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To my family and friends

ABSTRACT

Jussi Jaakkola

Asymptomatic atrial fibrillation: studies on significance and screening methods

University of Turku, Faculty of Medicine, Department of Cardiology and Cardiovascular Medicine, Doctoral Programme in Clinical Research; Heart Centre, Turku University Hospital

Annales Universitatis Turkuensis, Turku, Finland 2018

Background: The frequent asymptomatic presentation of atrial fibrillation (AF) may delay stroke-prophylaxis with anticoagulation therapy. In this thesis, the concurrence of AF diagnosis with ischaemic stroke and the performance of two potential screening methods were evaluated.

Methods: 1) Altogether, 3,623 AF patients treated for their first ischaemic cerebrovascular event were assessed from patient records. 2) The capability of 173 elderly subjects to assess cardiac rhythm by pulse palpation was assessed using a programmable anatomic model-arm. 3) Altogether, 205 elderly subjects instructed to palpate their pulse twice-daily and seek immediate medical attention if irregularity is noticed were followed for three years to record new AF diagnoses. 4) Three-minute smartphone-mechanocardiography recordings were obtained from 150 subjects in AF and 150 subjects in sinus rhythm (SR) (confirmed with simultaneous electrocardiography), after which an automated algorithm determined the rhythm during each recording.

Results: 1) AF was detected concurrently with the ischaemic cerebrovascular event in 753 (20.8%) patients. 2) Of the 148 (85.5%) subjects who reliably found the pulse, 97.3% identified SR, 81.8% slow AF, 91.9% fast AF and 74.3% SR with ventricular extrasystoles. 3) After 36 months, only 69 (33.7%) subjects palpated their pulse at least weekly, and only 1 new AF diagnosis was made due to pulse irregularity during three years. 4) Mechanocardiography demonstrated 95.3% sensitivity and 96.0% specificity to detect AF.

Conclusions: AF and stroke are frequently diagnosed concurrently. The elderly accurately distinguish SR by pulse palpation, but insufficient long-term motivation limits screening by pulse self-palpation. Smartphone mechanocardiography seems to reliably detect AF without additional hardware.

Keywords: atrial fibrillation, diagnostic method, screening, stroke

TIIVISTELMÄ

Jussi Jaakkola

Oireeton eteisvärinä: tutkimuksia sen merkityksestä ja seulontamenetelmistä

Turun yliopisto, Lääketieteellinen tiedekunta, Kardiologia ja kardiovaskulaarilääketiede, Kliininen tohtoriohjelma; Sydänkeskus, Turun yliopistollinen keskussairaala

Annales Universitatis Turkuensis, Turku, Suomi 2018

Tausta: Eteisvärinän yleinen oireeton ilmenemistapa viivästyttää rytmihäiriön diagnoosia ja aivoinfarkteilta suojaavan antikoagulaatiolääkityksen aloittamista. Tässä väitöskirjatyössä selvitettiin eteisvärinän ja aivoinfarktin diagnoosien yhtäaikaisuuden yleisyys ja arvioitiin kahden mahdollisen eteisvärinän seulontamenetelmän suoriutumista.

Menetelmät: 1) Yhteensä 3623 ensimmäisen aivoinfarktinsa tai ohimenevän aivoverenkiertohäirönsä vuoksi hoidettua eteisvärinäpotilasta tunnistettiin sähköisistä potilaskertomuksista. 2) Yhteensä 173 iäkkään henkilön kyky pulssia tunnustelemalla määrittää sydämen rytmi arvioitiin hyödyntämällä ohjelmoitavaa anatomista käsimallia. 3) Yhteensä 205 iäkästä henkilöä ohjeistettiin tunnustelemaan pulssiansa kahdesti päivässä ja ottamaan viiveettä yhteys terveydenhuollon yksikköön havaitessaan pulssin epäsäännöllisyyttä. Tutkittavia seurattiin kolmen vuoden ajan uusien eteisvärinädiagnoosien toteamiseksi. 4) Kolmen minuutin mekanokardiografiamittaus tehtiin älypuhelimen avulla 150:lle sinusrytmissä ja 150:lle eteisvärinärytmissä olevalle tutkittavalle (tutkittavien rytmi varmennettiin samanaikaisen telemetrianauhoituksen avulla). Tämän jälkeen mekanokardiografianauhoitukset analysoitiin tietokonealgoritmilla, joka määritti nauhoituksen aikaisen rytmin.

Tulokset: 1) Eteisvärinä diagnosoitiin aivoinfarktin yhteydessä 753 (20,8 %) potilaalla. 2) Yhteensä 148 (85,5 %) tutkittavista löysi pulssin luotettavasti. Heistä 144 (97,3 %) tunnisti sinusrytmin, 121 (81,8 %) tunnisti hitaan eteisvärinän, 136 (91,9 %) tunnisti nopean eteisvärinän ja 110 (74,3 %) tunnisti sinusrytmin aikaisen kammiolisälyöntisyyden oikein. 3) Kolmen vuoden seurannan jälkeen vain 69 (33,7 %) tutkittavaa jatkoi pulssinsa tunnustelua vähintään viikoittain. Pulssin epäsäännöllisyys johti vain yhteen uuteen eteisvärinädiagnoosiin seurannan aikana. 4) Mekanokardiografia-algoritmi erotti eteisvärinän sinusrytmistä 95,3 %:n sensitiivisyydellä ja 96,0 %:n spesifisyydellä.

Päätelmät: Aivoinfarktiin sairastuvilla eteisvärinäpotilailla eteisvärinä todetaan viidenneksellä vasta aivotapahtuman yhteydessä. Iäkkäät tunnistavat sinusrytmin tarkasti pulssia tunnustelemalla, mutta riittämätön motivaatio rajoittaa omatoimisen pulssintunnustelun soveltuvuutta eteisvärinän seulontaan. Älypuhelimella suoritettu mekanokardiografiamittaus vaikuttaa tunnistavan eteisvärinän luotettavasti ilman lisälaitteita.

Avainsanat: aivoinfarkti, diagnostiikka, eteisvärinä, seulonta

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ABBREVIATIONS

ABC	age, biomarkers, clinical history
ADP	adenosine diphosphate
AF	atrial fibrillation
AFI	Atrial Fibrillation Investigators
AHRE	atrial high rate episode
ASA	acetylsalicylic acid
CHA_2DS_2VASc	congestive heart failure, hypertension, age ≥75 (doubled), diabetes mellitus, prior stroke, transient ischemic attack or thromboembolism (doubled), vascular disease, age 65-74, sex category (female)
$CHADS_2$	congestive heart failure, hypertension, age ≥75, diabetes mellitus, prior stroke, transient ischemic attack or thromboembolism (doubled)
CI	confidence interval
ECG	electrocardiography
ESC	European Society of Cardiology
HAS-BLED	hypertension, abnormal renal or liver function, prior stroke, bleeding susceptibility, labile INR, elderly, drugs or alcohol
$HEMORR_2HAGES$	hepatic or renal disease, ethanol abuse, malignancy, older age, reduced platelet count or function, rebleeding, hypertension, anemia, genetic factors, excessive fall risk, stroke
HR	hazard ratio
INR	international normalized ratio
LAA	left atrial appendage
MCG	mechanocardiography

MMSE	Mini-Mental State Examination
NA	not applicable
NICE	National Institute for Health and Care Excellence
NOAC	non-vitamin K oral anticoagulant
OAC	oral anticoagulant
OR	odds ratio
PPG	photoplethysmography
SD	standard deviation
SPAF	Stroke Prevention in Atrial Fibrillation
SR	sinus rhythm
SVES	supraventricular extrasystole
TIA	transient ischaemic attack
TTR	time in therapeutic range
VES	ventricular extrasystole
VKA	vitamin K -antagonist

LIST OF ORIGINAL PUBLICATIONS

I. Jaakkola J, Mustonen P, Kiviniemi T, Hartikainen JE, Palomäki A, Hartikainen P, Nuotio I, Ylitalo A, Airaksinen KEJ. Stroke as the First Manifestation of Atrial Fibrillation. *PloS One*. 2016;11(12):e0168010.

II. Jaakkola J, Vasankari T, Virtanen R, Airaksinen KEJ. Reliability of pulse palpation in the detection of atrial fibrillation in an elderly population. *Scand J Prim Health Care*. 2017;35(3):293-298.

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IV. Jaakkola J*, Jaakkola S*, Lahdenoja O, Hurnanen T, Koivisto T, Pänkäälä M, Knuutila T, Kiviniemi TO, Vasankari T, Airaksinen KEJ. Mobile Phone Detection of Atrial Fibrillation Using Mechanocardiography – the MODE-AF Study. *Circulation.* 2018;137(14):1524-1527. (Research letter) *Equal contribution

1 INTRODUCTION

Atrial fibrillation (AF) is an exceedingly common arrhythmia and an important causative factor of ischaemic stroke (Björck et al. 2013; Wolf et al. 1991). However, oral anticoagulation (OAC) therapy, either with vitamin K -antagonists (VKA) or non-vitamin K anticoagulant (NOAC) drugs, has proven very effective in preventing strokes and improving outcomes in patients suffering from AF (Hart et al. 2007; Ruff et al. 2014). Indeed, stroke prevention is the most important clinical consideration for most patients with the arrhythmia (Kirchhof et al. 2016).

To allow for effective implementation of preventive OAC therapy, AF should be diagnosed as early during its course as possible. Unfortunately, as AF is asymptomatic in a substantial share of those suffering from the arrhythmia, its diagnosis and implementation of protective treatment are often delayed (Boriani et al. 2015). Further complicating the matter, AF often manifests as paroxysms that subside on their own and may be exceptionally difficult to verify. Consequently, screening measures to allow early diagnosis have been proposed during the last decade, although no widely accepted and implemented approaches have emerged.

The screening strategy promoted in the current European clinical guidelines on the management of AF is opportunistic pulse palpation in the ≥65 year-old population (Kirchhof et al. 2016; N.C.C.f.C.C. 2014). The approach constitutes taking the pulse of eligible patients during all healthcare consultations for any reason and recording a confirmatory ECG tracing whenever irregularity is detected (Fitzmaurice et al. 2007). Although the strategy has demonstrated efficacy in clinical studies, it seems mainly suited to screen for permanent forms of the arrhythmia, whereas detecting paroxysmal AF ought to be more difficult due to the relative infrequency of healthcare contacts on an individual level (Fitzmaurice et al. 2007). Moreover, it seems that opportunistic screening has been poorly adopted into clinical practice (Dobreanu et al. 2013). Indeed, recent screening studies, wherein repeated ECG recordings were performed, have demonstrated distinctly superior detection rates for AF in comparison to opportunistic screening, thus suggesting that frequent intermittent screening is required for better results (Engdahl et al. 2013; Svennberg et al. 2015).

The primary objectives of this thesis were: to assess in which proportion of ischaemic strokes occurring in patients suffering from AF the arrhythmia is diagnosed concurrently with the cerebrovascular event; to evaluate the capability of elderly subjects to determine cardiac rhythm by pulse palpation; to appraise the feasibility of regular self-palpation of pulse by the elderly as a screening strategy for AF; and to determine the accuracy of a smartphone-based method of measuring mechanical cardiac activity without any additional hardware in detecting AF.

2 REVIEW OF LITERATURE

2.1 Atrial fibrillation

Atrial fibrillation (AF) is a supraventricular cardiac arrhythmia first recognised at the beginning of the 20th century (Lewis 1909). The condition is characterised by the loss of the orderly propagation of electrical impulses from the sinus to the atrioventricular node and the coordinated atrial contractions encountered in normal sinus rhythm (SR), which are replaced by excessively fast and chaotic electrical and mechanical activity of the atria. During AF, electrical impulses constantly arrive at the atrioventricular node, which allows variable conduction to the ventricles, thus leading to an irregular and often fast heartbeat. The presentation of AF is variable: it may occur as short paroxysms, longer persistent arrhythmia periods reversible with medical therapy or as a permanent rhythm abnormality (Kirchhof et al. 2016).

2.2 Epidemiology and presentation of atrial fibrillation

AF is the most common longstanding cardiac arrhythmia across the globe. It is present in approximately 3% of the adult population in developed countries (Björck et al. 2013; Haim et al. 2015), but there is wide variation among other populations and ethnic groups (Lip et al. 2012). The prevalence of AF increases steeply with age (Björck et al. 2013; Go et al. 2001; Krijthe et al 2013; Naccarelli et al. 2009). In a representative Swedish population cohort, only 0.4% of those aged 40-49 years but as many as 22.9% of those at least 90 years old had history of AF (Björck et al. 2013). At 40 years of age, the lifetime risk of developing AF is approximately 25% (Lloyd-Jones et al. 2004). AF is also more prevalent in men than in women (Chugh et al. 2014; Go et al. 2001; Haim et al. 2015; Wolf et al. 1996). It must be noted though, that these figures most likely somewhat underestimate the actual prevalence of AF as the rhythm disorder is commonly asymptomatic and as a result undiagnosed (Savelieva et al. 2000).

The prevalence and incidence rates of AF have progressively been increasing during the past decades (Chugh et al. 2014) and are projected to further significantly increase in the future (Colilla et al. 2013; Go et al. 2001; Krijthe et al. 2013; Miyasaka et al. 2006; Naccarelli et al. 2009). In the European Union, the prevalence rate of AF is estimated to more than double from 8.8 million in 2010 to 17.9 million in 2060 (Krijthe et al. 2013). The increasing burden of AF is thought to be multifactorial. Largely, it can be attributed to the continuing ageing

of the population and growing incidence of AF due to conditions predisposing to it, such as diabetes and cardiovascular disease, becoming more prevalent. Additionally, part of the increase is probably explained by earlier and more efficient detection of the arrhythmia as compared to the past. Yet another contributing factor is speculated to be the improved survival from myocardial infarctions, which has led to a growing number of people in high risk for the development of AF.

It is established that AF leads to an increased risk of ischaemic stroke (Wolf et al. 1991), which is the most feared complication of AF. The relationship between AF and ischaemic stroke is discussed more thoroughly in the following chapters. AF also predisposes those suffering from it to heart failure (Stewart et al. 2002) and is associated with an increased risk of cognitive impairment and dementia (de Bruijn et al. 2015; Knecht et al. 2008) and significantly impaired quality of life (Dorian et al. 2000).

Furthermore, the independent risk of overall mortality is increased to almost two-fold in the presence of AF (Benjamin et al. 1998; Stewart et al. 2002). Unsurprisingly, the costs incurred by AF on the health care system are substantial. In the United Kingdom, AF alone accounted directly for approximately 1% of all health-care expenditure in 2000 (Stewart et al. 2004).

2.3 Atrial fibrillation and ischaemic stroke

2.3.1 Atrial fibrillation and the risk of stroke

AF is associated with a significant increase of risk of thromboembolism and stroke, which is the most important complication of the arrhythmia. AF was first established as a risk factor in patients with rheumatic heart disease in addition to the arrhythmia (Daley et al 1951; Weiss et al. 1933). However, the role of AF as a cause of stroke in the absence of rheumatic heart disease remained unclear and controversial for several decades, until evidence supporting a causative role began to accumulate during the 1970s and 1980s (Hinton et al. 1977; Tanaka et al. 1985; Wolf et al. 1978). In 1991, the Framingham Investigators largely settled the question, when they reported on 5,070 subjects who were followed for 34 years and described that AF was an independent risk factor of ischemic stroke mediating a 4.8-fold increase of risk (Wolf et al. 1991).

The risk of stroke is not uniform in all patients with AF, but rather varies from patient to patient according to age and the presence of other risk-modifying fac-

tors. Depending on an individual risk profile, the annual stroke rate in AF varies between 0% and 15% (Lip et al. 2010a). Patients with AF, who are under the age of 60 and have no additional risk factors of stroke, have a mere 1.3% cumulative risk of suffering an ischaemic stroke over 15 years (Kopecky et al. 1987). Whether the risk of stroke is similar in permanent and paroxysmal AF is a matter of some debate. While earlier studies indicated an equal risk irrespective of the type of AF (Friberg et al. 2009; Hart et al. 2000a; Hohnloser et al. 2007), more recent research suggests that the risk of thromboembolism and stroke in paroxysmal AF actually be approximately half of the risk in permanent and persistent AF (Koga et al. 2016; Steinberg et al. 2014; Takabayashi et al. 2015; Vanassche et al. 2014).

