The Yield of External Loop Recorder Compared to Pulse Palpation and ECG Rhythm to Detect Asymptomatic Atrial Fibrillation in a Community-Based Population

by

Abdulrazaq Sulaiman Albilali

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Abstract

Background and Purpose: Atrial fibrillation (AF) is one of the most common cardiac arrhythmia in the general population, and the most frequent source of cardiac emboli in patients with ischemic stroke. The majority of AF events are underdiagnosed, as they are often asymptomatic or intermittent, and may not be detected by standard 12-lead electrocardiogram (ECG) or Holter monitor. We have evaluated the diagnostic yield of a 21-day External-Loop Recorder (ELR) to detect AF events compared to pulse palpation and baseline ECG rhythm.

Methods: We enrolled 48 participants, 65 years of age or older with no history of atrial fibrillation, stroke or transient ischemic attack from three retirement/assisted facilities and one community clinic in Edmonton. The primary outcome was to detect any AF event (≥ 3 seconds) during the monitoring period.

Results: The median ELR monitoring duration was 19 days (range 1-22 days) resulting in an AF detection rate of 27% (13/48), of which 77% (10/13) were < 30 seconds. Paroxysmal atrial tachycardia (PAT) was detected in 50% (24/48) of the participants. Pulse palpation was irregular in 3 participants and only 15% (2/13) of the participants with positive ELR results had irregular pulse palpation (p = 0.01). ECG baseline rhythm detected non-sinus rhythm in 6 participants, of which only 3 (50%) had AF events detected by the ELR.

Conclusion: There is a significantly high rate of asymptomatic AF (mostly < 30 seconds) detected by the ELR compared to pulse palpation in the community population. The use of external loop recorders to evaluate for AF or PAF may be considered in patients at high risk for stroke.

Preface

Some of the research conducted for this thesis, including the ethics approval, is part of a large ongoing study called PEAACE study conducted by the Stroke Research Program and led by Professor Ashfaq Shuaib at the University of Alberta. This large study has examined the effectiveness of SORIN extended loop recorder in two different population, stroke patients and healthy participants. This thesis was dedicated for the healthy population.

The introduction and literature review in chapter 1 were my original work. Furthermore, the data collection, results, and data analysis in chapter 3 were all my original work, as well as the discussion in chapter 4. The study design in chapter 2 has been modified from PEAACE study design to suit this thesis population.

The research project of this thesis received research ethics approval from the Health Ethics Board at the University of Alberta, No. Pro00030398, June 27, 2013.

Dedication

I would like to dedicate this thesis to my parents, Suad Alhamdan and Sulaiman Albilali; they have been always blessing me with endless love, encouragement, and wisdom. To my wife, Reem Alzaid, for her continuous love and support.

I would also like to express my sincere gratitude to my great supervisor (Dr. Ashfaq Shuaib) for helping me out through my Master program journey, and to my supervising committee (Dr. Thomas Jeerakathil and Dr. Brian Buck) for their valuable efforts and advices. Without you all this work would not be happening.

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List of Abbreviation:

ACC	American College of Cardiology
AEMs	Ambulatory Event Monitors
AF	Atrial Fibrillation
AFI	Atrial Fibrillation Investigators
AFL	Atrial Flutter
AHA	American Heart Association
APB	Atrial Premature Beat
AT	Atrial Tachycardia
BMI	Body Mass Index
b.p.m	Beat per minute
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CBF	Cerebral Blood Flow
CHF	Congestive Heart Failure
CI	Confidence Interval
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CT	Computed Tomography
DM	Diabetes Mellitus
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
ELR	External Loop Recorder
ESC	European Society of Cardiology
g	Gram
GRE	Gradient –Recalled Echo
HITS	High-Intensity signals
HTN	Hypertension
ICH	Intracerebral Hemorrhage
ICM	Implantable Cardiac Monitoring
I_{Kur}	Ultrarapid Delayed Rectifier Current
I_{kr}	Rapidly Delayed Rectifier Current
I_{ks}	Slow Delayed Rectifier Current
IQR	Interquartile Range
INR	International Normalized Ratio
JVP	Jugular Venous Pressure

