in the Netherlands. Future research could focus on screening in a population with a higher risk of AF and on monitoring with user friendly tools,

In **chapter 11** we reflect on how our research can influence the world around us. It is split up in two parts, discussing societal and scientific impact. We place the negative results of our trial into the context of the research field of AF-screening. Several previous studies did find a positive effect of screening. It would be interesting to perform a meta-analysis in the future, which combines the results of these different studies. Furthermore, we discuss the impact this thesis may have on policy making, industry, health and on international collaboration. AF diagnosis was often the result of a multidisciplinary approach. We therefore recommend to facilitate this process, for instance by means of short referral routes or the option to share an ECG with a cardiologist. Different devices for AF detection are already available, this is a rapidly developing industry. Especially for rhythm monitoring at home patient friendly and reliable devices are still lacking.

Our aim was to find ways to detect AF in an earlier stage. Unfortunately, our opportunistic screening protocol did not yield more AF cases than usual care. However, our research does contribute substantially to the knowledge of AF-detection and will give guidance to future research.

Samenvatting



Samenvatting

Atriumfibrilleren (AF) komt veel voor, vooral onder ouderen. Patiënten kunnen echter lang onontdekt blijven, omdat AF asymptomatisch kan zijn of intermitterend (paroxysmaal) kan optreden. Het is belangrijk om het in een vroeg stadium vast te stellen, omdat het ernstige gevolgen kan hebben zoals een cerebrovasculair accident (CVA). De detectie van onontdekt AF is het onderwerp van dit proefschrift.

Hoofdstuk 1 geeft een algemene introductie in het onderwerp. Het beschrijft de pathofysiologie van AF, het belang van vroege diagnose en de problemen die medische professionals tegenkomen in de detectie ervan.

Een beschrijving van de huidige zorg kan leiden tot inzichten om AF detectie te verbeteren. Zowel huisartsen als cardiologen zijn centrale figuren in de detectie van AF. Ze kunnen patiënten met AF beiden diagnosticeren en behandelen, onafhankelijk of in samenwerking. In **hoofdstuk 2** focussen we op de diagnostische keuzes van cardiologen. We ontwikkelden een online enquête met zes vignetten, waarin een casus beknopt gepresenteerd werd. Eén vignet beschreef een patiënt zonder symptomen of afwijkingen bij lichamelijk onderzoek die bij AF passen, maar met cardiovasculaire risicofactoren uit de CHA_2DS_2VASc score. Het verrichten van diagnostiek in afwezigheid van symptomen of afwijkingen bij lichamelijk onderzoek, is (opportunistische) screening. Bijna de helft van de cardiologen antwoordde bij dit vignet dat ze diagnostiek zouden verrichten. De andere vijf vignetten beschreven patiënten met verschillende symptoomfrequenties en afwijkingen bij lichamelijk onderzoek. Op één cardioloog na, zouden alle respondenten diagnostiek uitvoeren in deze cases. De monitorduur was korter dan de richtlijnen aanraden bij patiënten die minder dan eenmaal daags symptomen hadden. Na de vignetten, inventariseerden we de beschikbaarheid van diagnostische apparatuur; cardiologen hadden veel verschillende apparaten voor ambulante monitoring, maar slechts 10% van hen had toegang tot een 1-kanaals elektrocardiografie (ECG) apparaat.

Na de uiteenzetting over de keuzes van cardiologen m.b.t. AF detectie, focussen we op huisartsen in **hoofdstuk 3**. We maakten de enquête passend voor de situatie van huisartsen, maar handhaafden de kern van de zes vignetten. Eén op de drie huisartsen zou diagnostiek verrichten bij de casus met enkel cardiovasculaire