The prevalence of AF among ischaemic stroke patients has ranged from 15% to 38% in various studies (Åsberg et al. 2010; Björck et al. 2013; Friberg et al. 2014; Hannon et al. 2010; Marini et al. 2005; Thygesen et al. 2009; Wolf et al. 1987). The prevalence increases steeply with age: in a Swedish population-based study, among patients who had suffered an ischaemic stroke, 0% of those under 40 years of age, but over 50% of those aged 80 or more had an AF diagnosis (Björck et al. 2013).

Furthermore, over a third of all ischaemic strokes are cryptogenic (i.e. no aetiology can be identified even after adequate diagnostic effort) (Kolomensky-Rabas et al. 2001), and AF has been speculated to be the culprit in many of such cases, and evidence supporting this view has emerged from recent studies. In CRYSTAL-AF, 221 subjects with cryptogenic stroke were monitored with implantable cardiac monitors for an extended period, and by 12 months AF was diagnosed in 12% and by 36 months in 30% of the subjects (Sanna et al. 2014). In EMBRACE, another study on 280 subjects who had suffered a cryptogenic stroke, AF was detected in 16% of the subjects utilizing event triggered cardiac monitors for a 30 days' duration (Gladstone et al. 2014). However, currently the role of the short AF paroxysms detected with cardiac monitors during extended periods in these studies as a causative factor remains unclear: in the ASSERT-II trial, short attacks of subclinical AF detected with implantable monitors were equally common in subjects with or without history of ischaemic stroke (Healey et al. 2017). It must also be noted that patients with AF usually possess risk factors predisposing also to atherothrombotic stroke, and ischaemic stroke is not always caused by the arrhythmia. Regardless, AF seems to be the culprit more often than not, as it has been reported in one previous study, that over two thirds of ischaemic strokes in patients with AF are cardioembolic in origin (Hart et al. 2000b).

Ischaemic strokes associated with AF are often more severe than strokes in patients without the arrhythmia: computed tomography scans reveal larger infarcted

areas (Jørgensen et al. 1996), initial symptoms and neurological deficit are more serious (Appelros et al. 2002; Brüggenjürgen et al. 2007; Dulli et al. 2003; Jørgensen et al. 1996; Kimura et al. 2005; Lin et al. 1996), hospital-stays are longer (Jørgensen et al. 1996; Thygesen et al. 2009), mortality is higher (Appelros et al. 2002; Jørgensen et al. 1996; Kimura et al. 2005; Lin et al. 1996, Thygesen et al. 2009) and long-term functional deficits are more severe (Jørgensen et al. 1996; Lin et al. 1996). Approximately 80% of AF-associated strokes are fatal or severely disabling (Gladstone et al. 2009). The costs incurred during the acute care of cardioembolic ischaemic strokes are approximately 40% higher compared to the care of non-cardioembolic strokes (Winter et al. 2009). The most likely explanation for the worse outcome of AF patients is that a cardioembolus may occlude large cerebral arteries and subsequently damage sizeable areas of cerebral tissue. Furthermore, collateral circulation in the brain may be better developed in those with previous arterial disease who suffer an atherothrombotic stroke, whereas AF patients with no arterial disease who suffer a sudden interruption of cerebral blood flow caused by a cardioembolus may have more modest compensatory collateral circulatory reserves leading to more severe outcomes.

2.3.2 Assessment of stroke risk

As the annual risk of stroke is highly variable in patients with AF, so is the benefit derived from therapeutic measures aimed to prevent stroke. While most patients benefit from treatment, in some the risk of stroke is too small to justify treatment as the risks would overshadow the benefits. To assist clinical decision-making and identify the patients who benefit from preventive treatment, several scoring systems measuring stroke risk in AF patients have been developed.

The earliest risk stratification schemes were introduced during the mid-1990s by the Stroke Prevention in Atrial Fibrillation investigators (SPAF) and the Atrial Fibrillation Investigators (AFI) (A.F.I. 1994; S.P.i.A.F. 1995). In 2001, the AFI and the SPAF schemes were amalgamated to form the $CHADS_2$ score, which demonstrated superior predictive accuracy compared to both the AFI and the SPAF scores (Gage et al. 2001). It was subsequently introduced into several guidelines and became widely implemented in clinical practice (Camm et al. 2010; Fuster et al. 2006; N.C.C.f.C.C. 2006; Singer et al. 2008).

The calculation of the $CHADS_2$ score is depicted in Table 1 and the annual risk of stroke according to the total score in Table 2. According to the total score, stroke risk is classified into three categories: low (0 points), intermediate (1 point in the revised and 1-2 points in the unrevised scheme) and high (2-6 points in the revised and 3-6 points in the unrevised scheme) (Wang et al. 2003). According to

the then-current guidelines, anticoagulation therapy was recommended for those at a high risk for stroke and acetylsalicylic acid (ASA) or oral anticoagulation (OAC) therapy for those at an intermediate risk, while in patients with a low risk, it was advised to restrain from preventive measures or initiate ASA (Fuster et al. 2006). However, in the $CHADS_2$ score, up to 64% of the patients are classified as having an intermediate stroke risk, significantly hindering clinical decision-making (Fang et al. 2008; Gage et al. 2004; Lip et al. 2006; Lip et al. 2010b; Poli et al. 2011). Furthermore, the scheme distinguishes those at a low risk for stroke (<1% stroke rate per year) inadequately, and subsequently some high risk patients who would benefit from treatment are classified as being at a low risk for stroke (Gage et al. 2001; Olesen et al. 2011a; Olesen et al. 2012; Potpara et al. 2012; van Staa et al. 2011).

Table 1. The calculation of the $CHADS_2$ and the CHA_2DS_2VASc total scores (Gage et al. 2001; Lip et al. 2010a).

Risk factor	$CHADS_2$	CHA_2DS_2VASc
Congestive heart failure	1	1
Hypertension	1	1
Age ≥75 years	1	2
Diabetes mellitus	1	1
prior **S**troke or TIA	2	2
Vascular disease	-	1
Age 65-74 years	-	1
Sex **c**ategory (female)	-	1
Maximum score	**6**	**9**

Abbreviations: TIA, transient ischaemic attack

Bearing the shortcomings of the $CHADS_2$ score and other risk schemes in mind, the CHA_2DS_2VASc score was introduced in 2009 (Lip et al. 2010b). The score was developed from the Birmingham 2006 risk scheme, itself a revised version of the original Birmingham score that had evolved from the AFI score in the United Kingdom during the 1990s (Lip et al. 2006; Lip et al. 2010b). In multiple studies, the CHA_2DS_2VASc score has demonstrated moderate and in comparison to the $CHADS_2$ score at most only slightly better predictive accuracy (c-statistics 0.61-0-72) to identify patients at a high risk of stroke (Friberg et al. 2012a; Lip et al. 2010a; Lip et al. 2010b; Poli et al. 2011; van Staa et al. 2011). However, the major benefit of the CHA_2DS_2VASc score over the $CHADS_2$ score is that it is more reliable in identifying those patients who are truly at a low risk of stroke and who consequently do not require preventive therapy (Olesen et al. 2011a; Olesen et al. 2012; Potpara et al. 2012; van Staa et al. 2011). The CHA_2DS_2VASc score has subsequently been introduced into all the major clinical guidelines and has replaced the $CHADS_2$ score in practice (Camm et al. 2010; Camm et al. 2012; January et al. 2014). The calculation of the CHA_2DS_2VASc

score is depicted in Table 1 and the annual risk of stroke according to total score in Table 2.

In the future, the inclusion of biomarkers in stroke risk stratification schemes in addition to clinical variables has the potential to further enhance stroke prediction. The ABC (age, biomarkers and clinical history) stroke score, the calculation of which incorporates age, the serum levels of high-sensitivity cardiac troponin and N-terminal fragment B-type natriuretic peptide, and history of ischaemic stroke or transient ischaemic attack, and the ATRIA score, which includes creatinine clearance in its algorithm, have demonstrated slightly superior predictive accuracy compared to the CHA_2DS_2VASc score in different studies (Hijazi et al. 2016a; Oldgren et al. 2016; Singer et al. 2013, van den Ham et al. 2015). However, the matter is still under debate, and, while no consensus on the role of biomarkers in risk stratification matter has been reached, the CHA_2DS_2VASc score remains the recommended scheme (Kirchhof et al. 2016).

Table 2. Adjusted annual risk of stroke according to the $CHADS_2$ and the CHA_2DS_2VASc total scores (Gage et al. 2001; Lip et al. 2010a).

Total score	$CHADS_2$	CHA_2DS_2VASc
0	1.9%	0.0%
1	2.8%	1.3%
2	4.0%	2.2%
3	5.9%	3.2%
4	8.5%	4.0%
5	12.5%	6.7%
6	18.2%	9.8%
7	-	9.6%
8	-	6.7%
9	-	15.2%

2.3.3 Assessment of bleeding risk

Antithrombotic therapy aimed to prevent strokes inherently increases the risk of haemorrhage. Hence, stroke prevention must be balanced against the risk of serious bleeding events, especially intracranial haemorrhage. To this end, several schemes to stratify the risk of bleeding have been developed.

The HEMORR2HAGES (Hepatic or Renal Disease, Ethanol Abuse, Malignancy, Older Age, Reduced Platelet Count or Function, Re-Bleeding, Hypertension, Anemia, Genetic Factors, Excessive Fall Risk and Stroke) score was the first bleeding risk stratification tool especially derived and validated in AF patients demonstrating moderate predictive accuracy for major bleeding events (Gage et al. 2006). In 2010, the HAS-BLED score was introduced, and it demonstrated

similar accuracy compared to the HEMORR2HAGES score with the added advantage of simplicity (Pisters et al. 2010). Thus, it was subsequently quickly adopted in treatment guidelines and became widely used in clinical practice (Camm et al. 2010; January et al. 2014). The HAS-BLED score has subsequently been validated in several studies, where it has demonstrated modest to moderate predictive accuracy (c-statistics 0.60-0.80) for major bleeding events (Apostolakis et al. 2012; Friberg et al. 2012a; Olesen et al. 2011b; Roldán et al. 2013). The calculation of the HAS-BLED score is depicted in Table 3. A score of three points or more, as assessed with the HAS-BLED score, is considered to indicate a potentially high risk of bleeding (Camm et al. 2010; January et al. 2014). The ORBIT and the ATRIA scores are more recent bleeding risk stratification schemes that have demonstrated variable predictive accuracy in comparison to the HAS-BLED score (Esteve-Pastor et al. 2016; O'Brien et al. 2015; Senoo et al. 2016a; Senoo et al. 2016b).

Table 3. The calculation of the HAS-BLED score (Pisters et al. 2010).

Risk factor	Points
Hypertension	1
Abnormal renal and/or liver function	1 for each
prior **S**troke	1
Bleeding (cancer, anemia, trombosythopenia, trombosytic disorder, prior bleeding)	1
Labile INR	1
Elderly (age ≥65 years)	1
Drugs and/or alcohol	1 for each
Maximum score	**9**

Abbreviations: INR, international normalised ratio

As in the case of stroke risk assessment, biomarkers have the potential to enhance bleeding risk stratification. The ABC bleeding risk score, a counterpart of the ABC stroke risk score, which accounts for age, blood haemoglobin, serum levels of growth differentiation factor-15 and high-sensitivity cardiac troponin T, and history of bleeding, has demonstrated somewhat superior predictive accuracy for major bleeding compared to the widely used HAS-BLED score (Hijazi et al. 2016b).

A significant obstacle for devising an effective and easily interpretable bleeding risk score is that the risk factors of stroke and bleeding are largely overlapping, which is also reflected in the many shared components of the different stroke and bleeding risk stratification schemes. Thus, patients with an elevated stroke risk are usually also at an elevated risk of bleeding. However, even patients in a high risk of bleeding usually benefit from oral anticoagulation therapy (Friberg et al. 2012b).

Currently, no single bleeding risk score is advocated over others in clinical guidelines (January et al. 2014; Kirchhof et al. 2016), although the HAS-BLED score is probably the most widely used. Considering the modest predictive capabilities of the present schemes and the significant overlap of stroke and bleeding risk factors, the current position is that the bleeding risk scores should not be used to identify patients from whom to withhold OAC therapy, but rather to identify modifiable risk factors and to allow closer observation of the high risk patients for adverse events (Kirchhof et al. 2016).

2.4 Stroke prevention

2.4.1 Oral anticoagulation medication

The primary stroke prevention modality in patients with AF is OAC medication. According to the current clinical guidelines, OAC medication should be considered for men with 1 point and women with 2 points and is indicated for men with ≥2 points and women with ≥3 points in the CHA_2DS_2VASc classification scheme (Kirchhof et al. 2016). Vitamin K antagonists (VKA) were since the 1950s for several decades the only OAC medications available until the 21st century, when several novel non-vitamin K antagonist oral anticoagulants (NOAC) have become commercially available.

2.4.1.1 Vitamin K antagonists

VKAs are a class of anticoagulant drugs that decrease clotting mainly by inhibiting the enzyme vitamin K epoxide reductase, thus preventing the reactivation of vitamin K1 and activation of clotting factors II, VII, IX, and X. Of the several VKAs developed, warfarin is almost exclusively used in clinical practice in Finland, although phenprocoumon and acenocoumarol are also in use in some other countries.

Warfarin is very effective in the prevention of AF-related strokes: a reduction of 64% was observed in the rate of strokes in comparison to placebo in an extensive meta-analysis (Hart et al. 2007). Although warfarin inherently also increases the risk of haemorrhage, nearly all AF patients, save for those with a low risk of stroke (CHA_2DS_2VASc score 0) and elevated bleeding risk as assessed with the HAS-BLED score, derive net clinical benefit from warfarin therapy (Friberg et al. 2012b).

Warfarin has a dose-dependent effect on blood coagulation that is further affected by many individual and external factors. Subsequently, frequent monitoring and dose-adjustments may be needed during warfarin therapy. The intensity of the anticoagulation effect during warfarin therapy can be quantified by determining the international normalized ratio (INR) of prothrombin time from a blood sample. INR values between 2 and 3 should normally be targeted during treatment to achieve the best balance between stroke prevention and adverse bleeding events (Hylek et al. 1996).

Time in therapeutic range (TTR) is a measure that describes the percentage of time that the INR value has spent between the values of 2 and 3. As high TTR values as possible should be targeted during warfarin therapy, as the risk of stroke, major bleeding and death increase with poor INR control (Kirchhof et al. 2016; Lehto et al. 2017; White et al. 2007). The efficacy and safety of warfarin therapy seems to be optimal when TTR is >80% (Lehto et al. 2017). However, optimal INR control is exceedingly difficult to achieve as can be observed from the warfarin arms of various randomized trials comparing NOACs against warfarin, where TTR values of only 55-68% were achieved (Connolly et al. 2009; Granger et al. 2011; Giugliano et al. 2013; Patel et al. 2011). There is some evidence that TTR can be improved by utilising point-of-care INR testing (Løkkegaard et al. 2015; Smith et al. 2012).

2.4.1.2 Non-vitamin K antagonist oral anticoagulants

NOACs act by inhibiting either the Factor Xa or thrombin, enzymes of the coagulation cascade, thus preventing thrombus formation. Among the currently available NOAC medications, dabigatran is a direct thrombin inhibitor, whereas rivaroxaban, apixaban and edoxaban are Factor Xa inhibitors. Unlike warfarin, the effect of the NOACs on coagulation is predictable and constant, and regular dose-adjustments are not needed.

In the RE-LY trial, dabigatran demonstrated superiority to warfarin in stroke prevention with a 34% smaller risk of stroke or systemic embolism, while the rate of major bleeding events was similar with both regimes (Connolly et al. 2009). In the ARISTOTLE trial, subjects who received apixaban experienced 21% fewer strokes or systemic embolisms and 31% fewer major bleeding events compared to subjects receiving warfarin (Granger et al. 2011). In the ROCKET AF trial, Rivaroxaban was non-inferior to warfarin for the prevention of stroke and systemic embolism, while similar rates of major bleeding events were observed in both groups (Patel et al. 2011). In the ENGAGE AF-TIMI 48 study, edoxaban demonstrated a 21% reduction in stroke or systemic embolism and a

reduction of 20% in major bleeding events when compared to warfarin (Giugliano et al. 2013).