Kv	Voltage-Gated Potassium Channel
LA	Left Atrium
LAA	Left Atrial Appendage
LOC	Level of Consciousness
MCA	Middle Cerebral Artery
MCOT	Mobile Cardiac Outpatient Telemetry
mm	Millimeter
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
ms	Millisecond
NPV	Negative Predictive Value
NSR	Normal Sinus Rhythm
NSVT	Non-sustained Supraventricular Tachycardia
NVAF	Non-valvular Atrial Fibrillation
OSA	Obstructive Sleep Apnea
PAF	Paroxysmal Atrial Fibrillation
PAT	Paroxysmal Atrial Tachycardia
PE	Pulmonary Embolism
PPV	Positive Predictive Value
PT	Prothrombin time
PSVT	Paroxysmal Supraventricular Tachycardia
PVD	Peripheral Vascular Disease
PVI	Pulmonary Vein Isolation
PV_S	Pulmonary Veins
PV_m	Myocardial Sleeves of Pulmonary Vein
RA	Right Atrial
TCD	Transcranial Doppler
TEE	Transesophageal Echocardiography
TIA	Transient Ischemic Attack
TTE	Transthoracic Echocardiography
S	Second
SAH	Subarachnoid Hemorrhage
SCI	Silent Cerebral Ischemia
SD	Standard Deviation
SFT	SpiderFlash
SPAF	Stroke Prevention in Atrial Fibrillation

SPSS	Statistical Package for the Social Sciences
SSD	Spectacular Shrinking Deficit
SVC	Superior Vena Cava

Chapter 1: Introduction

1.1Stroke

Stroke is the second leading cause of death worldwide after ischemic heart disease and the third most common cause of disability [1]. The incidence of stroke varies among countries and increased exponentially with age [2]. In Canada, stroke affects approximately 50,000 Canadians (with one stroke every 10 minutes) and 14,000 mortalities each year [3]. In addition, the total cost of physical inactivity secondary to stroke was estimated around $1.1 billion in 2009 [4], and around $18.8 million in the United State for the care provided to stroke survivors during year 2008 [5]. Advanced age is considered one of the most significant risk factors for stroke as the incidence increases dramatically in the elderly population. The incidence of stroke doubles each decade after 55 years of age, and half of all strokes occur in people older than 70 - 75 years [6].

Stroke is clinically characterized by the sudden onset of focal neurological deficits, though some patients have a stepwise or gradual progression of symptoms. Classically, the neurological deficits in stroke usually persist and last for 24 hours or longer. Transient Ischemic Attack (TIA), on the other hand, is characterized by the sudden onset of reversible focal neurological deficits that usually last less than 24 hours. Newer definitions for stroke and TIA take into account neuroloimaging in addition to the clinical presentation and place less emphasis on the symptoms duration [7].

Stroke can be divided into two broad categories: ischemic and hemorrhagic strokes. Globally, the incidence of ischemic stroke is about 87%, while the incidence of hemorrhagic stroke is about 13% [8]. Hemorrhagic stroke can be sub-divided into two subtypes: subarachnoid hemorrhage (SAH) and intracerebral hemorrhage (ICH). SAH occurs when there is extravasation of blood from ruptured intracranial arteries into the subarachnoid space, while an intracerebral hemorrhage is caused by rupture of the deep penetrating arteries within the brain tissue (brain parenchyma). In both hemorrhages (SAH and ICH), there is a reduction in blood flow to vital areas within the brain as well as hematoma formation that leads to a rise in intracranial pressure and rapid neurological deterioration.

Ischemic stroke occurs when there is a sudden interruption of adequate blood supply to the brain tissues. Two major mechanisms are responsible for cerebral ischemia in acute stroke: thromboembolism and hemodynamic failure [9]. Thromboembolism generally occurs as a result of a blood clot within the lumen of the major arteries that supply blood to the brain. In the case of thrombosis, the blood clot (thrombus) occurs as a result of in situ thrombosis formation. This usually leads to thrombotic stroke either by reduced blood flow (low flow) distal to the thrombosis site, or by an embolic fragment that breaks off and travels to a more distant vessel (artery-to-artery embolism) [10]. However, in embolism the blood clot or the embolic material is formed in remote sites, mainly within the heart or vasculature systems. This embolic material travels through the arterial system, lodging in a vessel and partially or completely occluding it [11]. Both Thrombosis and Embolism lead to an abrupt fall in regional cerebral blood flow (CBF) and the development of cerebral ischemia [9]. One of the important treatable sites (sources) for clot formation and the development of thromboembolism phenomenon is the heart. This phenomenon is referred to as cardiogenic embolism or cardioembolic stroke.