risicofactoren, ten opzichte van bijna de helft van de cardiologen. Dit is een reflectie van de lagere priorkans op pathologie in de eerste lijn vergeleken met de tweede lijn. Alle huisartsen zouden diagnostiek verrichten in de andere vignetten, wat overeenkomt met de cardiologen. Huisartsen lieten dezelfde trend als cardiologen zien, om korter te monitoren dan aangeraden in de richtlijnen. Aangezien huisartsen minder routine hebben dan cardiologen in het uitvoeren van diagnostiek naar AF, vroegen we hen om hun eigen competentie op dit vlak te beoordelen. Bijna alle huisartsen gaven aan dat ze genoeg kennis en ervaring hebben om AF vast te stellen. Bijna alle huisartsen konden een 12-kanaals ECG aanvragen zonder tussenkomst van een cardioloog. Vier van de vijf huisartsen zouden screening naar AF ondersteunen als het effectief zou blijken.

Na de fictieve patiënten van de vignetten, beschrijven we nu de basis van ons screeningsonderzoek in **hoofdstuk 4**. We presenteren het protocol van de 'Detecting and Diagnosing Atrial Fibrillation' (D_2AF) studie, een cluster gerandomiseerd gecontroleerd onderzoek (RCT) naar opportunistische screening naar AF onder mensen van 65 jaar en ouder in de eerste lijn. We pasten drie methoden (indextesten) toe: radiale pols palpatie en metingen met twee apparaten met een ingebouwd AF detectie algoritme, namelijk een elektronische bloeddrukmeter en een 1-kanaals ECG-apparaat. Bij minstens één positieve indextest, onderging de patiënt een 12-kanaals ECG, net als in een willekeurige steekproef van patiënten met drie negatieve indextesten. Alle patiënten zonder AF op het 12-kanaals ECG werden uitgenodigd om thuismetingen te verrichten voor twee weken met het 1-kanaals ECG en een Holter apparaat.

Drie andere studies uit dit proefschrift waren ingebed in de RCT. In de 'reguliere zorg' (controle) arm van de RCT voerden we een cohortstudie uit, om uit te vinden hoe patiënten met nieuw gediagnosticeerd AF gevonden worden in de dagelijkse praktijk. In de 'intentie-om-te-screenen' (interventie) arm, voerden we een onderzoek uit naar de diagnostische accuratesse van de drie screening methoden. Een tweede studie in deze arm bekeek de opbrengst van nieuw AF uit de thuismetingen en de testeigenschappen van herhaalde metingen met het 1-kanaals ECG in de thuissituatie.

In hoofdstuk 2 en 3 bestudeerden we de reguliere zorg met behulp van vignetten. In **hoofdstuk 5** beschrijven we hoe echte patiënten met nieuw gediagnosticeerd AF

gevonden werden in de praktijk. In de controlepraktijken van de D_2AF studie vonden we 285 patiënten met nieuw AF, na een gemiddelde follow-up van meer dan twee jaar. Van 258 van hen bekeken we de elektronische medisch dossiers. De onregelmatige pols werd het vaakst gevonden in de huisartspraktijk, maar cardiologen stelden de diagnose AF het vaakst vast. Hoewel het stellen van de diagnose vooral getriggerd werd door symptomen, werd een derde van de patiënten per toeval gevonden. Slechts negen patiënten werden gediagnosticeerd na een CVA. De diagnose was in de meeste gevallen gebaseerd op een 12-kanaals ECG. Deze cohortstudie liet zien dat de diagnose van AF een multidisciplinair proces is, waarbij huisartsen, cardiologen en andere artsen betrokken zijn in verschillende combinaties.

Voor opportunistische screening in de huisartspraktijk kost het verrichten van een 12-kanaals ECG te veel tijd. Verschillende testen – sommige innovatiever dan andere – kunnen in plaats daarvan gebruikt worden. In **hoofdstuk 6** presenteren we de diagnostische eigenschappen van de drie indextesten die we gebruikten voor opportunistische screening naar AF in de interventiearm van de RCT. In totaal werden 4339 patiënten gescreend met de indextesten. Als één of meer van deze testen op AF wees, werd een 12-kanaals ECG verricht. Een willekeurige steekproef van 10% van de patiënten met drie negatieve indextesten onderging een 12-kanaals ECG. De sensitiviteit, specificiteit en voorspellende waarden van het 1-kanaals ECG (MyDiagnostick) waren het hoogste, gevolgd door de elektronische bloeddrukmeter (WatchBP Home A) en radiale polspalpatie. De diagnostische karakteristieken verbeterden niet als we de indextesten combineerden.