In a meta-analysis of the four trials, the NOACs reduced stroke or systemic embolism by 19%, mainly due to a 51% reduction of haemorrhagic strokes, and intracranial haemorrhages were 52% less frequent in comparison to warfarin (Ruff et al. 2014). None of the NOACs have been directly compared with each other in randomized trials. Due to their superior efficacy and safety, NOACs are recommended to be preferred over warfarin when initiating OAC in patients with AF in the most recent European Society of Cardiology (ESC) guideline (Kirchhof et al. 2016).

The exception, however, are AF patients with moderate-to-severe mitral stenosis or a mechanical heart valve in whom warfarin should be administered (Kirchhof et al. 2016). While there is lack of evidence on patients with mitral stenosis, dabigatran has been compared against warfarin in patients with mechanical heart valves in a randomized study, wherein it demonstrated both inferior efficacy and more frequent adverse events (Eikelboom et al. 2013).

2.4.2 Antiplatelet therapy

Antiplatelet drugs are recommended not to be used to prevent strokes in patients with AF irrespective of their individual risk of stroke (Kirchhof et al. 2016).

2.4.2.1 Acetylsalicylic acid

ASA irreversibly inhibits the action of the cyclooxygenase enzyme and the formation of thromboxane A2 in platelets, thus reducing platelet aggregation and thrombosis for the lifetime of the affected platelets. In various studies, ASA has been observed to be effective, although substantially inferior to warfarin, in the prevention of stroke in patients with AF (Hart et al. 2007; Mant et al. 2007; van Walraven et al. 2002). In a meta-analysis published in 2007, ASA reduced stroke incidence in patients with AF by 22% when compared with placebo (Hart et al. 2007).

However, there is also evidence against even a small efficacy of ASA: in a Swedish registry study on 115,185 patients with AF, ASA had in fact no protective effect at all against stroke (Själander et al. 2014). Moreover, little to no increase in the rate of major bleeding events is observed with warfarin treatment in comparison to ASA (Hart et al. 2007; Mant et al. 2007; van Walraven et al. 2002).

Among the NOACs, only apixaban has been compared against ASA in a randomized trial, wherein the subjects who received apixaban suffered significantly fewer strokes, while the rate of major bleeding events was similar in both treatment groups (Connolly et al. 2011).

2.4.2.2 Adenosine diphosphate receptor inhibitors

Adenosine diphosphate (ADP) receptor inhibitors prevent thrombosis by antagonizing the platelet surface protein P2Y12, which in turn leads to reduced platelet aggregation. Among the currently available ADP inhibitors, ticlopidine, clopidogrel and prasugrel inhibit P2Y12 irreversibly, whereas ticagrelor and cangrelor are reversible P2Y12 inhibitors. ADP receptor inhibitor monotherapy has not been investigated in the prevention of stroke in patients with AF.

2.4.2.3 Dual antiplatelet therapy

In the randomized ACTIVE W trial, dual antiplatelet therapy with clopidogrel and acetylsalicylic acid was significantly less effective in stroke prevention when compared against warfarin treatment, while similar rates of major bleeding events were observed with both treatments (ACTIVE Investigators 2006). Furthermore, in the randomized ACTIVE A trial, wherein dual antiplatelet therapy with clopidogrel and acetylsalicylic acid was compared against acetylsalicylic acid monotherapy, significantly fewer strokes were observed in the dual antiplatelet arm with the trade-off of more frequent major bleeding events resulting in no difference in the overall event rate (ACTIVE Investigators (2006). Dual antiplatelet therapy with ticagrelor, cangrelor, prasugrel or ticlopidine has not been studied in the prevention of stroke in patients with AF.

2.4.3 Left atrial appendage occlusion

In autopsy studies, it has been observed that cardiogenic thrombi in patients with non-valvular AF commonly originate from the left atrial appendage (LAA) (Blackshear et al. 1996). Due to this observation, occlusion of the structure has been suggested as a means to reduce the risk of thromboembolism and stroke in patients with AF. The role of the LAA as the most important source of emboli has since been confirmed in the PROTECT AF trial (Holmes et al. 2009). Both percutaneous and surgical occlusion techniques have been described.

In percutaneous LAA occlusion, a device is introduced inside the left atrium via a catheter to close the LAA orifice. Although several occluding devices have been developed, only the Watchman device has been compared to long-term warfarin treatment in randomized trials. In the PROTECT AF and PREVAIL trials, LAA occlusion with the Watchman device demonstrated non-inferiority against warfarin therapy in stroke prevention and systemic embolism (Holmes et al. 2009; Holmes et al. 2014; Reddy et al. 2013a). Furthermore, in a meta-analysis that combined the data of the two trials, a lower rate of major bleeding events was observed in the patients who underwent LAA occlusion compared to the control group (Holmes et al. 2015).

However, it must be noted that the PROTECT AF and PREVAIL trials included only patients eligible for OAC therapy. Nevertheless, the results of the small non-randomized ASAP study suggest that a significant stroke risk reduction is attained also in patients with a contraindication for OAC therapy, while their risk of haemorrhagic stroke remains small (Reddy et al. 2013b). In a small percentage of patients, percutaneous LAA occlusion is associated with serious periprocedural complications, the most common of which are pericardial effusion, procedure-related stroke and device embolization (Holmes et al. 2014). According to current guidelines, percutaneous LAA closure should be considered in AF patients at a risk of thromboembolism but who cannot be managed with OAC (Camm et al. 2012; Kirchhof et al. 2016). A percutaneous LAA exclusion technique, in which the LAA is sutured epicardially by utilising a percutaneous suture delivery device, has also been introduced (Bartus et al. 2013).

In surgical LAA occlusion, the structure is either excised altogether or closed with sutures, staples or a separate device. LAA occlusion has been performed in conjunction with other cardiac surgery for years, and according to current guidelines, may be considered in AF patients undergoing cardiac or thoracoscopic surgery (Kirchhof et al. 2016). Current knowledge on the matter is based mainly on small observational studies, and no data from adequately-powered randomized trials are currently available. Hopefully, LAAOS III, an ongoing randomized trial, wherein 4,700 patients with AF in whom an on-pump cardiac surgical procedure is scheduled will be randomized to either undergo or not to undergo concomitant LAA occlusion, will provide some light on the issue upon conclusion (Withlock et al. 2014). Clinical guidelines recommend to continue administer OAC therapy to those indicated to receive it even after surgical LAA occlusion (Kirchhof et al. 2016).

2.5 Asymptomatic atrial fibrillation

AF can present with a variety of symptoms and signs, which often are caused by a rapid heart rate. The most typical symptoms associated with AF are palpitations, while some may also suffer from dyspnoea, general tiredness and exertion intolerance. The diagnosis is reached when an electrocardiographic (ECG) recording is made and irregular ventricular activations, absence of discernible P-waves and an oscillating baseline are noted on the ECG tracing.

However, absence of symptoms during AF is exceedingly common as noted earlier. A systematic review published in 2000 summarized that previous studies had reported widely variable rates of asymptomatic AF in different settings, but concluded that at least one third of patients with AF must be asymptomatic (Savelieva et al. 2000). A more current view to the matter was provided by the multinational EORP-AF Study, in which a complete absence of symptoms was observed in 40% of 3119 consecutive patients with AF supporting the previous estimate by Savelieva et al. (Boriani et al. 2015). The study also found that more than half of symptomatic patients have only mild symptoms. Another recent study reported that out of 476 patients with newly-diagnosed AF, 34% presented without symptoms and 26% with atypical symptoms (e.g. dyspnoea or tiredness), while only 41% had a typical presentation with palpitations (Siontis et al. 2016). Several other recent studies have also reported the symptom status and have provided widely differing proportions of asymptomatic AF (12-40%) (Flaker et al. 2004; Komatsu et al. 2010; Potpara et al. 2013; Rienstra et al. 2014; Senoo et al. 2014). This may be explained by these studies utilizing diverging methods to assess the subjects' symptom status and also applying different restrictions to patient selection. It has also been reported that in the setting of paroxysmal AF, even in symptomatic patients, the vast majority of AF episodes are asymptomatic (Hindricks et al. 2005; Page et al. 1994).

Varying and conflicting clinical characteristics associated with lack of symptoms in AF have been presented. However, male sex is unequivocally a predictor of asymptomatic AF, which was demonstrated in a meta-analysis comprising six of the eight studies presented in the previous paragraph (Xiong et al. 2015). Lack of symptoms is also associated with permanent and persistent forms of the arrhythmia (Boriani et al. 2015; Potpara et al. 2013), and slower ventricular rate compared to symptomatic AF (Flaker et al. 2004; Potpara et al. 2013).

2.6 Screening of atrial fibrillation

2.6.1 Rationale of screening

Due to the importance of AF as a risk factor of stroke and its frequent asymptomatic nature, the implementation of screening measures to detect asymptomatic AF prior to the occurrence of stroke has received increasing support during the last years. Indeed, AF fulfils most of the Wilson-Jungner criteria set by the World Health Organization to aid in the evaluation of the justification of screening programs (Table 4). Several screening methods and schemes have been proposed and studied. A summary of previously conducted screening studies is presented in Table 5.

Table 4. The Wilson-Jungner criteria of evaluating the justification of screening programs (Wilson et al. 1968).

1.	The condition sought should be an important health problem.
2.	There should be an accepted treatment for patients with recognized disease.
3.	Facilities for diagnosis and treatment should be available.
4.	There should be a recognizable latent or early symptomatic stage.
5.	There should be a suitable test or examination.
6.	The test should be acceptable to the population.
7.	The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8.	There should be an agreed policy on whom to treat as patients.
9.	The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10.	Case-finding should be a continuing process and not a “once and for all” project.

Table 5. Summary of previously conducted screening studies.

Author	Country	Population	Screening method	Number of subjects	Follow-up	New AF	Post-screening prevalence of AF
Hill et al. 1987	The United Kingdom	Symptomless primary care patients aged >65 years	Single 12-lead ECG recording	819	NA	10 /819 (1.2%)	30/819 (3.7%)
Furberg et al. 1994	The United States	Medicare beneficiaries aged ≥65 years	Single 12-lead ECG recording	5,151	NA	77/5,151 (1.5%)	277/5,151 (5.4%)
Wheeldon et al. 1998	The United Kingdom	Primary care patients aged ≥65 years	Single 12-lead ECG recording	1,207	NA	5/1,207 (0.4%)	Not reported
Mullenix et al. 2006	The United States	Military retiree and spouse members of a health maintenance organization	Single 12-lead ECG recording	294	NA	4/294 (1.4%)	21/294 (7.1%)
Tveit et al. 2008	Norway	General population aged 75 years	Singe 12-lead ECG recording	916	NA	10/916 (1.1%)	92/916 (10.0%)
Meschia et al. 2010	The United States	General population aged ≥45 years with over-sampling of African Americans	Single 7- or 12-lead ECG recording	29,861	NA	174/29,861 (0.6%)	Not reported
Schnabel et al. 2012	Germany	General population aged 35 to 74 years	Single 12-lead ECG recording	5,000	NA	25/5,000 (0.5%)	161/5,000 (3.2%)
Claes et al. 2012	Belgium	General population aged ≥40 years	Single one-lead ECG recording	13,564	NA	167/13,564 (1.2%)	999/13,564 (7.4%)

Table 5 continued.

Author	Country	Population	Screening method	Number of subjects	Follow-up	New AF	Post-screening prevalence of AF
Samol et al. 2012	Germany	Consecutive in- and out-patients aged ≥18 years without a history of AF and at least one risk factor for stroke	Single one-lead ECG recording	132	NA	7/132 (5.3%)	7/132 (5.3%)
Frewen et al. 2013	Ireland	General population aged ≥50 years	Single ten-minute 3-lead ECG record-ing	4,890	NA	45/4,890 (0.9%)	Not reported
Deif et al. 2013	Australia	Ambulatory patients aged ≥40 years under-going elective surgery	Single 12-lead ECG recording	2,802	NA	12/2,802 (0.4%)	112/2,802 (4.0%)
Walker et al. 2014	New Zealand	Pharmacy customers aged ≥55 years	Single one-lead ECG recording	121	NA	2/121 (1.7%)	Not reported
Kearley et al. 2014	The United Kingdom	Primary care patients aged ≥75 years	Single 12-lead ECG recording	1,000	NA	12/1,000 (1.2%)	79/1,000 (7.9%)
Tieleman et al. 2014	The Nether-lands	People attending influ-enza vaccination	Single one-lead ECG recording	676	NA	11/676 (1.6%)	55/676 (8.1%)
Lowres et al. 2014	Australia	Pharmacy customers aged ≥65 years	Pulse palpation and recording a single one-lead ECG trac-ing	1,000	NA	15/1,000 (1.5%)	119/1,000 (11.9%)

Table 5 continued.

Author	Country	Population	Screening method	Number of subjects	Follow-up	New AF	Post-screening prevalence of AF
Bury et al. 2015	Ireland	Primary care patients aged ≥70 years without a history of AF	Single 3-lead ECG recording	566	NA	12/566 (2.1%)	12/566 (2.1%)
Proietti et al. 2016	Belgium	General population aged ≥20 years	Single one-lead ECG recording	65,747	NA	603/65,747 (0.9%)	13,609/65,747 (20.7%)
Orchard et al. 2016	Australia	People aged ≥65 years attending influenza vaccination clinics	Single one-lead ECG recording	976	NA	8/972 (0.8%)	Not reported
Kaasenbrood et al. 2016	The Netherlands	People attending influenza vaccination	Single one-lead ECG recording	3,269	NA	37/3,269 (1.1%)	Not reported
Chan et al. 2016	China	Outpatients with hypertension, diabetes and/or aged ≥65 years	Single one-lead ECG recording	1,013	NA	5/1,013 (0.5%)	28/1,013 (2.8%)
Sandhu et al. 2016	Canada	Pharmacy customers aged ≥65 years	Single one-lead ECG recording	1,175	NA	27/1,175 (2.3%)	Not reported
Chan et al. 2017a	China	General population aged ≥18 years	Single one-lead ECG recording	13,122	NA	101/13,122 (0.8%)	1,111/13,122 (8.5%)
Rhys et al. 2013	The United Kingdom	Patients aged ≥65 years attending influenza vaccination	Pulse palpation followed by recording a single 12-lead ECG tracing in case of pulse irregularity	568	NA	2/568 (0.35%)	23/568 (4.0%)

Table 5 continued.

Author	Country	Population	Screening method	Number of subjects	Follow-up	New AF	Post-screening prevalence of AF
Sanmartín et al. 2013	Spain	People aged ≥65 years with no diagnosis of AF	Pulse palpation followed by recording a single 12-lead ECG tracing in case of pulse irregularity	1,532	NA	17/1,532 (1.1%)	17/1,532 (1.1%)
Omboni et al. 2016	Italy	General population aged ≥18 years	Assessment of rhythm with an automated blood pressure monitor algorithm followed by recording a single 12-lead ECG tracing in case of possible AF	220	NA	4/220 (1.8%)	Not reported
Wiesel et al. 2017	The United States	Nursing facility residents aged ≥65 years, without a history of AF	Assessment of rhythm with a blood pressure monitor followed by recording an ECG tracing in case of possible AF	101	NA	7/101 (6.9%)	7/101 (6.9%)
Morgan et al. 2002	The United Kingdom	Primary care patients aged >65 years					
			Single 12-lead ECG recording	1,499 randomised, 1099 (73.3%) screened	NA	12/1,499 (0.8%)	67/1,499 (4.5%)
			Pulse palpation followed by 12-lead ECG in case of pulse irregularity	1,502 randomised, 439 (29.2%) screened	6 months	7/1,502 (0.5%)	19/1,502 (1.3%)
Smyth et al. 2016	Ireland	Primary care outpatients aged ≥65 years	Pulse palpation followed by recording a single 12-lead ECG tracing in case of pulse irregularity	7,262	6 months	55/7,262 (0.8%)	Not reported

Table 5 continued.