1.2 Cardioemboilc Stroke

Embolism of cardiac origin accounts for about 20% of all ischemic strokes [12]. However, this estimated frequency (20%) of cardioembolic stroke might vary between epidemiological studies from 14% up to 57% depending on the criteria applied for definition, extent of the evaluation and study design [13, 14]. The incidence of any embolic heart disease in the population could be about 30 cases per 100,000 inhabitants per year, and its prevalence between 5 and 10 cases per 1,000 persons aged 65 years or older [15].

In general, the incidence of cardioembolic stroke increases with age. In the subgroup of patients younger than 65 years of age, cardioembolic stroke occurred in 14.6% of the cases, but in very old patients (age $\geq$ 85 years) cardioembolic stroke reached almost 36% [16]. Interestingly, one of the rapidly growing age groups, at the global level, is the one aged 80 and over and their numbers are

becoming increasingly important. This aging phenomenon is largely attributed to the increase in the fertility rate in addition to the dramatic increase in life expectancy in the 20th century [17]. For instance, life expectancy at birth in the United States in 1900 was 47 years, whereas at the end of the century, it was 77 years [18]. Similar gains have occurred in Canada (with 82.5 years for women and 77.7 years for men) as well as elsewhere around the world [17, 19]. As a result, we would expect a rise in the number of elderly patients with cardioembolic stroke, in addition to the other stroke etiologies, in the future.

Regarding stroke outcome, Cardioembolic infarction is a subtype of ischemic infarction with the highest in-hospital mortality and poor outcome during the acute phase of stroke [16]. The in-hospital mortality rate of cardioembolic infarction was 27.3% as compared with 21.7% for atherothrombotic stroke and 0.8% for lacunar stroke [16, 20, 21]. Furthermore, cardioembolic infarction is associated with a lower rate of absence of functional limitation at discharge from the hospital, which may be related to the greater size of the lesion of cardioembolic stroke [22, 23]. This might explain the high mortality from stroke in elderly people, as cardioembolic stroke is very common in this population, in addition to other comorbidities and their age.

The recurrence of cardioembolic stroke is another major issue. Several studies have shown that recurrences within the first 3 months of first stroke are more common in cardioembolic infarction than in atherothrombotic or lacunar infarcts [16, 24], with estimates between 1% and 22% for the risk of early embolic recurrence in cardioembolic stroke. For example, the Cerebral Embolism Task Force study has estimated around 12% of patients with cardioembolic infarctions would develop a second embolism within the first 2 weeks of the onset of the first stroke symptoms [25]. Another study has shown that 50% (12 out of 24) of the patients with cardioembolic stroke developed a recurrent embolism within the first 7 days of neurological deficit [26]. Furthermore, one Japanese community study found a ten-year cumulative recurrence rate of cardioembolic stroke to be significantly higher than lacunar infarction [24]. This high recurrence rate of cardioembolic stroke comparing to other cerebral infarction types is,

unfortunately, also associated with higher mortality rate for the first and recurrent events of cardioembolic stroke.

Different studies have shown consistent high in-hospital mortality of cardioembolic infarctions compared to the other stroke subtypes during the acute phase of stroke [20, 21, 27]. This mortality rate can be as high as 100% for patients who had an early recurrent cardioembolic stroke within the first 7 days of the initial stroke onset. Having other clinical variables such as older age, congestive heart failure, hemiparesis, and a decreased level of consciousness at the time of the occurrence of the early recurrent cardioembolic stroke have played a significant role in this high in-hospital mortality [16]. Therefore, early investigation and determination of the underlying etiologies and mechanisms that lead to cardioembolic stroke is necessary to initiate the appropriate treatments and to avoid this poor morbidity and mortality of cardioembolic stroke.