Naast de metingen in de huisartspraktijk, verrichtten patiënten ook thuis metingen. In **hoofdstuk 7** beschrijven we de resultaten daarvan. Na een negatief 12-kanaals ECG vroegen we patiënten om een Holter apparaat mee te nemen en om twee weken lang drie keer per dag het 1-kanaals ECG apparaat vast te houden. In totaal verrichtten 291 patiënten thuismetingen, van 205 van hen hadden we simultane metingen met beide apparaten. We stelden bij vier patiënten paroxysmaal AF vast op de Holter (prevalentie 1.5%). De diagnostische accuratesse van intermitterend gebruik van het 1-kanaals ECG was beperkt, er waren veel fout-positieven. De kwaliteit van de ritmestroken was slecht.

In **hoofdstuk 8** presenteren we de resultaten van de cluster RCT over opportunistische screening naar AF. We rekruteerden 96 huisartspraktijken, waarvan er 47 gerandomiseerd werden om opportunistische screening te verrichten en 49 gebruikelijke zorg. In elke praktijk selecteerden we willekeurig 200 patiënten van 65 jaar en ouder, niet bekend met AF. Als patiënten om welke reden ook de huisartspraktijk bezochten in de screening arm, dan werden ze gevraagd voor deelname aan de studie. Eerst werd polspalpatie verricht, gevolgd door metingen met de elektronische bloeddrukmeter en het 1-kanaals ECG apparaat in een vooraf vastgestelde volgorde per praktijk.
De follow-up was compleet voor 8874 patiënten in de interventiegroep en 9102 in de controlegroep. Binnen het studiejaar werden er 4106 patiënten gescreend, waarvan er bij 30 mensen nieuw AF gediagnosticeerd werd. Na het studiejaar vergeleken we het percentage nieuw AF in beide groepen. Onverwacht vonden we geen significant verschil tussen beide groepen; in de opportunistische screening arm vonden we nieuw AF bij 1.6% (n=144), vergeleken met 1.5% (n=139) in de controlearm.

De door ons uitgevoerde opportunistische screening leverde onvoldoende nieuwe AF gevallen op om in de praktijk toegepast te worden. Echter, andere methodes dan de onze kunnen nog steeds overwogen worden. In **hoofdstuk 9** werpen we een blik op wat de toekomst van AF detectie zou kunnen zijn. Op de consumentenmarkt zijn er apparaten en apps in overvloed voor het vaststellen van AF. Om de rol hiervan in screening te verhelderen, verrichtte de 'AF-SCREEN international collaboration' (een groep die onderzoek naar AF en de bespreking ervan promoot) een enquête onder zorgprofessionals. De enquête werd verspreid door leden van AF-SCREEN onder 2481 medische professionals, waarvan 588 de vragenlijst compleet invulden. Zevenenvijftig procent van de respondenten gaf aan dat ze ten minste soms apparatuur of apps aanraden. Bijna 70% van de respondenten gaf aan dat we nog niet klaar zijn voor massale consument-geïnitieerde screening naar AF met apparatuur en/of apps. Het kan angstklachten veroorzaken bij patiënten, foutpositieve en -negatieve uitslagen geven en bloedingen als gevolg van anticoagulantia. Daarnaast is er behoefte aan een passend behandelprotocol voor er op deze manier gescreend kan worden.