Author	Country	Population	Screening method	Number of subjects	Follow-up	New AF	Post-screening prevalence of AF
Fitzmaurice et al. 2007	The United Kingdom	Primary care outpatients aged ≥65 years without AF					
			Single 12-lead ECG recording	4,562 randomised, 2,357 (51.7%) screened	NA	74/4,562 (1.62%)	74/4,562 (1.62%)
			Pulse palpation followed by recording a single 12-lead ECG tracing in case of pulse irregularity	4,575 randomised, 3,278 (71.7%) screened	12 months	75/4,575 (1.64%)	75/4,738 (1.64%)
			Standard practice	4,513	12 months	47/4,513 (1.0%)	47/4,513 (1.0%)
Hendrikx et al. 2013	Sweden	Outpatients without AF and $CHADS_2$ ≥1	Twice-daily recordings with a one-lead ECG device	928	4 weeks	35/928 (3.8%)	35/928 (3.8%)
Engdahl et al. 2013	Sweden	General population aged 75 or 76 years	Single 12-lead ECG recording followed by twice-daily recording of a one-lead ECG tracing for two weeks in those with ≥2 $CHADS_2$ points	848	2 weeks	40/848 (4.7%)	121/848 (14.3%)
Svennberg et al. 2015	Sweden	General population aged 75 or 76 years	Single 12-lead ECG recording followed by twice-daily recording of a one-lead ECG	7,173	2 weeks	218/7,173 (3.0%)	884/7,173 (12.3%)

Table 5 continued.

Author	Country	Population	Screening method	Number of subjects	Follow-up	New AF	Post-screening prevalence of AF
Berge et al. 2017	Norway	General population aged 65 years and CHA_2DS_2VASc score ≥2 (men) or ≥3 (women)	Twice-daily recordings with a one-lead ECG device	1,742	2 weeks	13/1,742 (0.7%)	154/1,742 (8.8%)
Halcox et al. 2017	The United Kingdom	Patients aged ≥65 years with CHA_2DS_2VASc ≥2 and no AF					
			Twice-weekly single-lead ECG recordings	500	12 months	19/500 (3.8%)	19/500 (3.8%)
			Routine care	501	12 months	5/500 (1.0%)	5/500 (1.0%)
De Rujiter et al. 2007	The Netherlands	General population aged ≥85 years	Annual 12-lead ECG recordings	566	5 years	23/566 (4.1%)	56/566 (9.9%)
Tavernier et al. 2017	Belgium	Hospitalized geriatric patients	Routine care and daily one-lead ECG recordings	214	Duration of acute hospital stay	35/214 (16.4%)	99/214 (46.3%)
Turakhia et al. 2015	The United States	Patients aged ≥55 years with risk factors but no history of AF	Ambulatory patch ECG recorder	75	2 weeks	4/75 (5.3%)	4/75 (5.3%)
Wiesel et al. 2013	The United States	Outpatients aged ≥65 years, with hypertension, diabetes, heart failure and/or history of stroke	Daily assessment of rhythm with an automated blood pressure monitor algorithm and an ECG event recorder	139	30 days	2/139 (1.4%)	18/139 (12.9%)

Table 5 continued.

Author	Country	Population	Screening method	Number of subjects	Follow-up	New AF	Post-screening prevalence of AF
Benito et al. 2015							
		Self-palpation of pulse monthly in addition to clinical check-up involving ECG recording every 6 months	463	2 years	8/463 (1.7%)	8/463 (1.7%)	Self-palpation of pulse monthly in addition to clinical check-up involving ECG recording every 6 months
		Standard practice	465	2 years	1/465 (0.2%)	1/465 (0.2%)	Standard practice
Healey et al. 2017	The United States	Cardiology or neurology outpatients aged ≥65 years with no history of AF and CHA_2DS_2VASc score ≥2	Implantable loop recorder	256	18 months	90/256 (35.2%)	90/256 (35.2%)
Reiffel et al. 2017	The United States	Patients with a $CHADS_2$ score ≥3 but no history of AF	Implantable loop recorder	446 screened, 394 (88.3%) underwent device insertion	18 to 30 months	128/446 (28.6%)	128/446 (28.6%)
Nasir et al. 2017	The United States	Patients with no history of AF with a CHA_2DS_2VASc score ≥2	Implantable loop recorder	245	18 months	55/245 (22.4%)	55/245 (22.4%)

Although no data on stroke prevention in patients in whom AF has been detected due to screening are available, many studies suggest that such patients would usually benefit from OAC therapy. In various studies, equally severe risk of stroke has been observed in symptomatic and asymptomatic patients with AF (Boriani et al. 2015; Flaker et al. 2004; Komatsu et al. 2010; Potpara et al. 2013; Rienstra et al. 2014; Senoo et al. 2014, Siontis et al. 2016). Moreover, in several screening studies employing varying screening strategies, the great majority of subjects with screen-detected AF are indicated to receive OAC as evaluated with the CHA_2DS_2VASc or the $CHADS_2$ score (Chan et al. 2017a; Fitzmaurice et al. 2014; Kaasenbrood et al. 2016; Lowres et al. 2013; Lowres et al. 2014; Svennberg et al. 2015). Further evidence suggesting a benefit from OAC treatment in patients with screen-detected AF has been provided by Martinez et al. who reported on altogether 5,555 patients with asymptomatic incidentally detected AF, thus closely resembling screen-detected AF, and observed a significantly lower cumulative incidence of stroke at 1% in patients receiving OAC compared to 4% in those with no antithrombotic therapy during 1.5 years of follow-up (Martinez et al. 2014). Nevertheless, randomized controlled studies evaluating specifically the effect of screening on the occurrence of stroke and other hard end-points may need to be conducted in the future to further corroborate these findings in patients with screen-detected AF.

2.6.2 Screening strategies

Screening for AF may be conducted either opportunistically, i.e. during healthcare contacts for any reason, or systematically, i.e. in all members of a specific group (e.g. the general population, patients at a high risk for stroke or people living in a specific geographic area). Additionally, screening may be conducted either at a single time point or at multiple time points.

Screening at a single time point in otherwise unselected populations aged at least 65 years yields 1.4% of new AF diagnoses according to an extensive systematic review (Lowres et al. 2013). However, the rate of detection is profoundly dependent on the target population, and higher yields of up to 5.3% have been achieved with single ECG recordings in populations at a greater risk for AF (Bury et al. 2015; Samol et al. 2012). As healthcare contacts by individuals are usually infrequent, opportunistic screening approximates systematic screening at a single time point in the short-to-medium term, but inevitably provides more opportunities for arrhythmia detection during longer periods of follow-up.

To date, there have been two randomized controlled trials, in which systematic screening at a single time point and opportunistic screening have directly been

compared with each other. In 2002, Morgan et al. randomised altogether 1,499 patients aged ≥65 years to systematic screening with pulse palpation followed by the recording of an ECG tracing when irregularity was detected and 1,502 to opportunistic screening, in which the subjects had their pulse palpated only at healthcare contacts (Morgan et al. 2002). During a follow-up of six months, 73% of the subjects in the systematic arm and 29% in the opportunistic arm had their pulse palpated, and the respective yields of new AF were 0.8% and 0.5% (Morgan et al. 2002).

In 2007, Fitzmaurice et al. screened for AF in altogether 4,562 subjects aged ≥65 years systematically with single ECG-recordings and in 4,575 subjects opportunistically with pulse palpation at healthcare contacts followed by an ECG recording when irregularity was detected, while 4,513 subjects in whom no screening strategy was employed acted as controls (Fitzmaurice et al. 2007). During a 12-month follow-up, ECGs were recoreded in 52% of the subjects in the systematic arm and pulse was palpated in 72% of the subjects in the opportunistic arm (Fitzmaurice et al. 2007). The rate of new AF diagnoses in the control arm was 1.0%, while screening in the opportunistic and systematic arms produced similar detection rates of 1.6% (Fitzmaurice et al. 2007).

A pertinent difference between the studies is that there were substantially fewer subjects randomised to opportunistic screening in the work by Morgan et al. who were actually screened and subsequently diagnosed with AF compared to the study by Fitzmaurice et al. The most likely explanation for this disparity is that in the latter work the follow-up period was twice the length of that of the former, highlighting the obstacle of infrequency of healthcare contacts for opportunistic screening, a significant problem when screening for an often paroxysmal arrhythmia.

Subsequently, there have been several studies, wherein AF is systematically screened for at multiple time points to better allow the detection of paroxysmal arrhythmias. In 2015, the STROKESTOP investigators reported on altogether 7,173 subjects belonging to the general 75-76 year-old population who were screened for AF with a single 12-lead ECG recording at baseline followed by two weeks of twice-daily single-lead ECG recordings (Svennberg et al. 2015). During the intervention, new AF was discovered in only 0.5% of the subjects in the baseline ECG but in 3.0% during the full follow-up (Svennberg et al. 2015). When a similar intervention was restricted to patients with a $CHADS_2$ score of at least two, new AF was revealed in as many as 7.4% of the subjects (Engdahl et al. 2013). Moreover, it has previously been demonstrated that intermittent ECG recordings have a distinctly superior detection rate of AF in comparison to contin-

uous 24-hour ECG recordings, thus providing further evidence in favour of multiple time point screening (Doliwa Sobocinski et al. 2012).

In addition to the work by the STROKESTOP investigators, encouraging results have been reported from several other studies, in which AF was screened for at multiple time points (De Rujiter et al. 2015; Hendrikx et al. 2013; Turakhia et al. 2015). However, noticeably poorer results were achieved by Berge et al., who performed an identical intervention to the one conducted by Svennberg et al. in altogether 1,742 subjects aged 65 years with additional risk factors for stroke but uncovered new AF in only 0.7% of the cohort (Berge et al. 2017). The difference in yield in comparison to the STROKESTOP investigators' work can possibly be explained by the younger age of the subjects included in the study, thus strongly emphasizing the importance of careful selection of the to-be-screened population.

Although it seems that multiple time point screening is superior to single time point screening, it must be noted that the subjects included in the published studies had profound differences regarding their risk profile, thus rendering the comparison of the effectiveness of the two approaches difficult. Generally, the published single time point screening studies were conducted in populations that were both younger and possessed fewer risk factors for AF and stroke than the subjects in the studies on systematic screening of AF. An exception was the work by Berge et al., which was conducted in a younger population and, indeed, reported poorer results, thus casting some doubt on the seemingly superior efficacy of multiple time point screening. Consequently, adequately powered systematic controlled trials comparing the two approaches head-to-head should be conducted to more conclusively clarify their relative effectiveness.

2.6.3 Cost-effectiveness of screening

Opportunistic screening with pulse palpation at healthcare contacts in patients aged at least 65 years has been estimated to be cost-effective (Hobbs et al. 2005; Moran et al. 2016). Similarly, opportunistic screening with single-lead ECG recorders during pharmacy visits and during annual influenza vaccinations is likely cost-effective and potentially even cost-saving (Jacobs et al. 2016; Lowres et al. 2014). Furthermore, single time point screening, with either ECG recordings or pulse palpation, seems to maintain its cost-effectiveness when repeated on an annual basis (Maeda et al. 2005). Systematic screening with twice-daily ECG recordings during a two-week period in the general 75-year old population has also exhibited excellent cost-effectiveness in a simulation analysis (Aronsson et al. 2017).

In addition to the effectiveness of the utilised screening method, several factors affect the cost-effectiveness of a screening intervention, the foremost of which is the age and risk profile of the target-population and the prevalence of AF in it. According to a simulation model constructed by Aronsson et al., the lowest cost per gained quality-adjusted life-year would be attained when screening in subjects aged 75 years or older (Aronsson et al. 2017). Furthermore, the initiation rate of OAC treatment after screening positive for AF has a significant effect on the cost-effectiveness of screening (Lowres et al. 2014). This may be an important obstacle when devising an effective screening scheme, as currently undertreatment is a significant problem for patients with AF, a large share of whom, despite being indicated to, do not receive any OAC medications (Engdahl et al. 2013; Palomäki et al. 2016).

A notable weakness of the cost-effectiveness studies published to date is that they all rely on simulation models, which inherently contain multiple potential sources of bias. Subsequently, the cost of case-finding and averted strokes and other end-points should in the future be determined in prospective studies to attain more robust evidence on the matter.

2.6.4 Pulse palpation in the screening of atrial fibrillation

AF typically presents with an irregularly irregular pulse, which may be utilised in its detection. However, the irregular pulse of a patient with AF may occasionally be difficult to appreciate, while on the other hand, in addition to AF, there are several other factors and conditions, which can cause pulse irregularity. Due to this uncertainty, ECG confirmation is always required for AF diagnosis.

The diagnostic accuracy of pulse palpation for AF has been explored in various studies. Pulse palpation by nurses and other healthcare professionals has demonstrated good sensitivity at 92-100% and moderate specificity at 71-98% for differentiating AF from SR (Kallmünzer et al. 2014; Morgan et al. 2002; Somerville et al. 2000; Sudlow et al. 1998). The accuracy of pulse palpation is very dependent on the chosen threshold of abnormal irregularity: in the study by Morgan et al., a sensitivity of 94% and a specificity of 74% were attained if any irregularity was considered abnormal, while the respective figures were 54% and 98%, if continuous irregularity was required for abnormal classification (Morgan et al. 2002). The capability of non-healthcare professionals to differentiate AF from SR after minimal education has been investigated in three studies in which sensitivities of 54-77% and specificities of 86-96% were reported (Baxter et al. 1998; Kallmünzer et al. 2014; Munschauer et al. 1999).

To date, pulse palpation has been utilised mainly in opportunistic screening studies, wherein healthcare professionals palpate the subjects' pulse and record a confirmatory ECG tracing, when irregularity is detected as discussed previously (Fitzmaurice et al. 2007; Lowres et al. 2014; Morgan et al. 2002; Rhys et al. 2013; Sanmartín et al. 2013; Smyth et al. 2016). No previous screening studies, in which self-palpation of pulse alone is exploited have been published, although Benito et al. conducted an intervention, wherein the subjects arrived for clinical check-ups every six months in addition to which they palpated their pulse monthly, thus uncovering new AF in 1.7% of the subjects during a follow-up of two years (Benito et al. 2015).

2.6.5 Mobile modalities to detect and screen for atrial fibrillation

AF has traditionally been diagnosed from a 12-lead ECG tracing, the recording of which is somewhat laborious and thus of limited suitability for systematic screening of the arrhythmia. Consequently, several mobile devices have been developed during the last years to allow more efficient screening. Save for the ECG-based technologies, the new modalities, however, always require a confirmatory ECG recording before a diagnosis can be set.

2.6.5.1 Single-lead ECG devices

Unlike the 12-lead ECG machines, single-lead ECG recorders are small, portable and easy-to-use devices that are consequently well suited to screening purposes to be used either by healthcare professionals or the to-be-screened subjects themselves. Several devices utilising automated algorithm-detection of AF have been developed, some of which are standalone devices (Hendrikx et al. 2013; Vaes et al. 2014) and some smartphone-integrated technologies, of which only AliveCor has been widely researched (Lau et al. 2013). Varying accuracy has been reported for the different standalone recorders: in various studies, respective sensitivity and specificity were 82-100% and 93-97% for the MyDiagnostick device (Desteghe et al. 2016; Tavernier et al 2017; Tieleman et al. 2014; Vaes et al. 2014), 96% and 92% for the Zenicor device (Doliwa et al. 2009) and 99% and 76-96% for the Omron HeartScan device (Kaleschke et al. 2009; Kearley et al. 2014). In initial trials, AliveCor provided good sensitivity and specificity at 94-99% and 91-97% (Lau et al. 2013; Lowres et al. 2014; Orchard et al. 2016), but the specificity of the algorithm has since been maximised at the cost of sensitivity, and in subsequent trials sensitivities of 67-71% and specificities superior to 99% have been reported (Chan et al. 2016; Chan et al. 2017b).

An important advantage of using single-lead ECG recorders is that the recordings may be interpreted by physicians to confirm or discard the diagnosis made by the algorithm, and thus no additional diagnostic effort is needed as in the case of other modern mobile AF detection modalities. However, single-lead ECG tracings may sometimes be of insufficient quality rendering the diagnosis of AF difficult even for experienced clinicians (Kearley et al. 2014; Lau et al. 2013). Single-lead ECG recorders, AliveCor in particular, have been widely used in prospective screening studies utilizing both opportunistic and systematic as well as single and multiple time point strategies during the recent years as can be observed from Table 5.

2.6.5.2 Continuous ECG recorders

Continuous ECG recording for extended periods with external patch ECG recorders or external or implantable loop recorders could be used to screen for AF. However, this approach has notable disadvantages as large amounts of data needing physician-evaluation are generated, while external monitoring for prolonged periods is problematic due to skin-irritation and compliance issues, whereas utilising implantable recorders is justified only for certain high-risk patient groups due to their invasiveness.