1.2.1 Mechanisms of Cardioembolic Stroke

Embolism from the heart to the brain can result from one of three mechanisms: (1) Thrombus formation within a cardiac chamber because of local hemostasis (e.g., atrial fibrillation or left ventricular aneurysm); (2) release of material from an abnormal valvular surface (e.g., infective endocarditis vegetation); (3) abnormal passage of thrombus from the venous to the arterial circulation (paradoxical embolism) [28]. This cardiac thrombus material is commonly composed of platelet, fibrin, platelet-fibrin or calcium as well as neoplastic or microorganisms fragments [29]. A number of cardiac conditions have been proposed as potential sources to one of these mechanisms of cardioembolic stroke. These sources were divided into major and minor sources [29, 30]. Among major sources are atrial fibrillation (AF), mechanical prosthetic valve, recent myocardial infarction, dilated cardiomyopathy, and mitral rheumatic stenosis, infective endocarditis, marantic endocarditis, and atrial myxoma. Whereas the minor sources of cardioembolism are patent foramen ovale, atrial septal aneurysm, atrial or ventricular septal defects, calcific aortic stenosis, and mitral annular calcification [29, 30]. Currently, there is no gold standard for diagnosing cardioembolic stroke. The presence of a potential major cardiac source of

cardioembolism in the absence of significant arterial disease remains the mainstay of clinical diagnosis of cardioembolic stroke [16].

Considerable efforts have been devoted to the identification of these potential cardioembolic sources in stroke patients. Echocardiography, especially transesophageal echocardiography (TEE), has allowed a more accurate examination of the cardiac structures. Both, Transthoracic echocardiography (TTE) and TEE are by far the most commonly used diagnostic techniques to search for cardiac embolic sources, with approximately 25% of all TEEs performed for this indication [29]. Nevertheless, when cardiac and arterial diseases coexist (such as AF and ipsilateral carotid atheroma) or paroxysmal AF (PAF) is present with no structural cardiac abnormality, determining the etiology of the ischemic stroke becomes more difficult. The patient's history, physical examination, and neuroimaging are essential supportive tools in making the diagnosis of cardioembolism [16].

1.2.2 Clinical Features of Cardioembolic Stroke

There are several clinical features that can support the diagnosis of cardioembolic stroke. These include sudden unheralded focal neurological deficits that are worse at onset (<5 min) and decreased level of consciousness (LOC) at onset. The sudden onset clinical feature was found in 47-74% of cardioembolic cases, while the decreased LOC was found in 19-31% [16]. The presence and recognition of spectacular shrinking deficit (SSD) syndrome, which is defined as a major hemispheric ischemic stroke syndrome followed by dramatic improvement and disappearance of most of the deficit, is important for a clinical suspicion of cardioembolic stroke [31, 32]. This dramatic improvement of an initially severe neurological deficit is likely because of the distal migration of the embolus and recanalization of the initially occluded vessel [33]. Although this phenomenon can also be seen in other ischemic stroke etiology like proximal large-artery lesion (carotid occlusion or high grade stenosis), it is still suggestive of embolism from either a cardiac or large-artery source [31]. The presence of Wernicke's aphasia or homonymous hemianopia without hemiparesis or hemisensory disturbances are other common symptoms of cardioembolic stroke. In addition, in the posterior

circulation, cardioembolism can cause Wallenberg's syndrome, cerebellar infarct, or top-of-the basilar syndrome. Most of the embolic events occur during typical activities of daily living but some embolic strokes start during rest or sleep [34]. However, Valsalva-provoking activity (coughing, sneezing, or rising at night to urinate) at the time of stroke onset was found to be a classic presentation of cardioembolism. It can also suggest a paradoxical embolism facilitated by a transient rise in right atrial pressure by the Valsalva maneuver and the co-occurrence of cerebral and systemic emboli [16, 35, 36].