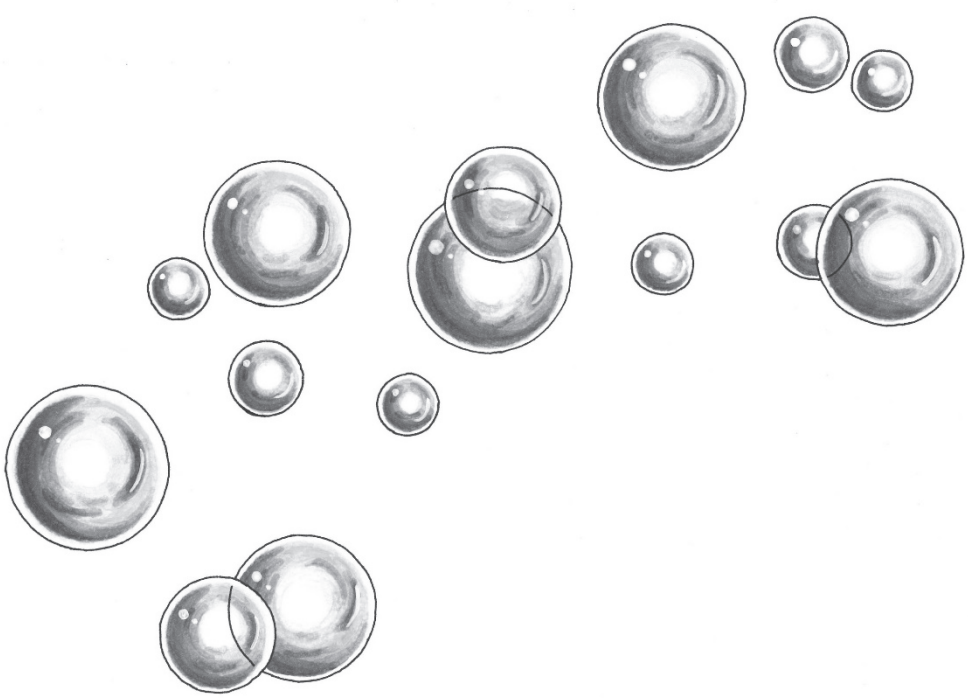
De algemene discussie van dit proefschrift is te vinden in **hoofdstuk 10**. Hier bieden we een overzicht van onze bevindingen en plaatsen ze in een breder perspectief. We beschrijven de methodologische en praktische overwegingen bij ons onderzoek.

Een karakteristieke eigenschap van de studie was de combinatie van vier deelstudies in één overkoepelend design. Dit leidde tot een aantal praktische uitdagingen rondom o.a. looptijd en populatiekeuze. Echter het stelde het ons wel in staat om diagnostische testeigenschappen vast te stellen in een grote populatie zonder gediagnosticeerd AF. Daarnaast konden we de MyDiagnostick testen in verschillende situaties; hij bleek het in de spreekkamer erg goed te doen, maar niet bij herhaalde metingen door de patiënt thuis.
Verder reflecteren we op de implicaties voor de huisartspraktijk en toekomstig onderzoek. De vele apparaten die momenteel op de markt zijn voor AF-detectie, zijn nog niet klaar voor massale screening. Er moet nog meer onderzoek gedaan worden om apparaten te valideren. We vonden geen effect van opportunistische screening en raden dus momenteel niet aan om dit in Nederland te implementeren. In de toekomst zou onderzoek zich kunnen richten op screening in een populatie met een hoger risico op AF en op thuismonitoring met toegankelijke apparatuur.

In **hoofdstuk 11** reflecteren we hoe ons onderzoek de wereld om ons heen kan beïnvloeden. Dit hoofdstuk is in twee parten onderverdeeld, waarin de impact op de maatschappij en de wetenschap behandeld wordt. We plaatsen de negatieve resultaten van onze trial in de context van het onderzoeksveld van screening naar AF. Verscheidene eerdere onderzoeken vonden wel een positief effect van screening. Het zou interessant zijn om in de toekomst een meta-analyse te verrichten waarin de resultaten van de verschillende studies gebundeld worden. Daarnaast bespreken we de impact die dit proefschrift kan hebben op beleidsvorming, industrie, gezondheid en internationale samenwerking. De diagnose AF was vaak het resultaat van een interdisciplinaire samenwerking. We raden daarom aan om dit proces zo veel mogelijk te faciliteren, bijvoorbeeld met korte verwijsroutes of de optie om een ECG te delen met een cardioloog. Er zijn al verscheidene diagnostische apparaten voor AF detectie, de ontwikkeling ervan staat niet stil. Met name voor het thuis monitoren van het ritme ontbreekt nog patiëntvriendelijke en betrouwbare apparatuur.