To date, continuous ECG recording has mainly been studied in diagnosing AF after cryptogenic stroke, but recently patch recorders and implantable loop recorders have been demonstrated feasible also in the screening of AF (Healey et al. 2017; Nasir et al. 2017; Reiffel et al. 2017; Turakhia et al. 2015). However, the clinical significance of the short AF attacks detected with implantable recorders as a risk factor of stroke is currently unknown. Multiple studies aiming to resolve this question are currently underway.

2.6.5.3 Automated blood pressure monitors

Automated blood pressure monitors that incorporate algorithms to detect AF have been introduced. Their diagnostic accuracy has been tested in multiple studies, where sensitivities of 90-100% and specificities of 86-99% were reported, while multiple measurements seem to somewhat improve their performance (Chan et al. 2017b; Gandolfo et al. 2015; Kearley et al. 2014; Marazzi et al. 2012; Stergiou et al. 2009; Wiesel et al. 2004; Wiesel et al. 2009; Wiesel et al. 2013; Wiesel et al. 2014). A recent meta-analysis reported a pooled sensitivity of 98% and specificity of 92% for the modality (Verberk et al. 2016). To date,

blood pressure monitors have been used in two prospective screening studies as the initial step in an opportunistic strategy (Omboni et al. 2016; Wiesel et al. 2017).

2.6.5.4 Photoplethysmography

In photoplethysmography (PPG), cardiac rhythm is assessed from an optically obtained plethysmogram measuring changes occurring in tissue light absorption during cardiac cycles. Although a standalone finger-probe instrument to obtain PPG recordings has been described in literature (Lewis et al. 2011), the potential of the methodology is firmly related to the applicability of smartphones to be used as recording devices without any additional hardware. With smartphones, PPG recordings are obtained by placing a fingertip on the camera and flash of the device and extracting a pulse wave signal from a video recording, and afterwards, an automated algorithm classifies the cardiac rhythm during the recording.

Reporting on 76 subjects with persistent AF undergoing cardioversion from whom PPG recordings were obtained pre- and post-cardioversion with a smartphone, McManus et al. achieved a sensitivity of 96% and a specificity of 97% to detect AF (McManus et al. 2013). To study the effect of extrasystoles on the method, they further supplemented their study cohort with 30 additional subjects with competing causes of pulse irregularity, and respective sensitivity and specificity of 97% and 94% were maintained (McManus et al. 2016). However, when Krivoshei et al. applied the algorithm used by McManus et al. to 80 in- and outpatients (40 in AF and 40 in SR), they achieved markedly poorer results as sensitivity and specificity were only 90% and 85%, respectively, although an enhanced algorithm detected AF with 95% sensitivity and 95% specificity (Krivoshei et al. 2016). In 2016, Chan et al. conducted a population study on altogether 1,013 subjects with risk factors for stroke who were screened for AF with smartphone PPG at a single time point (Chan et al. 2016). The intervention yielded new AF diagnoses in 2.8% of the subjects, while respective sensitivity and specificity of 92.9% and 97.7% compared to cardiologist interpretation of concurrent single-lead ECG recordings were reported for PPG (Chan et al. 2016).

2.6.5.5 Mechanocardiography

In seismocardiography, vibrations of the thorax caused by contractions of the myocardium are recorded by utilising accelerometers, while ballistocardiography

is a similar method, in which vibrations of the whole body instead of the chest wall alone are measured (Inan et al. 2015). Gyrocardiography is a method, recently described by our research group, in which gyroscopes are used to measure mechanical cardiac activity (Tadi et al. 2016). Together, seismocardiocraphy and gyrocardiography constitute mechanocardiography (MCG). Pertaining to the screening of AF, MCG holds great potential, as modern smartphones contain high-quality accelerometer and gyroscopes, and thus they can be used to obtain accurate MCG recordings.

Brüser et al have demonstrated the feasibility of detecting AF with ballistocardiography in 10 subjects with AF undergoing cardioversion (Brüser et al. 2011). Subsequently, our research group has extended this research and demonstrated the feasibility of seismocardiography-detection of AF (Pänkäälä et al. 2016). Combining accelerometer- and gyroscope data obtained with a smartphone to detect AF was first demonstrated in our proof-of-concept study on 39 subjects (23 with SR and 16 with AF), wherein MCG demonstrated 94% sensitivity and 100% specificity to detect AF (Lahdenoja et al. 2016).

2.6.6 Cardiac implanted electronic device detected atrial high rate episodes

Cardiac implanted electronic devices, e.g. pacemakers and defibrillators, with atrial monitoring capability detect atrial high rate episodes (AHRE), which may indicate AF but also other atrial tachyarrhythmias or oversensing by the device. The incidence of AHREs in patients with implanted devices has ranged from 28% to 55% in different studies depending on the target population and utilised algorithm (Healey et al. 2012; Healey et al. 2013; Ziegler et al. 2010; Ziegler et al. 2012). AHREs significantly increase the risk of ischaemic stroke or systemic embolism (hazard ratio (HR): 2.49; 95% confidence interval (CI): 1.28-4.85), although the increase is lesser than expected in clinically manifest AF when taking into individual stroke risk (Healey et al. 2012). There is also uncertainty regarding the minimum AHRE burden that is clinically significant. Recently it was reported that only episodes of 24 hours or more are associated with an increased risk of thromboembolic complications (Van Gelder et al. 2017). Moreover, in the ASSERT trial, no temporal association was observed between the occurrences of AHREs and iscahemic stroke (Brambatti et al. 2014). Therefore, these device-detected AHREs cannot straightforwardly be ruled AF requiring OAC treatment, and additional ECG or device electrogram confirmation is recommended in the 2016 ESC guideline (Kirchhof et al. 2016).

2.6.7 Guideline positions on the screening of atrial fibrillation

Since 2012, the ESC has recommended opportunistic screening with pulse palpation by healthcare professionals in patients aged 65 years or older followed by the recording of ECG when irregularity is detected for early diagnosis of AF (Camm et al. 2012). In their most recent guideline on the management of AF published in 2016, the ESC repeated their recommendation for opportunistic screening, while adding that systematic ECG screening may be considered in patients aged over 75 years or those at a high risk of stroke (Kirchhof et al. 2016). Further recommendations are given to screening for AF by short-term ECG recording followed by continuous ECG monitoring for at least 72 hours in patients with transient ischaemic attack (TIA) or ischaemic stroke and interrogating pacemakers and implantable cardioverter defibrillators on a regular basis for AHREs and monitoring patients with such episodes by ECG before diagnosing AF (Kirchhof et al. 2016). Moreover, it is stated that additional ECG monitoring by long-term non-invasive ECG monitors or implanted loop recorders should be considered in stroke patients to document silent AF (Kirchhof et al. 2016).

Opportunistic pulse palpation and ECG confirmation of detected pulse irregularity is also recommended by the British National Institute for Health and Care Excellence (NICE), but unlike the ESC, only for patients presenting with dyspnoea, palpitations, syncope, dizziness, chest discomfort or stroke or TIA (N.C.C.f.C.C. 2014). A further recommendation given in the NICE medical technologies guidance is to use automatic blood pressure monitors with implemented AF detection systems in primary care to opportunistically screen for AF during blood pressure measurements and to perform a confirmatory ECG recording when AF is suspected (Willits et al. 2014). Modified blood pressure monitors and single-lead ECG devices are accepted as alternatives to pulse palpation in an opportunistic screening scheme also by the European Primary Care Cardiovascular Society (Hobbs et. al 2016).

The joint guideline by the American College of Cardiology, the American Heart Association and the Heart Rhythm Society on the management of AF published in 2014, makes no specific recommendation on screening for AF, but it is stated that efforts for early detection of AF may be needed in individuals at risk for stroke (January et al. 2014). Similarly reserved on the matter, the Canadian Cardiovascular Society give recommendations on the screening of AF only in the setting of secondary prevention of stroke (Verma et al. 2014).

3 AIMS OF THE STUDY

I. To determine the proportion of patients who have suffered an AF-associated ischaemic stroke or a transient ischaemic attack (TIA) in whom AF is diagnosed concurrently with the cerebrovascular event.

II. To evaluate the ability of elderly cognitively unimpaired subjects to differentiate SR, AF and SR with ventricular extrasystoles by pulse palpation after a short education.

III. To study whether regular self-palpation of pulse by the elderly is a feasible screening strategy for AF.

IV. To assess the accuracy of smartphone MCG in differentiating between AF and SR and validate the method in a large clinically representative cohort of hospitalised patients.

4 MATERIALS AND METHODS

4.1 Study population and design

4.1.1 Study I

The first study was part of the wider FibStroke Study, which included all patients aged at least 18 years who were diagnosed with AF at any time and who suffered an ischaemic stroke, a TIA or an intracranial haemorrhage during 2003-2012 treated in four university or central hospitals (Turku University Hospital, Turku; Kuopio University Hospital, Kuopio; Satakunta Central Hospital, Pori; Central Finland Central Hospital; Jyväskylä). Altogether, 5,885 ischaemic events (4,547 of which were strokes and 1,338 TIAs) and 830 intracranial haemorrhages were identified in 5,676 patients. All events were adjudicated by a neurologist and confirmed by computed tomography or magnetic resonance imaging. After identification, each case was individually reviewed from patient records according to a standardised data collection protocol. Data were documented on patient characteristics, cardiac rhythm at the time of the cerebrovascular event, use of medications, operations during the preceding month and all-cause mortality during the 30-day period following the index event. Data were recorded in a structured electronic case report form in an online database.

For this study, a study group and a control group were established. In the study group, only patients who suffered their first ever ischaemic event (stroke or TIA) during the study period and who were diagnosed with AF prior to the ischaemic event or during hospitalisation for it were included. Thus, the study group consisted of 3,623 patients, who suffered 2,914 ischaemic strokes and 709 TIAs. These patients were then divided into two groups according to the time of AF diagnosis: ‘previous AF’ (i.e. patients with a history of AF before the ischaemic stroke or TIA) and ‘new AF’ (i.e. patients in whom AF was detected at the presentation of the ischaemic stroke or TIA in the emergency room or during hospitalisation within the following week).

Central nervous system injury may affect autonomic nervous system, which plays an important role in the pathogenesis of AF and support the hypothesis that stroke may trigger AF (Chen et al. 2014; González Toledo et al. 2013). To elucidate the role of cerebrovascular events as a trigger of new arrhythmias, a control group of 781 patients with intracranial haemorrhages was established according to the same exclusion criteria used with the ischaemic events in the study group.

These patients were then divided into ‘previous AF’ and ‘new AF’ groups using the same criteria as with the ischaemic events.

To uncover potential clustering of AF diagnoses around the first ischaemic event, a supplementary analysis including also the patients in whom AF was diagnosed after the index hospitalisation was carried out. Patients in whom AF was diagnosed more than five years before (808 patients) or after (58 patients) the ischaemic event, or with inaccurate timing of AF diagnosis (740 patients) were excluded resulting in 2,605 patients. This analysis focused on AF diagnoses made within 8-30 days after hospitalisation for the ischaemic event, since these late diagnoses may also reflect the potential role of silent paroxysmal AF as the cause of the index ischaemic event.

4.1.2 Studies II-III

Studies II-III are part of the LietoAF Study, the study population of which consisted of 205 subjects aged at least 75 years with no history of chronic AF, who were not receiving OAC therapy and were not in permanent institutional care. The subjects were randomly selected from among 300 willing and eligible subjects living in Lieto, a municipality in South-Western Finland, at the end of 2011.

During a baseline visit, information was recorded on the subjects’ medical history, medications, lifestyle factors, social factors and previous education, key physical measurements were performed (height, weight, waist circumference and blood pressure), 12-lead ECGs recorded, a validated EQ-5D-3L health state questionnaire assessing quality of life completed and a Mini-Mental State Examination (MMSE) performed. A trained cardiac nurse educated the subjects on pulse palpation with special focus on the evaluation of heart rate and rhythm regularity and assessed the subjects’ achieved pulse palpation capacity during a structured 10-minute training session. The subjects were asked to continue self-assessment of pulse on a permanent basis twice-daily and when symptoms occur. For four months, they recorded their heart rate in a follow-up diary in an attempt to encourage habit formation. In case of detected pulse irregularity that persisted after 20 minutes, the subjects were advised to contact healthcare professionals without any delay.

A follow-up visit occurred after one month, while further follow-ups at four, 12 and 36 months were conducted with mailed questionnaires. During the one-month follow-up, the subjects’ continuing motivation and capability for pulse palpation were assessed: if the study nurse graded the subjects’ capability as good and at least 80% of all diary entries were completed, the subjects were clas-

sified as having good motivation/capability; otherwise they were classified as having inadequate motivation/capability. During each follow-up, the subjects were inquired about pulse palpation activity, detected pulse irregularity and possible AF diagnoses and an EQ-5D-3L health state questionnaire was repeated. Information on AF diagnoses was also searched from hospital and municipal health centre records. The results of the intervention during the full three years of follow-up are reported in Study III.

For Study II, an additional investigation was carried out on altogether 173 willing LietoAF subjects and a control group consisting of 57 healthcare personnel (10 nurses, 17 final year paramedic students, 15 final year nursing students and 15 paramedic students with one full year of studies left). Each subject was individually given a brief five minutes' education covering the concepts of SR, AF and ventricular extrasystoles (VES), in which it was elaborated that SR features a regular pulse, SR with VESs features an irregular pulse with underlying regularity and that AF presents as an irregularly irregular pulse with no underlying regularity.

Right afterwards, the ability of each subject to discriminate AF, SR and SR with VESs by pulse palpation was assessed by utilising an anatomic model of a human arm (SimPad BloodPressure Trainer; manufacturer: Laerdal) programmable with various rhythms and rates and with three locations for pulse palpation (the radial, cubital and axillary arteries). The subjects were told that the pulse palpation arm would be programmed to present one of three possible rhythms (SR, SR with VESs or AF) with different ventricular rates one after another and that the rhythms presented would vary by number, order and ventricular rate between subjects. However, all subjects were actually presented with four rhythms (SR (rate 60), slow AF (rate 60), fast AF (rate 120) and SR with VESs (rate 80)) in the following order: SR, fast AF, slow AF, SR and SR with VESs. The subjects were asked to palpate the pulse of the model at a preferred site and verbally identify each consecutive rhythm as SR, AF or SR with VESs, for which task they had a maximum allowed time of 120 seconds per rhythm.

The outline of the LietoAF Study as a flow chart is presented in Figure 1.

4.1.3 Study IV

The fourth Study was a case-control study in which 150 consecutive patients in AF and 150 age- and sex-matched patients in SR were enrolled from among patients treated in the cardiology and acute internal medicine wards of Turku University Hospital, Turku, Finland between April and September 2017. An MCG

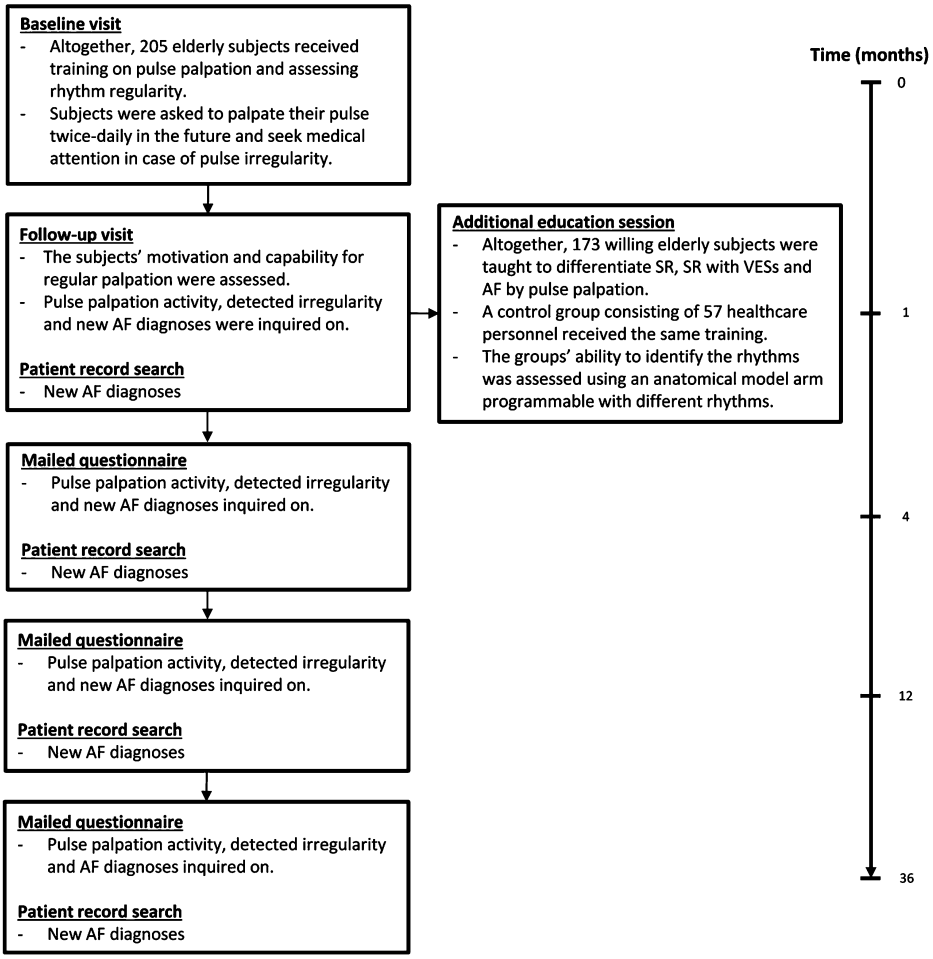

Figure 1. The outline of the Lieto AF study as a flow chart.

recording of three minutes' duration was obtained from each subject, while they were in a supine position, using a Sony Xperia Z1 or Z5 smartphone placed on their bare chest longitudinally, the screen facing upwards and the bottom edge of the phone at the level of the lower edge of the body of sternum. A continuous 5-lead telemetry ECG (Philips IntelliVue MX40) recording was acquired simultaneously with the MCG recordings and was used as the comparison method to assess cardiac rhythm and the number of possible supraventricular extrasystoles (SVES) or VESs during recording. The ECG rhythm classifications were confirmed by two independent cardiologists, and a third cardiologist made the final decision if interpretations diverged. Additionally, key physical measurements (blood pressure, pulse, chest circumference, height and weight) were acquired and data regarding the subjects' clinical history and the results of 12-lead ECG recordings, cardiac ultrasound examinations, chest radiographs and laboratory

tests conducted during hospitalisation were extracted from individual electronic patient records and documented in a structured electronic case report form in an online database.