1.2.3 Neuroimaging features of Cardioembolic Stroke

Neuroimaging data provides further supportive evidence of cardiac sources in patients with cardioembolic stroke. The presence of superficial wedge-shaped infarcts in multiple different vascular territories, hemorrhagic infarction, or visualization of thrombi within arteries on computed tomography (CT) or magnetic resonance imaging (MRI) is suggestive of cardioembolic infarct [34]. Additionally, the existence of bihemispheric combined anterior and posterior circulation and bilateral or multilevel posterior infarcts on CT scan are suggestive of cardioembolism [16, 37]. Despite that, it is possible for emboli on occasion to block a single intracranial artery such as the middle cerebral artery (MCA) and cause a lone deep infarct if the superficial territory has good collateral flow.

Due to their large size, cardiac emboli flow to the intracranial vessels in most cases and cause massive, superficial, single large striatocapsular or multiple infarcts in the MCA territory. Therefore, cardioembolic infarctions predominate in the carotid and middle cerebral artery distribution territories [16, 33, 36]. Nevertheless, tiny emboli also exist and may cause small deep or superficial infarcts, too [38, 39]. Hemorrhagic transformation of an ischemic infarction has been considered, for a long time, as one of the characteristics of embolism, particularly when the artery leading to the infarct is patent [28, 37, 39]. The explanation for hemorrhagic transformation in cardioembolism is that the infarct is caused by blockage of a large artery by the thrombus; this blockage then causes local vascular spasm. Release of this local spasm and fragmentation of the thrombus allow the thrombus to migrate distally, exposing ischemic tissues and

damaged vessel walls and capillaries to reperfusion. Typically, hemorrhage occurs into the proximal reperfused regions of brain infarcts caused by this embolic clot [16, 39].

MRI is more sensitive for the detection of acute brain infarcts in comparison to CT, particularly with the use of MR diffusion-weighted and MR gradient-recalled echo (GRE) imaging and it is also superior in detecting hemorrhagic infarction by imaging hemosiderin [39]. Another neuroimaging modality that can detect cerebral embolic signals is a Transcranial Doppler (TCD) [40]. Embolic particles passing under TCD probes produce transient, short-duration, high-intensity signals referred to as (HITS) [39]. A relatively high frequency of embolic signals has been detected with TCD in patients with atrial fibrillation, cardiac surgery, prosthetic valves, and left ventricular assist devices [41-43]. In addition, TCD may guide treatment decisions by monitoring emboli, such as performing TCD pre- and post initiation of anticoagulation to assess whether HITS has ceased [39, 44]. All the above-mentioned supportive tools are helpful to diagnose a cardioembolic mechanism in stroke patients and identify the underlying cardiac sources for this embolic phenomenon. However, up to 30-40% of all stroke cases remain without a definite cause even after extensive work-up and they are classified as “Cryptogenic” stroke.

1.3 Cryptogenic Stroke

Cryptogenic stroke is defined as brain infarction that is not attributable to a definite source of cardioembolism, large artery atherosclerosis, or small artery disease despite extensive vascular, cardiac, and serologic evaluation [45]. Having patients with two or more potential causes of strokes can be also considered as cryptogenic stroke especially when the physician is not able to make a final diagnosis. For example, a patient with a medium-risk cardiac source of embolism who also has another possible cause of stroke identified would be classified as having stroke of undetermined etiology [45]. Approximately 40% of patients with ischemic stroke have no discernible cause found on initial workup and are considered to have had a cryptogenic stroke [46].

There are several reasons that make a stroke undetermined or cryptogenic for several reasons. One of the most important reasons is having a cause of stroke that is transitory or reversible, resulting in undertaking the diagnostic workup at the wrong time [47]. An important example of a transitory or reversible cause is Atrial fibrillation (AF), which may account for about 5% to 20% of cryptogenic strokes and 50% of cardioembolic strokes [47-49]. Other reversible or transitory causes are vasospasm, such as in migraine infarct, or embolic artery occlusion as the embolus can disappear without any residual evidence when detected by CT scan, MRI, or cerebral angiography [47]. Inadequate investigation into known causes of stroke may also lead to labeling patients with cryptogenic or undetermined stroke. This includes patients with cryptogenic stroke in whom specific causes were suspected but not proven (i.e. significant stenosis, ≥ 50%, of non-relevant artery or mild stenosis, 30-50 %, of a relevant artery) [50]. Lastly, some causes of stroke are still unknown and/or may only be hypothesized through epidemiological studies (e.g. patent foramen ovale) [47].