Ons doel was om manieren te vinden om AF in een vroeg stadium vast te stellen. Helaas leidde ons opportunistische screeningsprotocol niet tot meer nieuwe AF-diagnoses dan gebruikelijke zorg. Ons onderzoek draagt echter wel substantieel bij aan de kennis rondom AF detectie en zal richting geven aan toekomstig onderzoek.

Dankwoord



Dankwoord

Klaar (bn):

af, afgehandeld, afgelopen, bereid, gedaan, gepiept, gereed, paraat, ready, rond, uit, voltooid, voor elkaar, voor mekaar, voorbij [*]

Na ruim acht jaar, mag ik nu zeggen dat het KLAAR is! Op de vaak gestelde vraag hoe ver ik was met mijn promotie, heb ik zo ongeveer de laatste drie jaar gezegd dat ik *bijna* klaar was. Ik kon goed sympatiseren met de ezel die een wortel voorgehouden krijgt aan het eind van een stok, zo leek het einde van mijn promotie namelijk ook steeds een beetje op te schuiven. Bereid om concessies te doen op de kwaliteit en eerder af te ronden, was ik echter ook niet. Daarom is de voldoening nu des te groter, om een flinke hap uit die wortel te nemen!
Zonder de steun van anderen, zou de wortel nog steeds buiten bereik zijn. Daarom wil ik in dit deel van mijn proefschrift iedereen bedanken die eraan heeft bijgedragen. Ik noem een aantal mensen in het bijzonder.

Hoe kan ik anders, dan te beginnen met **Jelle**. Jelle, bedankt dat je mij hebt uitverkoren om jouw promovendus te worden. Zo voelde ik me namelijk, toen je zei dat je mij wilde hebben op het D_2AF project. Als ridder aan jouw ronde tafel op kamer A 3.041, streed ik samen met jou voor een goed verloop van de studie. Het vertrouwen dat je altijd in mij had, heeft mij doen groeien als onderzoeker en persoon. Jouw zorgvuldigheid en gedrevenheid tilden ons werk steeds weer naar een hoger level. Je grapte tijdens een overleg eens dat we best wel op elkaar lijken, en dat zie ik als een mooi compliment.

Petra, dank je wel voor je steun en geduld. Jij had het pad waar ik op liep al eens bewandeld en ik kon veel leren van jouw ervaringen. Ook in ons persoonlijk leven hadden we veel raakvlakken, wat onze gesprekken bij een kopje thee heel fijn en waardevol maakte.

Op afstand aanwezig, maar toch ook zo ontzettend benaderbaar wanneer ik je nodig had. **André**, veel dank voor je rol in deze studie. Ik waardeer je niet alleen als promotor

[*] Synoniemen.net

en leider, maar ook als officieuze mediator en niet in de laatste plaats als persoon. Na een gesprek met jou, voelde ik me altijd lichter.

Vaste prik op dinsdagmiddag, was bellen met Wim. Wim, door de gesprekken met jou leek de afstand tussen Amsterdam en Maastricht een stuk kleiner. Dank voor je snelle antwoorden en bedankt dat je zo laagdrempelig benaderbaar was.

Tijdens de studie hadden we geregeld met zijn allen overleg in Den Bosch, halverwege tussen Amsterdam en Maastricht. Henk, voor jou was dat een thuiswedstrijd. Je humor gaf kleur aan de soms ingewikkelde discussies. Ook onze telefoongesprekken aan het eind van de studie waren voor mij erg waardevol. Houdoe en bedankt!