After the MCG recordings consisting of accelerometer and gyroscope data (both with three data axes) were acquired, the raw data were delivered to the algorithm developer's site at the Department of Future Technologies, University of Turku, Finland. The recordings were analysed by investigators blinded to the underlying rhythm by utilising a beforehand-developed computer algorithm, which classifies cardiac rhythm as either SR or AF.

Before algorithm-analysis, the data were first pre-processed by applying a band-pass filter to the raw data to remove any signal noise and bias, while targeting to preserve the shape of the signal. During algorithm-analysis, each data axis was examined with short 5-second autocorrelation windows to find evidence of constant beat-to-beat intervals. Due to the differing quality of the various accelerometer and gyroscope data axes, the algorithm combines the information from the various axes to provide a more reliable estimate of heart rhythm.

In the final phase, to classify the rhythm of each subject as either AF or SR, the share of signal segments with regularity was determined. The resulting rhythm classifications were returned through a password-protected web-page to evaluators at the Heart Centre, Turku University Hospital, Finland, who then compared the, against the previously made visual ECG rhythm interpretations. The relationship between ECG, accelerometer and gyroscope signals during an MCG recording is presented in Figure 2.

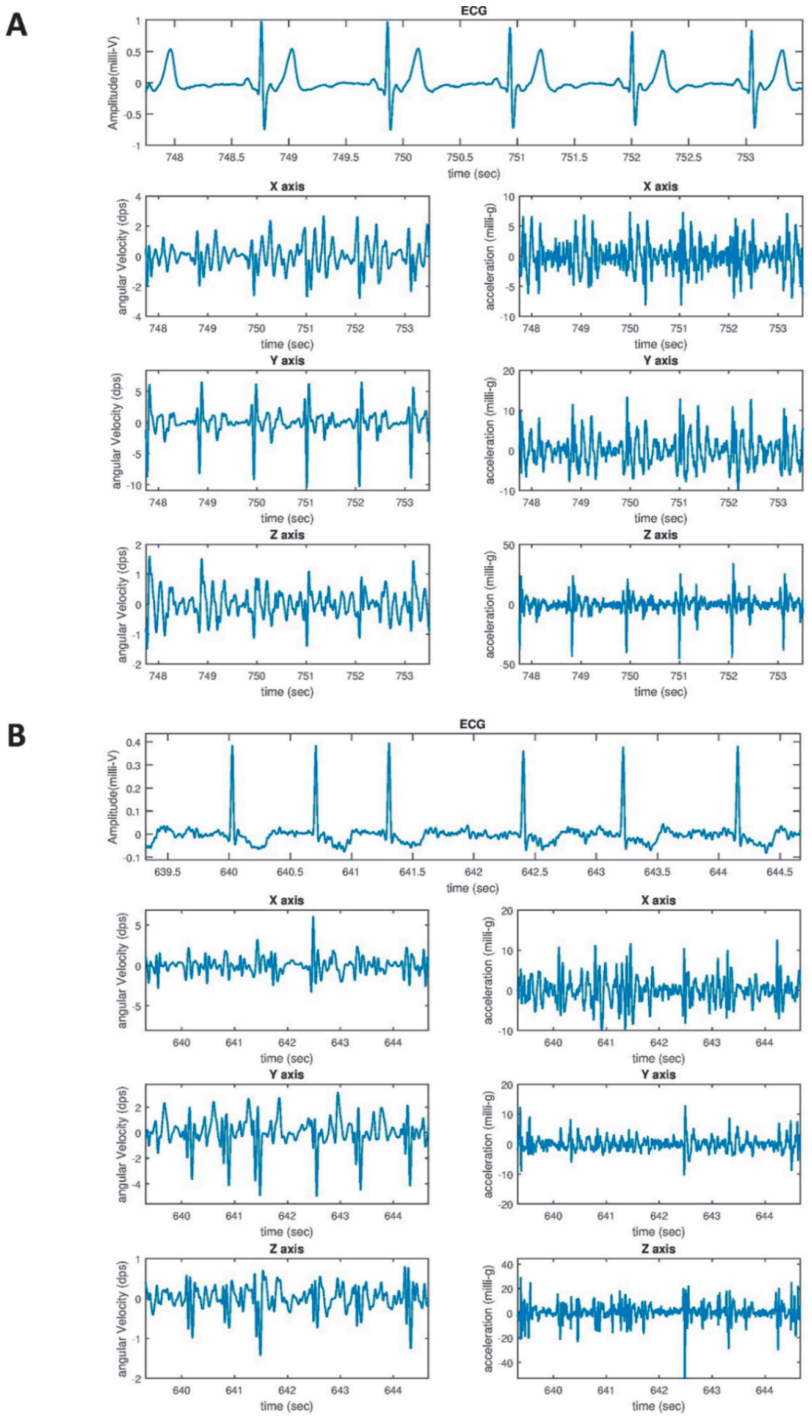

Figure 3. ECG-, accelerometer- and gyroscope signals in sinus rhythm (A) and atrial fibrillation (B). ECG signals are depicted on the top row, while the three gyroscope signal axes are presented in the left panel and the three accelerometer axes in the right panel. Modified from original publication IV.

4.2 Study ethics

The study protocols of all four studies were approved by the Medical Ethics Committee of the Hospital District of Southwest Finland. All patients enrolled in Studies II-IV provided written informed consent for participation, whereas for Study I, informed consent was not required due to the retrospective registry nature of the work. All four studies conform to the Declaration of Helsinki.

4.3 Statistical analyses

In Study I, continuous data are presented as median [interquartile range] and categorical variables as absolute number and percentage. The Chi-square and Fisher's exact tests were used to compare differences between proportions, and the Mann-Whitney U test was used to analyse continuous variables. Based on the results of bivariable comparisons, stepwise binary logistic regression (backward Wald method) analyses were performed to analyse the independent predictors of new AF and 30-day mortality after ischaemic stroke. Two-sided differences were considered significant if the null hypothesis could be rejected at the 0.05 probability level.

In Study II, continuous data are presented as median [interquartile range] and categorical variables as absolute number and percentage. Fisher's exact test was used to compare differences between proportions for unpaired data, while McNemar's test was used for repeated measures. The Mann-Whitney U test was used for the analyses of continuous variables. Based on the results of bivariable comparisons, stepwise binary logistic regression (backward Wald method) analyses were conducted to analyse the independent predictors of correct identification of different rhythms by pulse palpation. Two-sided differences were considered significant if the null hypothesis could be rejected at the 0.05 probability level.

In Study III, continuous data are presented as mean ± standard deviation for normally distributed variables or median [interquartile range] for variables not from the normal distribution and categorical variables as absolute number and percentage. The Chi-square test and Fisher's exact test, as appropriate, were used to compare differences between proportions. For unpaired data, the Mann-Whitney U test or the independent-samples t-test were used in the analyses of continuous variables. For repeated measures, the Friedman test was used to analyse continuous variables and Cochran's Q test to analyse dichotomous variables. After the Friedman tests, the Wilcoxon Signed Rank test was used for post-hoc analyses, and the Bonferroni correction was applied to the post-hoc two-sided levels of

significance. Based on the results of bivariable comparisons, stepwise binary logistic regression (backward Wald method) analyses were conducted to analyse the independent predictors of continuing pulse palpation activity. Differences were considered significant if the null hypothesis could be rejected at the 0.05 probability level. All analyses were conducted according to the intention-to-treat principle, unless otherwise is stated.

In Study IV, continuous data are presented as mean (95% CI) for normally distributed variables or median [interquartile range] for variables not from the normal distribution and categorical variables as absolute number and percentage. The Chi-square test and the Fisher's exact test, as appropriate, were used to compare differences between proportions. For the analyses of continuous variables, the independent-samples t-test was used for variables that were normally distributed and the Mann-Whitney U test for variables that were not from the normal distribution. Cohen's kappa coefficient was calculated to evaluate the level of agreement between rhythm determination by the MCG algorithm and visual interpretation of ECG recordings. Two-sided differences were considered significant if the null hypothesis could be rejected at the 0.05 probability level.

To perform the statistical analyses, IBM SPSS Statistics software (version 22.0, SPSS, Inc., Chicago, Illinois) was used in all four Studies, in addition to which MedCalc Statistical Software (version 17.9, MedCalc Software bvba, Ostend, Belgium) was used in Study IV.

5 RESULTS

5.1 Ischaemic stroke as the first manifestation of atrial fibrillation (I)

AF was diagnosed concurrently with the stroke or TIA in 753 (20.8%) patients (new AF group), whereas 2,870 (79.2%) patients had a prior diagnosis (previous AF group). Among those who suffered an ischaemic stroke, altogether 637 (21.9%) were diagnosed with new AF, while among patients with TIA, new AF was found in 116 (16.4 %) subjects. In the new AF group, AF or atrial flutter were present already on admission in 534 (70.9%) and 21 (2.8%) patients, respectively, and were detected later during the index hospitalisation in 198 (26.3%) patients. Altogether, 633 (84.1%) of the patients with new AF, had a CHA_2DS_2VASc score ≥ 2 prior to the ischaemic event. In comparison, new AF was diagnosed in only 15 of the 781 patients (1.9%) with an intracranial haemorrhage.

The baseline characteristics of the patients are presented in Table 6. In the multivariable logistic regression analysis, the independent predictors of a new AF diagnosis in patients with an AF-associated ischemic event were the absences of histories of coronary artery disease (OR: 1.45; 95% CI: 1.16-1.82; p=0.001), other vascular diseases (OR: 1.75, 95% CI: 1.09-2.79. p=0.020), heart failure (OR: 2.62; 95% CI: 1.94-3.54, p<0.001) and hypertension (OR: 1.22; 95% CI:1.01-1.47; p=0.041), younger age (OR: 1.01; 95% CI: 1.00-1.02; p=0.014) and high heart rate (OR: 1.02, 95% CI: 1.02-1.03; p<0.001). The proportion of new AF diagnoses at the time of an ischaemic stroke according to the patients' age and history of cardiovascular diseases is presented in Figure 3 and according to their CHA_2DS_2VASc score in Figure 4.

In the supplementary analysis, AF was diagnosed during the first month (excluding the first week of the index hospitalisation) after the ischaemic event in 49 patients (incidence of 14.9/week). During a later follow-up of 5 years (excluding the first month after the event) AF was diagnosed in an additional 481 patients (mean incidence rate of 2.0/week). The mean number of first AF diagnoses per week according to temporal distance from the first ischemic event is depicted in Figure 5.

Table 6. Baseline and clinical characteristics of the patients at the time of the ischaemic stroke or TIA.

	Previous AF	**New AF**	**P value**
N	**2870**	**753**	
Age, years	78.7 [12.9]	76.6 [13.6]	<0.001
Female gender	1592 (55.5)	417 (55.4)	0.967
Heart rate	75.0 [28.0]	94.0 [43.0]	<0.001
Hypertension	1886 (65.8)	442 (58.7)	<0.001
Dyslipidemia	990 (34.7)	238 (31.8)	0.141
Diabetes	607 (21.2)	125 (16.6)	0.006
Coronary artery disease	968 (33.8)	151 (20.1)	<0.001
Previous myocardial infarction	415 (14.5)	58 (7.7)	<0.001
Other vascular diseases	202 (7.0)	23 (3.1)	<0.001
Heart failure	635 (22.1)	66 (8.8)	<0.001
CHA_2DS_2VASc score	4.0 [2.0]	3.0 [2.0]	<0.001
Surgery or other procedure <30 days prior to event	179 (6.2)	17 (2.3)	<0.001
Cardioversion (electrical or chemical) <30 days prior to event	93 (3.2)	0 (0.0)	<0.001
Type of AF			<0.001
Paroxysmal	1105 (42.6)	474 (87.0)	
Persistent	30 (1.2)	8 (1.5)	
Chronic	1461 (56.3)	63 (11.6)	

Values are presented as median [interquartile range] or number (%).
Abbreviations: AF, atrial fibrillation; TIA, transient ischaemic attack.
Modified from original publication I.

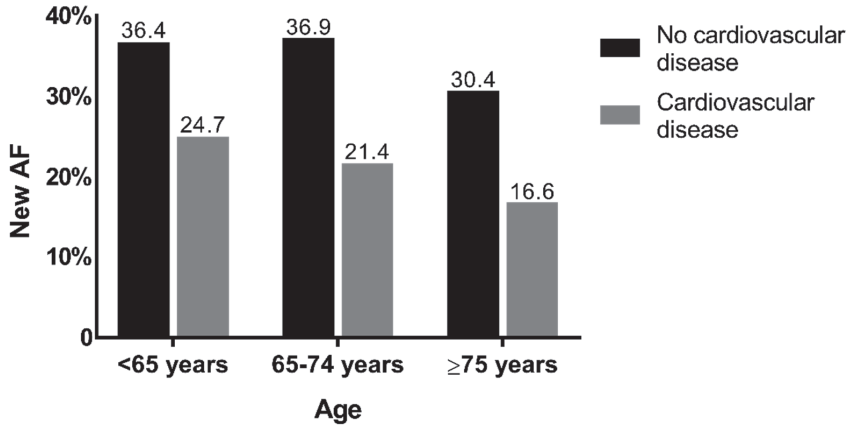

Figure 3. The proportion of new AF diagnoses in patients with ischaemic stroke according to their age and status of cardiovascular diseases. Cardiovascular diseases include coronary artery disease, other vascular diseases, congestive heart failure and hypertension. Cardiovascular disease: N=2,271 (<65 years: N=215; 65-74 years: N=533; ≥75 years: N=1,523). No cardiovascular disease: N=643 (<65 years: N=107; 65-74 years: N=187; ≥75 years: N=349). Modified from original publication I.

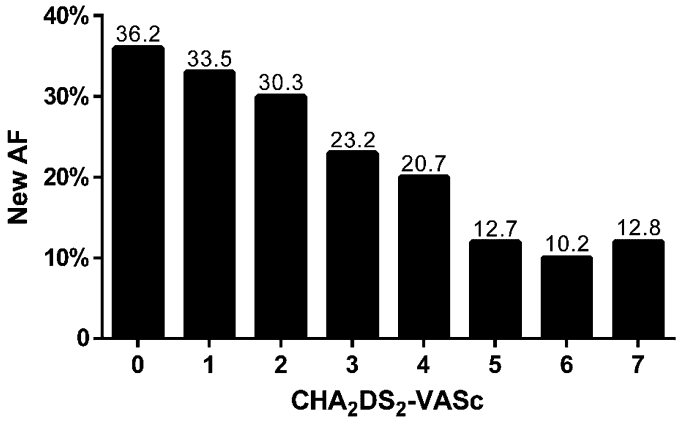

Figure 4. The proportion of new AF diagnoses in patients with ischaemic stroke according to their CHA_2DS_2VASc score. The CHA_2DS_2VASc score is calculated at the time of the ischaemic event and scoring does not include the current event. N=2,914 (score 0: N=105; score 1: N=191; score 2: N=419; score 3: N=667; score 4: N=786; score 5: N=502; score 6: N=205; score 7: N=39). Modified from original publication I.