As mentioned above, a significant proportion of strokes (~40%) remain unexplained despite thorough investigation (cryptogenic stroke), and several recent studies revealed that a proportion (≈25.5%) of those with cryptogenic stroke have undiagnosed AF [51].

1.4 Atrial Fibrillation

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and accounts for more physician visits and hospital stays than any other cardiac rhythm disturbance [7, 52]. It accounts for the majority of cardioembolic stroke and is associated with an increased risk of both silent and clinically evident stroke [25, 53]. The prevalence and incidence of AF have been increasing over the last several decades [54, 55]. During the past 20 years, there has been a 66% increase in hospital admissions for AF. This increase is due to a combination of multiple factors including (1) the aging of the population, (2) a rising prevalence of chronic heart disease, and (3) more frequent diagnosis through use of ambulatory monitoring devices [56-58].

1.4.1 Incidence and Prevalence of AF

The prevalence of AF depends upon the population studied, but generally the risk increases with age and underlying heart disease [59-61]. Prevalence is also influenced by the duration, sensitivity, and specificity of the screening techniques. Most of the epidemiological studies that will be mentioned in this section have used data derived primarily from Echocardiogram (ECG) results during an office visit to measure the prevalence of AF rather than using ambulatory monitoring. The prevalence of PAF, which is more likely to be detected with ambulatory monitoring, would be much higher and will be mentioned under Paroxysmal Atrial Fibrillation section.

The prevalence of AF has been estimated to be between 2%-5% in the general population [61, 62]. In United States and European community-based cohort studies, the lifetime risk of AF is 22-26% in men and 22-23% in women by age 80 years [61, 63]. AF risk doubles with each progressive decade of age; ≤1% of individuals 50-59 years are affected, whereas about 10% of those 80-84 years and 11-18% of those ≥85 years have AF [54, 55, 64, 65]. Several community-based cohort studies have estimated the overall incidence of AF is approximately 7-9 per 1000 person-years with a significant increase in the incidence with age for both men and women, however, the incidence of AF, interestingly, was found to decline slightly for those older than 85 years in the same studies [55, 61, 62].

1.4.2 Classification of AF

Several classification systems have been proposed for AF based on different clinical interests. However, some experts believe that some of these classification systems do not fully account for all aspects of AF [58, 66-68]. To be clinically useful, they believe a classification system must be based on a sufficient number of features and carry specific therapeutic implications [58]. The American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) proposed a classification scheme that is formed by consensus and driven by a desire for simplicity and clinical relevance. This classification demonstrates different terminologies with regard to AF types [58, 69, 70]:

1- First detected or diagnosed AF, independent of the duration of AF or the presence or absence of symptoms. First detected AF can be either paroxysmal or persistent AF.
2- Paroxysmal (i.e. self-limiting, or intermittent) AF (PAF) defined as recurrent AF (≥2 episodes) that terminates spontaneously in seven days or less, usually in less than 24 hours.
3- Persistent AF defined as AF that fails to self-terminate within seven days. Episodes often require pharmacological or electrical cardioversion to restore sinus rhythm.
4- Long-standing persistent AF, which refers to AF that has lasted for one year or more.
5- Permanent AF, which is a term used to identify patients with persistent AF where a decision has been made to no longer pursue a rhythm control strategy.

Patients who have had persistent AF can have later episodes of PAF and vise-versa. In patients with PAF, progression to persistent and permanent AF occurs in > 50% after 10 years despite antiarrhythmic treatment; therefore, AF is generally considered a progressive disease [71]. This classification applies to recurrent episodes of AF that last longer than 30 seconds and are unrelated to reversible causes, though they mentioned that AF < 30 seconds may be important in certain clinical situations such as in symptomatic episodes [58]. When the AF is secondary to cardiac surgery, pericarditis, myocardial infarction (MI), hyperthyroidism, pulmonary embolism, or other reversible causes, therapy directed toward the underlying disorder as well as the AF episode usually terminates the arrhythmia without recurrence [58].

