The detection and diagnosis of atrial fibrillation in Dutch general practice

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Introduction

PREVENTION OF CARDIOVASCULAR DISEASE

Cardiovascular disease (CVD) is the second leading cause of death in the Netherlands.(1) CVD encompasses an array of diseases including coronary heart disease, cerebrovascular disease, peripheral artery disease, aortic disease, deep vein thrombosis, pulmonary embolism and cardiac arrhythmias. Common risk factors for development of CVD are hypertension, high blood cholesterol, diabetes, smoking and obesity. The age-standardised mortality of CVD has declined in high income countries over the last decades, because of improved management of risk factors and treatment of established CVD.(2, 3)

In the Netherlands 1.55 million patients have a registered CVD.(1) Dutch general practitioners (GPs) regard indicated CVD disease prevention, both primary and secondary, as a core task and manage care for 60 to 70% of Dutch CVD patients.(4, 5) GPs have organised health care programmes, that focus on cardiovascular risk management (CVRM) and diabetes. With these programmes, GPs aim to reduce the burden of CVD. Ischemic heart disease and stroke are the two leading causes of mortality and morbidity related to CVD.(3, 6)

Atrial fibrillation (AF) is a common CVD, but also increases the risk of stroke fivefold. (7) Thereby, stroke in AF patients has a higher morbidity and mortality in comparison to non-AF related stroke.(8) Treatment of AF with oral anticoagulant (OAC) drugs reduces the risk of stroke with more than 60%,(9) but unfortunately, in nearly a quarter of patients with stroke, AF is detected after the damage has been done.(10) If prevention of stroke (e.g. by treating hypertension and diabetes) is considered a core task of GPs, shouldn't early detection of AF be added? If so, since AF can present itself without symptoms, the only way to do so is through screening.

CHARACTERISTICS OF ATRIAL FIBRILLATION

Atrial fibrillation is a heart disease characterised by an irregular heart rhythm. The prevalence of AF is strongly related with age, ranging from 1.4% in the overall population up to 7-8% in people aged 65 years and older.(11, 12) Due to the aging population, the prevalence of AF in the Netherlands is expected to increase to 3.2% in 30 years' time (see figure 1).(13) Without intervention this expected increase in AF prevalence could lead to an increase in strokes as well.

Ischemic and structural heart disease, aging and hypertension are associated with AF. Current theory assumes that these risk factors lead to structural changes of the heart that causes the atria and the adjacent pulmonary veins to produce electrical signals leading to the ar-

rhythmia.(14) The first episodes of AF often have a short duration and are self-terminating, so-called paroxysmal AF.(15) Once developed, AF causes contractile dysfunction and stasis, which increases the risk of thromboembolism. Also, the arrhythmia can cause further structural remodelling. Progression of the atrial cardiomyopathy can eventually lead to progression of AF, with episodes of AF becoming more frequent and longer lasting or even permanent.(15)