Steven, mijn 'partner in crime'. We hebben dit project samen gedragen. Het was fijn dat jij de honneurs waarnam als ik in de praktijk zat, zoals ik andersom voor jou deed. Ondanks de druk waaronder we werkten, heb ik ervan genoten om samen syntaxen te schrijven, om alle data bij elkaar te voegen en te analyseren. We spraken dezelfde taal, hadden aan een half woord genoeg. Bedankt dat je mijn sparringpartner was.

Bjorn, een promovenda zonder statisticus, is als Frodo zonder Sam. Jouw hulp was van onschatbare waarde. Bedankt voor je geduld en je heldere uitleg. Fijn dat je altijd tijd vond om mij verder te helpen.

Research assistentie was onmisbaar in onze studie. De meeste kilometers heb ik afgelegd met Marion, voor de vele praktijkbezoeken. Regelmatig kwamen we in het foute uur terecht, wat je gelukkig niet erg vond. Ik ben je heel dankbaar voor jouw rol in de studie, je was een onmisbare schakel. Mascha, datacleaning is een vak wat jij als de beste verstaat. Je werkte secuur en deed het ook nog eens in een handomdraai. Veel dank voor jouw ondersteuning. Sylvia, bedankt voor het vele werk wat je verzet hebt. Je pakte alles aan met frisse moed en een lach op je gezicht.

Door de wisselende trajecten van AIOTHO's heb ik meerdere kamergenoten gehad. Het was altijd weer een verrassing wie er was, maar de sfeer was altijd goed. Roomies Jolijn, Ruud, Lennart, Stijn, Michelle, Raissa en Brechtje, bedankt voor de gezelligheid en voor het uitwisselen van jullie ervaringen met mij. De meeste tijd

bracht ik door met **Eefje**, **Eva** en **Krista**. Als ik aan jullie denk, denk ik aan onze goed gevulde snoepjespot, schattige foto's van onze kroost, Omi op repeat en thee in overvloed ondanks de waterkoker die blijkbaar elk moment kon ontploffen. Lieve roomies, bedankt dat jullie mijn klankbord wilden zijn.

Dit proefschrift is door het AIOTHO-traject niet los te zien van de huisartsopleiding. In dat kader wil ik jou, **Willemjan**, bedanken. Als mijn eerstejaars huisartsopleider liet je mij zien hoe je het huisartsenvak combineerde met je eigen promotietraject. Ik had respect voor je lange adem, maar nam me voor er zelf nooit zo lang over te zullen doen. Toen dat toch het geval bleek te worden, kon ik kracht putten uit jouw voorbeeld. Daarnaast wil ik ook mijn derdejaars huisartsopleider bedanken. Bedankt lieve **Marcelle** Maria Wedemeijer. Ik ben door jou enorm gegroeid als persoon. Je daagde me uit om af en toe mijn middelvinger op te steken naar de wereld, in plaats van altijd binnen de lijntjes te kleuren. Wat voelde dat bevrijdend. Jouw voorbeeld liet mij zien dat ik ook een gelukkige huisarts kon worden.

Speciale dank aan **Kees** en **Ria** van Atelier Chaam. Wat zijn jullie fijne mensen. Jullie hebben mij geholpen om een goed ontwerp te maken voor de kaft, en wilden er niet eens iets voor terug. Door de gezellige avonden bij jullie aan de keukentafel, besefte ik dat het ontwerpen van een kaft ook een proces is, net als promoveren. Het eerste ontwerp is niet meteen het juiste, maar elk idee en elke tekening brengt je steeds dichter bij het eindresultaat. Bedankt voor jullie tijd en expertise.

Lieve **papa**. Jouw hand in dit proefschrift is onmiskenbaar (zie pagina 95). Ik weet nog goed dat je mij als kind, onder de blauwe regen in onze achtertuin, vertelde over wat een 'doctor' is. Misschien is toen het zaadje al geplant, voor het resultaat wat hier nu ligt. Jij hebt mij altijd het vertrouwen gegeven dat ik alles kan wat ik wil. Jij leerde me om groot te dromen en niet op te geven. Ik weet dat je trots op mij bent, maar ik wil je laten weten dat ik ook ontzettend trots ben op jou. Ik kan me geen betere vader wensen.