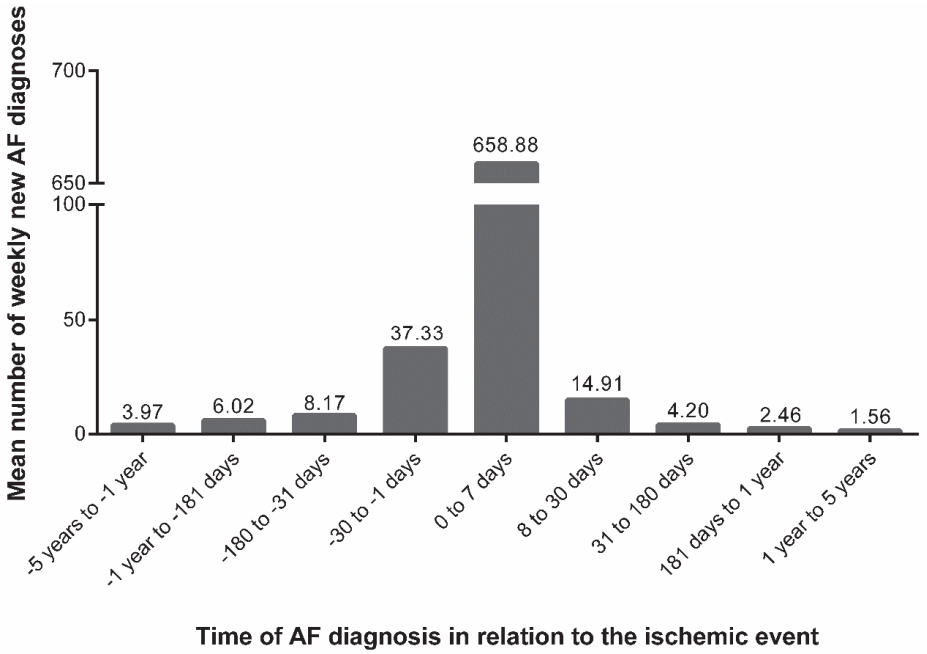

Figure 5. First AF diagnoses according to temporal distance from the first ischaemic event. The mean number of first AF diagnoses per one week is presented according to temporal distance from the first ischaemic event. Ischaemic stroke/TIA has occurred at time point zero. Negative values portray time before the event and positive values time after the event. Modified from original publication I.

5.2 Accuracy of pulse palpation by the elderly in the detection of atrial fibrillation (II)

The baseline characteristics of the elderly subjects are presented in Table 7. Among all 173 elderly subjects, 148 (85.5%) could correctly identify SR, 124 (71.7%) slow AF, 142 (82.1%) fast AF and 110 (63.6%) SR with VESs. Altogether, 25 elderly subjects (14.5%) could not find the pulse of the model during at least one of the presented rhythms, and thus they were excluded from subsequent analyses resulting in 148 subjects in the elderly group. All healthcare personnel found the pulse during each rhythm.

Table 7. Baseline characteristics of the elderly subjects.

N	**173**
Age, years	78.4 [3.9]
Female gender	98 (56.6)
Secondary or higher level of education	76 (43.9)
Functional independence	163 (94.2)
Computer at home	66 (38.2)
At least weekly exercise	138 (79.8)
MMSE score	29 [2]
MMSE score ≥24	170 (98.3)
History of AF or another arrhythmia	8 (4.6)
History of participation in competitive sports	13 (17.5)
Previous experience of pulse palpation	62 (35.8)
Ability to count own heart rate	129 (74.6)

Values are presented as number (percentage) or median [interquartile range]
Abbreviations: AF, atrial fibrillation; MMSE, Mini-Mental State Examination
Modified from original publication II

The elderly and healthcare groups identified SR (97.3% vs. 96.5%, p=0.671) and SR with VESs (74.3% vs. 71.4%, p=0.723) with equal accuracy, whereas the elderly group, in comparison to the healthcare group, detected slow AF (81.8% vs. 56.1%, p<0.001) and fast AF (91.9% vs. 80.7%, p=0.045) significantly better. The ability of the elderly group to correctly identify SR with VESs was independently predicted by previous experience of pulse palpation (OR: 8.05; 95% CI: 2.55-25.42; p<0.001), secondary or higher level of education (OR: 2.78; 95% CI: 1.17-6.60; p=0.020) and one-point increase in MMSE score (OR: 1.34; 95% CI: 1.05-1.70; p=0.019). Their ability to correctly classify SR or fast or slow AF had no independent predictors.

To control for the possibility of guessing, SR was presented twice to the subjects. The second SR rhythm was correctly identified by 95.2% of the elderly group and 96.4% of the subjects in the healthcare group, and no differences were detected in comparison to the first presented SR rhythm in either the elderly (p=0.344) or the healthcare group (p=1.000).

5.3 Feasibility of regular self-palpation of pulse in the screening of atrial fibrillation (III)

Altogether, 139 (67.8%) subjects were classified as having good motivation/capability at the one-month follow-up, while 66 (32.2%) subjects had inadequate motivation or capability. The clinical and demographic characteristics of the subjects are presented in Table 8. The independent predictors of good motivation/capability at one month were high MMSE Score, computer use at home, independence at daily activities and low heart rate as described previously (Virtanen et al. 2014). A total of 39 (19.0%) subjects interrupted the study and 11 (5.4%) subjects died during the three years of follow-up. Drop-out was significantly more common in subjects with inadequate motivation/capability than in those with good motivation/capability (37.9% vs. 10.1%, $p<0.001$).

At the four months' follow-up, 112 (80.6%) subjects with good motivation/capability and 26 (39.4%) with inadequate motivation/capability continued self-assessment of pulse on a daily basis, but at 12 months, only 17 (8.3%) palpated their pulse daily, 103 (50.2%) weekly and 54 (26.3%) less often. At 12 months, no difference was detected in pulse palpation activity between the subjects deemed to have good motivation/capability and those with inadequate motivation/capability at the outset of the follow-up ($p=0.075$). Continuing pulse palpation at least weekly at 12 months was independently predicted by weekly physical exercise (OR: 2.84; 95% CI: 1.41-5.69; $p=0.003$) and high MMSE score (OR: 1.19; 95% CI: 1.02-1.38; $p=0.025$). At 36 months, 12 (5.9%) subjects palpated their pulse daily, 57 (27.8%) weekly and 70 (34.1%) less often. Pulse palpation activity at 36 months did not differ significantly between those with good and those with inadequate motivation/capability at the beginning ($p=0.41$). Continuing pulse palpation at least weekly at 36 months had no independent predictors.

A total of 34 (16.6%) subjects reported irregular pulse findings during the first month, 44 (21.5%) during the first four months, 55 (26.8%) during the first year and 67 (32.7%) during the three years of follow-up. New AF was diagnosed in 10 (4.9%) subjects during the follow-up. In only one subject, pulse irregularity was the factor that led to the diagnosis, while in three subjects the arrhythmia was diagnosed during the baseline or the one-month follow-up visit to the study centre. Altogether, seven subjects with new AF had reported pulse irregularity during the follow-up, which constitutes 70.0% of those with a new AF diagnosis and 10.4% of those with detected pulse irregularity.

Table 8. Clinical and demographic data of the study subjects at enrolment.

	Good motivation and capability	**Inadequate motivation and/or capability**	**P value**
N	**139**	**66**	
Age, yrs	77.8 [3.3]	79.4 [5.8]	0.002
Women	78 (56.1)	38 (57.6)	0.881
BMI	26.1 [4.1]	26.6 [6.8]	0.308
Heart rate	61.6 ± 9.3	66.1 ± 9.2	0.001
Hypertension	75 (54.0)	36 (54.5)	1.000
Diabetes	20 (14.4)	15 (22.7)	0.165
Coronary artery disease	20 (14.4)	16 (24.2)	0.115
Dyslipidaemia	53 (38.1)	21 (31.8)	0.438
Previous stroke or TIA	14 (10.1)	14 (21.2)	0.048
Heart failure	4 (2.9)	2 (3.0)	1.000
Paroxysmal AF or atrial flutter	4 (2.9)	3 (4.5)	0.683
Smoking			0.946
Never smoked	109 (78.4)	53 (80.3)	
Ex-smoker	28 (20.1)	12 (18.2)	
Current smoker	2 (1.4)	1 (1.5)	
Alcohol consumption			0.970
Never	43 (30.9)	21 (31.8)	
Less than weekly	72 (51.8)	33 (50.0)	
Weekly	24 (17.3)	12 (18.2)	
MMSE Test Score	29.0 [2.0]	28.0 [4.0]	<0.001
Functional independence	134 (96.4)	53 (80.3)	<0.001
Weekly physical exercise	112 (80.6)	46 (69.7)	0.109
EQ-5D VAS	80.0 [15.0]	70.0 [30.0]	<0.001
Education level			0.007
Basic	71 (51.1)	47 (71.2)	
Secondary or higher	68 (48.9)	19 (28.8)	
Computer at home	63 (45.3)	10 (15.2)	<0.001

Values are presented as number (%), mean ± standard deviation or median [interquartile range]
Abbreviations: BMI, body mass index; TIA, transient ischaemic attack; MMSE, Mini-Mental State Examination
Modified from original publication III

No change was observed in quality of life as assessed with the EQ-5D-3L summary index (p=0.14), the EQ VAS self-report score (p=0.68) or the anxiety/depression dimension of the EQ-5D-3L system (p=0.95) during the follow-up in those subjects who continued pulse palpation at least weekly at 36 months.

5.4 Accuracy of smartphone mechanocardiography to detect atrial fibrillation (IV)

The clinical characteristics of the subjects according to cardiac rhythm are presented in Table 9. The MCG algorithm correctly classified AF in 143/150 (95.3%) subjects and SR in 144/150 (96.0%) subjects. Altogether, 4 of the 6 cases in SR misclassified as AF had marked sinus arrhythmia, while no potential

reasons for the other misclassifications could be identified. The key measures describing the accuracy of the MCG algorithm in rhythm classification are described in Table 10. Cohen's kappa coefficient of 0.913 (95% CI: 0.866-0.960) was reached, indicating excellent agreement in rhythm classification between the MCG algorithm and visual interpretation of telemetry ECG recordings.

Table 9. The clinical characteristics of the subjects according to cardiac rhythm.

Clinical variable	**SR** (n=150)	**AF** (n=150)	**P value**
Age, y	74.5 (73.0-76.1)	75.0 (73.5-76.6)	0.660
Female sex	66 (44.0)	66 (44.0)	1.000
Chest circumference, cm	103 (101-104)	105 (103-107)	0.043
BMI, kg/m^2	27.5 (26.7-28.2)	29.0 (28.1-29.9)	0.013
CHA_2DS_2VASc	3.7 (3.5-4.0)	4.1 (3.8-4.4)	0.049
History of heart failure	24 (16.0)	73 (48.7)	<0.001
Hypertension	101 (67.3)	103 (68.7)	0.902
Diabetes	27 (18.0)	40 (26.7)	0.096
History of ischaemic stroke	12 (8.0)	10 (12.7)	0.255
Coronary artery disease	90 (60.0)	54 (36.0)	<0.001
History of AMI	68 (45.3)	26 (17.3)	<0.001
Peripheral artery disease	7 (4.7)	13 (8.7)	0.247
Prior CABG	16 (10.7)	23 (15.3)	0.303
Pulmonary disease	24 (16.0)	23 (15.3)	1.000
History of AF	30 (20.0)	150 (100)	<0.001
LVEF*			0.021
<40%	13 (40.6)	19 (59.4)	
40-49%	16 (44.4)	20 (55.6)	
≥50%	75 (63.6)	43 (36.4)	
Heart rate, beats/min	70.8 (68.7-73.0)	88.0 (84.6-91.4)	<0.001
Respiratory rate	16.9 (16.2-17.5)	19.2 (18.2-20.2)	<0.001
Systolic blood pressure, mmHg	145 (141-149)	137 (134-141)	0.003
Diastolic blood pressure, mmHg	70.0 (67.7-72.2)	80.9 (77.7-84.1)	<0.001
LBBB configuration in ECG	15 (10.0)	12 (8.0)	0.687
RBBB configuration in ECG	10 (6.7)	10 (6.7)	0.597
Oedema in Chest X-ray	38 (37.6)	67 (54.5)	0.015
ProBNP (pg/mL)†	1095 [3596]	2965 [5603]	<0.001
Patients with SVES during MCG	47 (31.3)	0 (0.0)	<0.001
Patients with VES during MCG	52 (34.7)	73 (49.0)	0.014

Values are presented as number (%), median [interquartile range] or mean (95% confidence interval)

Abbreviations: AMI, acute myocardial infarction; BMI, body mass index; CABG, coronary artery bypass grafting; CHA_2DS_2VASc, congestive heart failure, hypertension, 75 years of age and older, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, 65 to 74 years of age, female; ECG, electrocardiogram; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; proBNP, pro-brain natriuretic peptide; RBBB, right bundle branch block; SVES, supraventricular extrasystolia; VES, ventricular extrasystolia

*Data missing on 114 (38.0%) subjects

†Data missing on 94 (31.3%) subjects

Table 10. The key accuracy figures of MCG detection of AF.

	Value	95% confidence interval
Sensitivity	95.3%	90.6-98.1%
Specificity	96.0%	91.5-98.5%
Positive predictive value	96.0%	91.6-98.1%
Negative predictive value	95.4%	90.9-97.7%
Positive likelihood ratio	23.8	10.9-55.8
Negative likelihood ratio	0.05	0.02-0.10

A false negative classification result (i.e. SR instead of AF) by the MCG algorithm was not significantly associated with any recorded clinical characteristic. The subjects in whom a false positive result (i.e. AF instead of SR) was obtained were, in comparison to those in whom SR was correctly classified, older (85 [12] vs. 75 [14] years, p=0.008), had a history of heart failure more frequently (4 (66.7%) vs. 20 (13.9%), p=0.006), had pulmonary oedema in chest X-ray more often (5 (100%) vs. 33 (34.4%), p=0.006) and presented with VESs during the recording more often (5 (83.3%) vs. 47 (32.6%), p=0.019). However, a left ventricular ejection fraction <40% was not significantly associated with obtaining a false positive result (p=0.494), and furthermore, only one subject with a false positive result had a left ventricular ejection fraction <40% (data missing on 1 subject). The median VES count was 1 [0-6] (maximum count 7) in those with a false positive classification result, while it was 0 [0-1] (maximum count 16) in those in whom SR was correctly classified (p=0.011). However, the presence of SVESs during the MCG recording was not significantly associated with obtaining a false positive result (p=0.378). The median SVES count was 1 [0-8] (maximum count 18) in those with a false positive classification result, while it was 0 [0-1] (maximum count 49) in those with a true negative result (p=0.265).

6 DISCUSSION

6.1 Ischaemic stroke as the first manifestation of atrial fibrillation (I)

In Study I, it was demonstrated that in more than 20% of AF-associated ischaemic strokes, there is no previous diagnosis of the arrhythmia. Remarkably, the diagnosis of AF was more often concurrent with an ischaemic stroke in younger patients free of cardiovascular disease. Furthermore, over 80% of patients with new AF had a high pre-event risk for stroke, thus justifying OAC therapy.