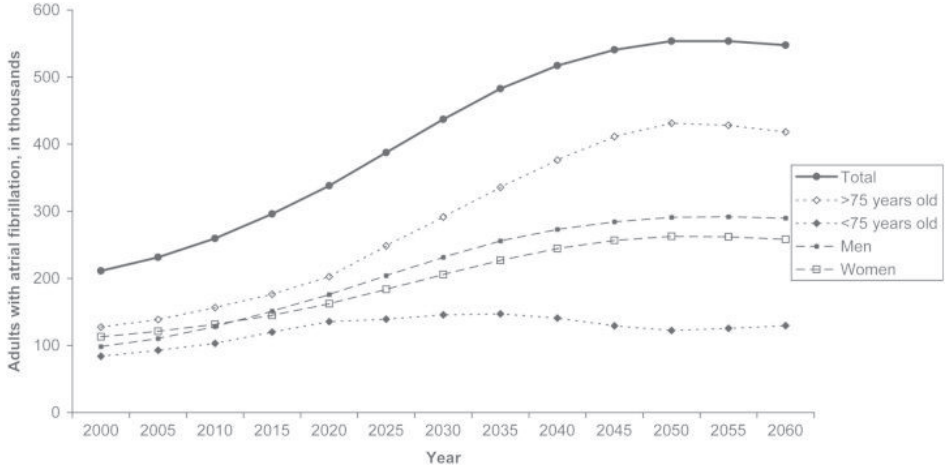

Figure 1 Predicted increase in prevalence of atrial fibrillation in the Netherlands based on the age and gender structure of the population (absolute numbers) (original figure by Krijthe BP et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. Eur Heart J 2013;34(35):2749, by permission of Oxford University Press).

DETECTING ATRIAL FIBRILLATION

Patients with undiagnosed AF can present with symptoms such as palpitations, dyspnoea, and fatigue. Asymptomatic patients can be detected during routine care, for instance during blood pressure measurement.(16) Usually, pulse palpation and auscultation are used to detect an irregular rhythm, followed by a 12-lead electrocardiogram (ECG) to confirm the diagnosis. Paroxysmal AF can be difficult to diagnose. A 12-lead ECG can be false negative if an episode spontaneously converts to sinus rhythm between the detection of the irregular heartrate and the recording. In these situations, prolonged monitoring of heart rate, such as Holter monitoring, may reveal paroxysmal AF.

We know that GPs detect patients with asymptomatic AF, because chance findings during daily practice are not uncommon. However, we do not know the exact prevalence of undiagnosed asymptomatic AF – so-called silent AF - in the Netherlands. Based on screening studies in primary care we estimate that the prevalence is between 0.6 and 3.0%.(17-24) In

this thesis we evaluate the problem of silent AF in Dutch primary care and how GPs can detect these patients.

STROKE RISK AND ANTICOAGULANT TREATMENT.

After the diagnosis, the physician weighs the risk of stroke with the risk of bleeding before starting OAC-therapy.(15) Stroke risk increases with advancing age and the presence of risk factors. The CHA_2DS_2-VASc score has been developed to assess the risk of stroke for patients with AF (see table 1) and as can be seen, the risk of stroke rapidly increases with increasing number of risk factors.(25, 26) In patients with an increased risk of stroke (in male patients with a score ≥ 1 and females with a score ≥ 2), the benefit of treatment with OAC outweighs the risk of bleeding.

Table 1a. The criteria of the CHA_2DS_2-VASc score (Congestive heart failure, Hypertension, Age, Diabetes mellitus, Sex, prior Stroke or TIA or thromboembolism, Vascular disease) used to determine the risk of stroke in patients with AF. Treatment with oral anticoagnulant therapy should be considered in male patients with a score ≥ 1 and females with a score ≥ 2.(25)

Criteria		Points
Age	<65 years old	0
	65-74 years old	+1
	≥75 years old	+2
Sex	Male	0
	Female	+1
Congestive heart failure history		+1
Hypertension history		+1
Stroke/TIA/thromboembolism history		+2
Vascular disease history (prior MI, peripheral artery disease, or aortic plaque)		+1
Diabetes mellitus history		+1

Table 1b. CHA_2DS_2-VASc score and annual stroke risk (25)

CHA_2DS_2-VASc score	Annual stroke risk (%)
0	0.2
1	0.6
2	2.2
3	3.2
4	4.8
5	7.2
6	9.7

SCREENING FOR ATRIAL FIBRILLATION

Evaluating the characteristics of screening for AF according to the criteria for screening as defined by Wilson and Jungner,(27) AF seems to qualify as a suitable candidate. Patients with untreated AF have an increased risk of stroke which is reduced if AF is detected and treated with OAC. With the prevalence of AF expected to rise, this presents an important health issue. For screening for AF to be effective, several questions need to be answered:

What population should be screened? The majority of screening studies focussed on patients over 65 years old. First, because prevalence of AF greatly increases with age. In the Rotterdam study, the incidence of AF increased from 1.1/1000 person years for patients between 55 and 60 years old, up to 20.7/1000 person years in the age group 80–85.(11) Second, because age is also a risk factor for AF patients to develop a stroke. Looking at the CHA_2DS_2-VASc score, all female patients and all males, 65 years and over, with an additional risk factor should be considered for stroke prevention with OAC-therapy.(25)

Is there a potential for screening for undetected AF among primary care patients aged 65 years and over? Several studies evaluated the effect of screening in primary care populations aged 65 years and over. In 1987 Hill et al. found a prevalence of 3.7% (30/819) of which 1.2% (n=10) consisted of new cases.(28) In 1998 Wheeldon et al. evaluated screening using electrocardiography and detected 4.6% (65/1422) new cases of AF.(29) In 2002 Morgan et al. used pulse palpation to screen during a six month period, and detected 2.9% (86/3001) of new AF cases.(21) Although these studies show a potential for screening, they lacked a control group with usual care. Studies without a control group cannot evaluate the added value of screening in the detection of newly found AF. In 2007 the SAFE study, a randomised controlled trial (RCT) used a control group receiving usual care. It evaluated the effect of screening in a primary care population aged 65 years and over.(17) Screening increased the annual detection rate from 1.04% in control practices to 1.63% in screening practices (difference 0.59%, 95% confidence interval (95% CI) 0.20% to 0.98%). Within the screening practices, two different screening methods were applied: Systematic screening in which all patients were invited for electrocardiography and opportunistic screening with pulse taking during routine clinic attendances, after which those with an irregular pulse were referred for a 12-lead ECG. Systematic and opportunistic screening detected similar numbers of new cases (1.62% v 1.64%, difference 0.02%, 95% CI -0.5% to 0.5%). The investigators preferred opportunistic screening for financial and practical reasons.

At the start of this thesis, we had several reasons to re-evaluate, whether opportunistic screening for AF would still be effective. First, the publication of the SAFE study was several years ago and no new RCTs had been published. Over time awareness of AF had changed.

Since the revision of the AF guideline in 2009, the Dutch College for General Practitioners recommended assessing the heart rhythm in each patient when measuring the blood pressure.(30) Second, following the introduction of non-vitamin K oral anticoagulants (NOAC) in 2008, which made anticoagulant therapy more convenient and more effective, much focus and attention had been given to undiagnosed and untreated AF. And third, better, more convenient and easy to apply diagnostics became available, which made paroxysmal atrial fibrillation better accessible to diagnosis. Therefore we decided to start an opportunistic, cluster randomised screening trial.

METHODS OF DETECTING ATRIAL FIBRILLATION

Pulse palpation is readily available, but its test characteristics are dependent on the threshold chosen to determine irregularity. If any irregularity is considered as a positive test, it has a high sensitivity (ranging between 92 to 94%), but a low specificity (ranging between 72 to 82%) which would lead to high numbers of false positive screenings and unnecessary ECG's.(31-33) If pulse palpation is only regarded as positive if the physician defines it as completely irregular, specificity rises to 98.0%, but at the cost of a lower sensitivity of 54%.(21) In addition, the test characteristics of pulse palpation are dependent upon who performs the test.(34)

In the last two decades several new technologies have been developed to detect AF. New technologies that were less dependent on the experience of the performer, were less dependent on the chosen threshold and possibly had better test characteristics than pulse palpation. Therefore the trial decided to use two new methods of screening and to compare them with pulse palpation.

1. An automated blood pressure monitor (BPM) with an integrated AF detection algorithm. The monitor showed promising test characteristics with a high sensitivity and specificity (97% and 89% respectively).(35) Measuring blood pressure is a common procedure in general practices and therefore this device offers a practical means of integrating screening with daily practice.
2. A handheld device which can record a single-lead ECG (lead I) with a built-in AF detection algorithm. This recorder offers physicians (and patients) a fast and easy method to check for arrhythmias. We chose the MyDiagnostick (www.mydiagnostick.com, MyDiagnostick Medical BV), which showed promising test characteristics in validation studies (sensitivity 94-100% and specificity 93-96%).(36, 37) Like most single-lead recorders, this device can store an rhythm strip for later review.