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eens te vragen, want jij kent me door en door. Ik prijs mezelf enorm gelukkig met zo'n geweldige en lieve moeder als jij.

Casper, wat fijn dat jij mijn paranimf wil zijn. Sinds onze verhuizing terug naar Chaam zien we elkaar gelukkig weer vaker. Op de tennisclub, op een feestje, of even op de thee. Jouw morele kompas is enorm goed ontwikkeld. Ik heb bewondering voor je integriteit, maar bovenal kan ik zo ontzettend met je lachen. Tijdens die momenten met jou, kon ik de werkdruk even achter me laten. Ik ben heel blij met onze band, lieve broer.

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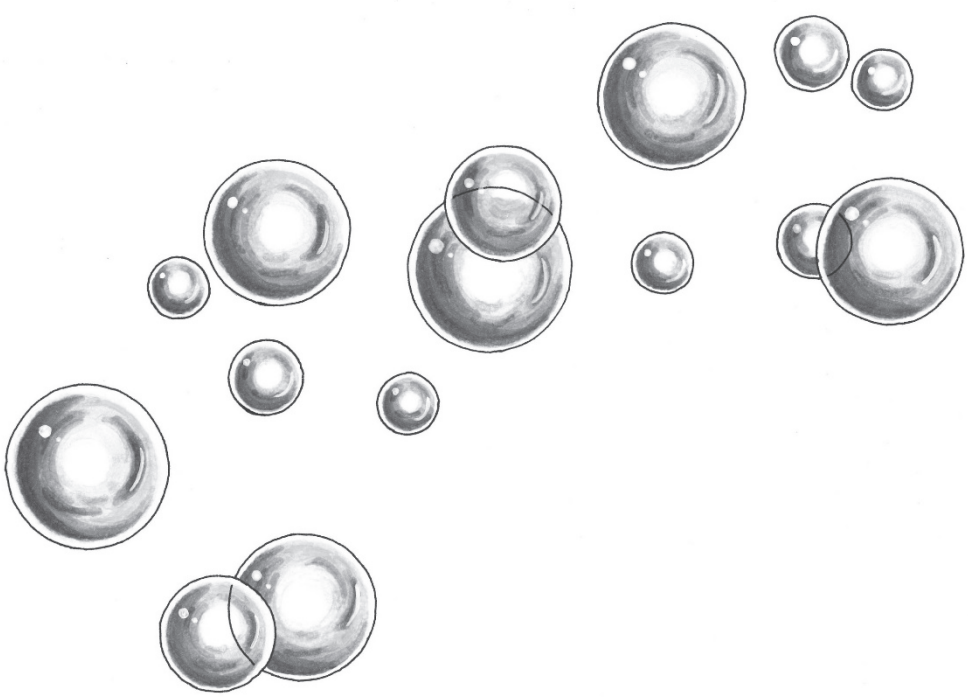
Gerard, liefde van mijn leven. Je bent niet alleen mijn echtgenoot, maar ook mijn beste vriend en mijn rots in de branding. Jij stond steeds weer voor me klaar; je leidde me af als mijn hoofd te vol was en als ik stuiterde kreeg jij me weer rustig. Je gaf mij het vertrouwen dat ik het goed deed, door jou ben ik een sterker persoon geworden. Ook inhoudelijk kon ik bij jou terecht. Door jouw eigen werk als wetenschapper kon jij mij ondersteunen als geen ander. Je was geen mede-auteur, maar de meeste stukken in deze thesis zijn ook door jou bekeken en van tips voorzien. Daarnaast maakte je me wegwijs in Adobe Illustrator zodat ik mooie plaatjes kon maken en hielp je me door data van PDF-jes automatisch te verwerken met Matlab. Bedankt dat je nu ook mijn paranimf wil zijn, zoals ik ook de jouwe was. Zonder jou was dit proefschrift er niet geweest, maar nog belangrijker: zonder jou zou mijn leven veel minder kleur hebben.