Two prior studies that reported on patient cohorts compiled in the 1950s-1990s with small event rates have described the proportional co-occurrence of AF and ischaemic stroke. The Framingham investigators observed AF being diagnosed during hospitalisation for stroke in 23% of 115 patients with an AF-associated ischaemic stroke. In another work on 185 patients with an ischaemic stroke, AF was diagnosed at the presentation of or within 3 days from the cerebrovascular event in 22.2% of the patients (Vingerhoets et al. 1996). Considering the substantial development in the understanding and treatment of AF since these patient cohorts were compiled, it is quite surprising to find that their results closely compare with those of the current work. On one hand, it may be that little progress has been made in the early detection of AF during the past years, as it is a matter that has received widespread attention only during the last decade. On the other hand, a more benign explanation may be that effective implementation OAC therapy, by the way of preventing ischaemic strokes in those with recognised AF, elevates the share of new AF, thus negating the effect of earlier detection. However, this alternative interpretation seems quite unlikely considering the only recent emergence of interest in screening for AF and the exceedingly common underuse of OAC drugs irrespective of the CHA_2DS_2VASc score (Engdahl et al. 2013; Palomäki et al. 2016). Since the completion of the current study, its findings have further been corroborated by those of a similar medium-sized work, where AF was diagnosed concurrently with stroke in 18% of 856 patients with an AF-associated stroke (Borowsky et al. 2017).

An essential finding of the current study was that AF diagnosis was concurrent with an ischaemic stroke more commonly in younger patients and those with no history of cardiovascular disease. This is a challenging discovery in patients, who according to risk stratification schemes should be at a comparatively low risk of AF and stroke, and indeed there is no obvious explanation. One possibility is that in older patients with several comorbidities, silent AF may be more easily revealed during frequent healthcare contacts, thus reducing the share of new AF. Another option is that patients with a high risk of thromboembolic stroke have

also many of the risk factors of competing stroke aetiologies, such as carotid atherosclerosis or small artery disease, which could inflate the share of previous AF in relation to new AF in these patients. However, none of the possible explanations transcend speculation, and no definite conclusions on this important question can be drawn based on the current findings.

As mentioned previously, it has been hypothesised that central nervous system injury itself may provoke AF by affecting the functioning of the autonomic nervous system. However, in the current work, new AF was a seldom finding (1.9%) in patients with an intracranial haemorrhage compared to those with an ischaemic cerebrovascular event (20.8%) indicating that previously undiagnosed AF observed after stroke is in most cases the cause and not the consequence of stroke. Thus, it seems reasonable to assume that AF was often present either in an asymptomatic or minimally symptomatic form in the majority of the patients with new AF prior to the ischaemic event. Findings from a prior study, wherein AF either persisted or recurred in over 90% of patients with newly-diagnosed AF at the presentation of stroke, provide further support for this assumption (Lin et al. 1995). The neurogenic hypothesis of AF itself has also been questioned in subsequent research (Rizos et al. 2017), although the matter is still unclear and requires additional research.

Arguably, the figures presented here are an underestimation as they represent only patients in whom AF was diagnosed during hospitalisation for the ischaemic event. To diagnose paroxysmal AF, the duration of acute hospitalisation may often be too short, a problem acknowledged in the most recent ESG guideline on the management of AF, which states that non-invasive ECG monitors or implanted loop recorders should be considered in cryptogenic stroke patients to document silent AF (Kirchhof et al. 2016). As discussed previously, a third of all ischaemic strokes have been classified as cryptogenic in origin in the past (Kolominsky-Rabas et al. 2001), but recent evidence has changed the picture significantly, as it has been demonstrated that AF is uncovered in up to 30% of such patients during prolonged monitoring (Sanna et al. 2014). Thus, it is evident that more than a substantial share of AF-related strokes occur in people with no prior knowledge of the arrhythmia, providing a strong case for research into potential screening programs.

6.2 Self-palpation of pulse in the screening of atrial fibrillation (II-III)

6.2.1 Accuracy of pulse palpation by the elderly to detect atrial fibrillation (II)

Among the elderly subjects in Study II, 97% correctly identified SR, 92% fast AF and 82% slow AF, while 74% correctly distinguished SR with VESs. These figures are markedly better than the 54-77% sensitivities and 86-96% specificities to detect AF reported in previous studies, where the capability of non-medical personnel to assess cardiac rhythm by pulse palpation has been evaluated (Baxter et al. 1998; Kallmünzer et al. 2014; Munschauer et al. 1999). The most reasonable explanation for the difference in relation to these other studies is that the subjects of the current study had a repeated pulse palpation education session and a month of experience of regular pulse palpation before testing, whereas in the other studies, a comparatively minimal education program was utilised. Unsurprisingly, good cognitive capacity and experience of pulse palpation predicted correct identification of SR with VESs, which was the most difficult task included in our protocol.

Importantly, the elderly subjects identified AF with superior accuracy in comparison to the healthcare personnel. A compelling explanation for this discrepancy, again, is that the healthcare group, in contrast to the elderly subjects, had only one short education session and lacked a month's worth of regular pulse palpation experience, while another contributing factor may be that a significant share of the healthcare group consisted of nursing students with limited clinical experience. As discussed previously, prior studies have reported sensitivities of 92-100% and specificities of 71-98% for pulse palpation by nurses in differentiating AF from SR (Kallmünzer et al. 2014; Morgan et al. 2002; Somerville et al. 2000; Sudlow et al. 1998). Indeed, the performance of the healthcare personnel in the current study highlights that even healthcare professionals require practice and tutoring to be able to reliably interpret the findings of pulse palpation.

Evidently, pulse palpation, by healthcare professionals or the elderly, has a quite high sensitivity, but only moderate specificity for detecting AF. Consequently, pulse palpation could feasibly be used to find the subjects to whom more laborious ECG-based screening methods could be targeted. In the most recent ESC guideline on the management of AF, opportunistic pulse palpation by healthcare professionals in patients aged 65 years or older, followed by the recording of an ECG when irregularity is detected is recommended for the screening of AF (Kirchhof et al. 2016). The obvious shortcoming of opportunistic screening, however, is that healthcare visits by individuals are usually rare and far apart and present only a narrow window to catch paroxysmal AF. Thus, this problem could

be overcome by utilising regular self-assessment of pulse in the screening of AF, a prospect potentially feasible in light of the excellent accuracy in distinguishing normal SR demonstrated by the elderly subjects in the current Study.

6.2.2 Feasibility of regular self-palpation of pulse in the screening of atrial fibrillation (III)

Although a simple and short nurse-led education is effective in training pulse palpation to the elderly, it became evident in Study III that maintaining sufficient motivation to continue palpation regularly beyond a few months is very challenging. After 4 months, in all 67% of the LietoAF subjects palpated their pulse daily, but at 12 months, this figure was down to 8% and at 36 months merely 34% continued palpation at least weekly. Four months of diary keeping clearly proved ineffective in encouraging habit formation. It could be speculated that better persistence may have been achieved by certain measures or with a different setting. It is possible that twice-daily palpation was too strenuous and discouraged continuing palpation in the long term or that the subjects would have benefited from further follow-up visits. It may also be that by associating pulse palpation to an often encountered external context could have enhanced the formation and persistence of a regular palpation habit (Gardner et al. 2012).

During the follow-up, pulse irregularity was reported by 1/3 of all subjects. Although 7/10 subjects diagnosed with AF during the follow-up had reported pulse irregularity, which was also an independent predictor of new AF, it was the factor that led to AF diagnosis in only 1 subject. Unfortunately, the events following detected irregularity were not recorded, and it thus is unclear whether the subjects appropriately contacted healthcare professionals. Therefore, it is impossible to determine, whether the disappointing yield of the intervention was related to inadequate responses or some other factor. A significant point of consideration is that after detected pulse irregularity there is inevitably a delay before a confirmatory ECG recording can be performed, which allows time for an AF paroxysm to subside. Moreover, even if the subjects had sought medical attention after passed pulse irregularity, it is highly unlikely that any comprehensive follow-up rhythm screening was conducted rendering it difficult to catch possible cases of paroxysmal AF. It is also easy for both healthcare professionals and non-medical personnel to dismiss pulse irregularity as being caused by frequent VESs. Furthermore, the significance of the intervention might have been unclear to the subjects, as there is evidence that even patients with known AF have limited grasp of the arrhythmia and its serious implications (Lane et al. 2006; McCabe et al. 2008).

Although the current study was to date the first to utilise self-palpation of pulse alone in the screening of AF, self-palpation has been employed as part of a more intricate screening protocol in one previous study (Benito et al. 2015). In the work in question, altogether, 928 subjects with risk factors for AF were divided into intervention and control groups; the subjects in the intervention group were taught to palpate their pulse monthly and seek medical attention as needed in addition to which office visits including ECG recordings were conducted with six-month intervals, while the subjects in the control group received no education and contacted healthcare providers only of their own initiative (Benito et al. 2015). After two years, the intervention had yielded 2.5% new AF diagnoses, while 1.3% of the subjects in the control group were diagnosed with new AF (Benito et al. 2015). Although promising, in light of the findings of the current study and those of previous studies wherein repeated ECG recordings during prolonged periods during extended periods, pulse palpation was probably not a major factor in achieving better yield in the intervention group (De Rujiter et al. 2007; Halcox et al. 2017).

Among the main concerns regarding the current intervention was whether it would negatively impact quality of life or cause increased anxiety. However, no discernible change in these measures was observed during the intervention. Although these were encouraging findings, it must be noted that the subjects' poor adherence to palpation may somewhat weaken their reliability.

Although pulse palpation evidently is a skill that can be learned even at an older age, it is challenging to maintain a continuing habit of monitoring heart beat on a regular basis. Consequently, self-monitoring of pulse regularity is of limited value in the screening of AF unless better persistence of active palpation can be promoted and an efficient and clearly defined follow-up algorithm to detected irregularity is devised. With these preconditions fulfilled, pulse palpation might be an adequate preliminary screening method before more laborious and expensive ECG methods are used. However, it also is apparent that research into alternative screening methods is needed.

6.3 Accuracy of smartphone mechanocardiography to detect atrial fibrillation (IV)

In Study IV, smartphone MCG was externally validated in discriminating AF from SR in a cohort of 300 clinically representative hospitalised subjects. Excellent accuracy was demonstrated, as both sensitivity and specificity exceeded 95%, and a recording duration of 60 seconds was determined to be sufficient for optimal discriminative performance by the modality.

As discussed previously, multiple time point screening seems likely to be superior to single time point and opportunistic screening strategies, therefore establishing a demand for self-operated rhythm screening tools. Smartphones are fast becoming ubiquitous, even among the elderly and in third world countries, where low-cost healthcare solutions are especially crucial (Poushter J. 2016). Thus, their ready availability presents a unique opportunity for cost-effective screening of AF, provided that they can be harnessed to reliably detect the arrhythmia.

As described in the Review of Literature, several standalone and smartphone-integrated single-lead ECG recorders have been introduced, but automated algorithm-detection of AF by the different devices has demonstrated variable and suboptimal accuracy. However, the irrefutable advantage of utilising single-lead ECG recorders as screening tools is that they allow a one-step screening strategy, in which a physician can read the recorded tracings and either confirm or discard the diagnosis of AF made by the algorithm, whereas MCG-screening necessitates further ECG confirmation of screen-positive subjects before AF can be diagnosed. On the other hand, all ECG approaches require additional hardware for recording, rendering the method relatively impractical for large-scale screening in comparison to MCG, which is readily available for a large share of the population as is. Moreover, the frequently insufficient quality of single-lead ECG tracings to reliably detect AF provides some further hindrance for the method's seemingly straightforward applicability to screening (Kearley et al. 2014; Lau et al. 2013).

Similarly to MCG, PPG is method, which allows detection of AF with smartphones, while no additional hardware is needed. Smartphone PPG recordings are obtained by placing a fingertip on the camera and flash of the device and extracting a pulse wave signal from a video recording. In previous studies, smartphone PPG has demonstrated 90-97% sensitivity and 85-98% specificity to detect AF when compared to physician-interpreted concurrent single-lead ECG recordings (Chan et al. 2016; Krivoshei et al. 2016; McManus et al. 2013; McManus et al. 2016). Although the current MCG algorithm and the recent PPG algorithms seem to have comparable accuracy, MCG has several advantages over PPG. Holding a fingertip precisely against the camera lens of a smartphone and maintaining a proper contact for several minutes is difficult and may prove unfeasible for elderly people (Krivoshei et al. 2016). Additionally, motion artefact caused by finger movement during recording has been reported to cause false positive results, which is a major limitation considering the difficulty of maintaining a static finger position (Chan et al. 2016). MCG recordings, however, are not affected by this problem, as the subject is merely required to passively lay supine for the duration of recording, while potential motion artefacts are managed by the algorithm. Furthermore, while the current MCG algorithm retained

optimal performance even when the duration of the analysed section of recording was reduced to 60 seconds, PPG seems to require longer recording durations of up to 5 minutes for best performance (Krivoshei et al. 2016).

The presence of SVESs during recording was statistically not associated with obtaining a false positive result, whereas the presence of VESs was. However, it seems that the association between VESs and false positive classification was possibly merely a coincidence, as most subjects with a false positive classification result had a very low absolute VES count (up to 7 in three minutes) during the recording, which was well exceeded by the VES count of several subjects with a true negative classification result (up to 18 in three minutes). This reasoning is further supported by the fact that the algorithm correctly classified subjects with up to 49 SVESs during the recording to be in SR. Thus, it seems that a low to moderate number of extrasystoles does not impede the reliability of MCG rhythm classification, although the number of falsely classified recordings was very low, and thus no definite conclusions can be drawn.

A false positive classification was also associated with a history of heart failure. Although it is intuitive that systolic heart failure, which is associated with weaker myocardial contractile function, could lead to a poorer MCG signal, it seems questionable, whether heart failure in reality significantly impedes MCG rhythm classification as only one subject with a false positive rhythm classification result had a left ventricular ejection fraction less than 40%. Further important findings were that body composition, respiratory rate or pulse rate did not impede the classification. However, while these findings are definitively encouraging, it again is impossible to conclusively assess the matter as the rate of false classifications was very low. Therefore, while smartphone MCG is accurate in the detection of AF and provides an entirely new screening methodology, there currently is not enough evidence on the effect of possible confounding factors on the modality, leaving a gap to be addressed by future research.

6.4 Limitations

Study I has the inherent limitations of a retrospective registry-study, and the approach prevents as accurate characterisation of subjects achievable in prospective designs. On the other hand, the retrospective design and identification of all consecutive cerebrovascular events from institutional discharge registries and patient records avoids the selection bias of prospective studies and thus better represents ‘’real-world’’ clinical practice. A further limitation is that it could not account for patients with cryptogenic strokes in some of whom AF is the causative factor, and thus the presented proportion of new AF inevitably is an underestimation.

The use of an artificial anatomic model as opposed to an actual human model for pulse palpation in Study II can be seen as a limitation. On the other hand, it ensured standardised and uniform circumstances for all subjects, which undoubtedly is an advantage of the current work. Further limitations are the relatively small size of the healthcare group and its lack of physicians, which prevented conducting comparisons between different healthcare professionals regarding their ability to distinguish AF. The relative lack of clinical experience of a large share of the control group may also be a limitation. It is also likely that the majority of those who could not identify AF or SR with VESs did recognize the pulse irregularity, but this information was not recorded, which is a limitation.

The most notable limitation of Study III was that a control group receiving usual care was not included. This approach was chosen mainly due to the small population base of Lieto, which would probably have led to any control group being "contaminated" by the information received by the intervention group. Another important limitation was that the dropout rate was relatively high, 19%. The interpretation of results was also limited by the unavailability of the information of individual subject responses to detected pulse irregularity. Finally, the subjects' poor adherence to pulse palpation somewhat diminishes the reliability of the assessment of the effect of the intervention on quality of life and experienced anxiety.

The main limitation of Study IV was that its case-control design might somewhat overestimate the accuracy of the algorithm, thus necessitating further evaluation of the modality during large-scale population screening studies. It is also notable that the good performance of the algorithm resulted in too few false classifications to reliably assess the effect of potential confounding factors, especially body composition, extrasystoles and heart failure, on the discriminative performance of the modality. The reliability of the method, when operated by the screened subjects themselves also remains to be determined. A further potential limitation is that only devices from one manufacturer were included in the current study, and their reliability may not be generalizable to devices of other companies.

7 CONCLUSIONS

In more than 20% of patients with AF-associated ischaemic stroke, the arrhythmia is diagnosed concurrently with the cerebrovascular event. (I)

Pulse palpation can be learned also by the elderly, and they discriminate normal SR by pulse palpation with excellent accuracy, thus facilitating the use of self-palpation of pulse in the screening of AF. (II)

It is challenging to form a continuing habit of regular self-palpation of pulse, which limits its value in the screening of AF. Research into alternative screening modalities is warranted. (III)

Smartphone MCG seems to discriminate AF from SR with excellent accuracy. (IV)

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