However test characteristics - and even more so the yield - of these devices are dependent on the type of population in which they are applied.(38) Therefore, when used in a screening program, validation in a similar primary care population as the population that should be screened has to be done to evaluate how the BPM and the single-lead ECG device will perform in a GP's office during consultations.

Besides the test characteristics of those instruments, these should also be convenient to use in a busy daily practice without disturbing daily routine too much. Therefore it is also important to consider how health care workers within practices experience these different methods. Which methods are easily implemented in daily care? What hurdles are experienced? In **Chapter 5,** we explore these questions using interviews among participating practices of the D_2AF-study.

PAROXYSMAL AF

In-office screening will miss a proportion of patients with asymptomatic paroxysmal AF. Continuous ambulatory monitoring allows to screen for these cases. Several studies have demonstrated that prolonged monitoring in patients with cryptogenic stroke increases chances of detecting paroxysmal AF. The EMBRACE-study investigated the use of a 30-day monitoring period with an event recorder in a population of patients of 55 years or older with a recent cryptogenic ischemic stroke. The long term monitoring detected paroxysmal AF in 16.1% of patient as compared to 3.2% in the group screened with a 24 hour Holter.(39) The high prevalence in this group raised the question how often asymptomatic paroxysmal AF is present in the general population. The Swedish STROKESTOP study showed that in a population of 75- to 76-year-old individuals using twice daily, intermittent ECG-recording for two weeks detected AF in 3.0% of the screened population, of which only 0.5% was found on the first ECG.(40) How effective would prolonged monitoring be in detecting additional cases in a general care population? To evaluate this the D_2AF-study also explored the added value of two weeks of prolonged monitoring, both continuous and intermittent, in addition to in-office screening. **Chapter 2 and 3** describe the design of the screening procedure and results of the prolonged monitoring**. Chapter 4** shows the characteristics of the tests used in the trial.

The downside of prolonged monitoring is that it may "catch" episodes of paroxysmal AF with a short duration, for which the risks on stroke are not very clear. The European Society of Cardiology (ESC) defined paroxysmal AF as lasting for a minimum duration of 30 seconds.(15) This arbitrary threshold was chosen to have matching outcomes for trials evaluating the effect of ablation of AF. It is unclear however whether patients with asymptomatic

short episodes of paroxysmal AF benefit from OAC-treatment. As we discussed earlier, the presence of the arrhythmia leads to the stasis of blood in the atria, but other factors also contribute to the risk of stroke. It is unclear what should be the minimum duration of an AF-episode to consider treatment with anticoagulant treatment. **Chapter 6** describes the results of a systematic review evaluating the relation between the duration of AF episodes and the risk of stroke.

AIM AND OUTLINE OF THIS THESIS

The aim of this thesis is to determine the effectiveness of opportunistic screening for AF in GP's offices as compared to usual care. Furthermore, it evaluates the role of new methods of irregular heart rate detection and prolonged monitoring.

Chapter 2 describes the protocol for the randomised controlled trial (the D_2AF-study) evaluating the effectiveness of opportunistic screening for AF as compared to care as usual.

Chapter 3 shows the results of the randomised controlled trial**.**

Chapter 4 describes the diagnostic test characteristics of the three different index tests that were used.

Chapter 5 shows results of a qualitative study to increase our understanding of what is needed for GPs and associated health care assistants to implement opportunistic screening.

Chapter 6 presents the results of a systematic review that describes the relation between the frequency and duration of episodes of AF and risk of stroke.

Chapter 7 discusses the main findings and conclusions of this thesis.

Chapter 8 contains summaries of the thesis in English and Dutch and other appendices**.**

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