Curriculum vitae



Curriculum vitae

Op 23 januari 1988 werd Nicole Verbiest – van Gurp geboren in Breda. Ze groeide op in het Brabantse dorpje Chaam. Van 2000 tot 2006 ging zij naar het Gymnasium op De Nassau in Breda. Direct aansluitend studeerde ze geneeskunde aan Maastricht University. Haar wetenschappelijke stage – onder leiding van dr. Jelle Stoffers in het laatste jaar van de studie – resulteerde in een publicatie over de toepassing van echocardiografie in de eerste lijn. Ze haalde haar geneeskunde diploma in 2012. Daarna begon ze met het eerste jaar van de huisartsopleiding in Rotterdam, aan het Erasmus Medisch Centrum. Toen de kans zich voordeed, stapte ze in 2013 over naar Maastricht om Arts In Opleiding Tot Huisarts en Onderzoeker (AIOTHO) te worden op het Detecting and Diagnosing Atrial Fibrillation (D_2AF) project, onder supervisie van Prof. dr. André Knottnerus, dr. Jelle Stoffers en dr. Petra Erkens. In 2017 won ze de Professor Huygenprijs voor haar onderzoeksvoorstel voor een vignettestudie onder huisartsen, waarvan de resultaten zijn beschreven in hoofdstuk 3.

In maart 2020 studeerde Nicole af als huisarts, sindsdien werkt ze als waarnemend huisarts in regio Brabant vanuit haar woonplaats Chaam. Daar woont ze samen met haar man Gerard en kinderen Thijmen en Merel.

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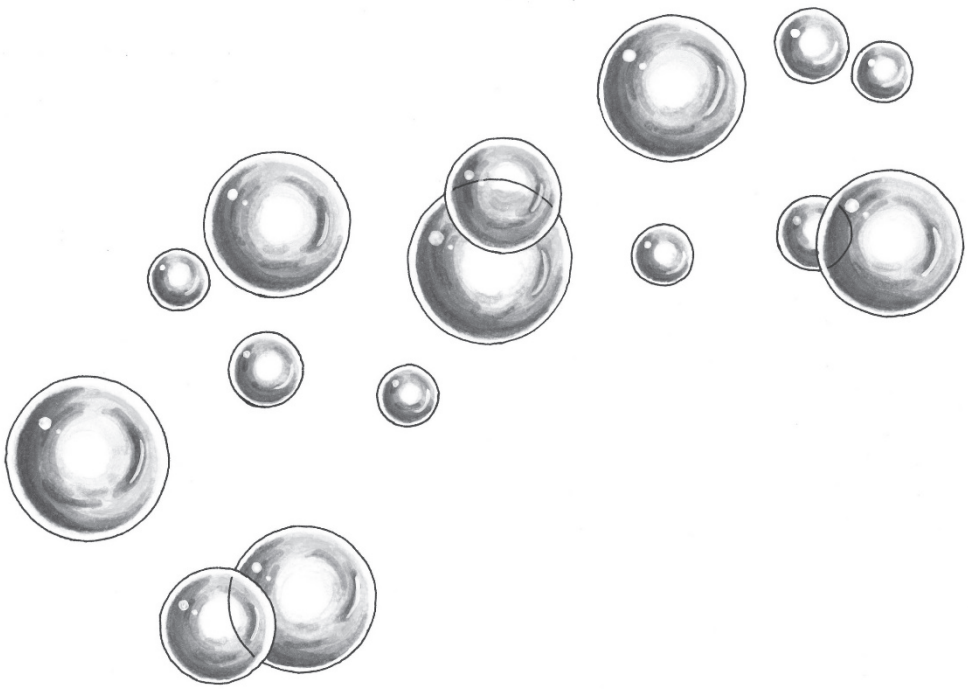

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