The term “lone AF” is less often used than in the past and was not included in the above guideline. It referred to patients with paroxysmal, persistent, or permanent AF without structural heart disease [72, 73]. It used to be applied to patients ≤ 60 years of age and identified individuals at a lower risk of AF complications, including embolization [72]. Affected patients with lone AF are

usually younger than those with structural heart disease and are often male [72, 74]. Patients with lone AF are often symptomatic and exhibit certain triggers usually associated with this type of AF such as sleeping, exercising, eating, and consuming alcohol [75]. Furthermore, the risk of developing lone AF significantly increases if the patient has a family history of lone AF specifically when AF developed at a younger age [76, 77]. In any case, the term "lone AF" decreased in use than before especially after the development of new AF classification including the ones that we mentioned previously.

In addition to understanding this classification and features of the different types of AF, knowing the underlying mechanism of AF is also important to improve our investigation tools and treatment for AF.

1.4.3 Mechanism of AF

1.4.3.1 Atrial Electrophysiology

AF is a form of cardiac arrhythmia in which the normal sinus rhythm (NSR) is replaced by rapid irregular atrial depolarizations, often with an atrial rate of 350 to 600 beats per minute [52]. The atrial myocardium consists of so-called "fast-response" tissues that depend on the rapidly activating sodium for phase 0 of the action potential. It also has specific properties that plays a role in the development to AF, including the following: (1) a short action-potential duration; (2) rapid cellular reactivation due to the short refractory period (in contrast to Purkinjie fibers and ventricular muscle); (3) very rapid electrical conductivity compared to other heart tissues; (4) the refractory period shortens with increasing heart rate. In the aggregate, these electrophysiologic properties permit the development of very complex patterns of conduction and an extremely rapid atrial rate as seen in AF [78-80].

The predominant shape of the atrial action potential is triangular with a gradual repolarization phase. The plateau phase of the atrial action potential is less pronounced than in ventricular myocytes' action potential and this difference is mainly caused by a difference in ion channel current density and the kinetics of repolarizing currents. Some types of ion channels are selectively expressed by atrial myocytes that represent interesting targets for cardioversion of AF [81-83].

Cardiac repolarization is controlled by two types of potassium channels; the rapidly (I_{Kr}) and slowly (I_{Ks}) activating delayed rectifier potassium channels [84]. Atrial myocytes, however, have what it is called an ultrarapid delayed rectifier current (I_{Kur}) that plays a significant role in human atrial repolarization [85]. This I_{Kur} activates ~100 times more quickly than the I_{Kr}. The subunit of this voltage-gated potassium channel (Kv1.5) is expressed (Messenger Ribonucleic Acid [mRNA] and protein expression of Kv1.5) by atrial myocytes, but to a much lower extent in ventricular myocytes [81, 86, 87]. Despite this expression in both atrial and ventricular myocytes, the I_{Kur} current is confined to atrial myocytes and virtually absent in ventricular myocytes in all species [88].

Inside the atria, there is considerable regional variation in action potential morphology, particularly the action potential difference between pulmonary vein and left atrial myocytes [81]. Pulmonary veins' (PVs) myocytes are the anatomical extension of the cardiac muscle (myocardium) from the left atrium LA into the PVs wall. The length of this myocardial extension varies considerably from species to species; however, it is about several centimeters in humans [89]. This area also called the myocardial sleeves of the pulmonary vein (PV_m) where the left atrial tissue surrounds the insertion of the pulmonary veins [90]. PVs myocytes have more depolarized resting membrane potential, lower upstroke velocity, and shorter action potential than the atrial myocytes [81, 91, 92]. Therefore, muscle fibers in the PVs are excitable and play an important role as a trigger for AF, as suggested by several clinical studies [89, 93]. In general, the onset and maintenance of any tachyarrhythmia require both an initiation event and an anatomical substrate. However, in AF the situation is often complex, and available data support a "focal" mechanism concept that involves automaticity or multiple reentrant wavelets for development of AF [58].

1.4.3.2 Automatic focus or trigger Theory

It has been known for decades that a single focus firing rapidly in the atria can be a trigger for fibrillatory conduction throughout the atria [94, 95]. The most common site of this rapid atrial firing focus that can trigger AF is PVs. Other sites include the superior vena cava (SVC), ligament of Marshall, left posterior free

wall, crista terminalis, and coronary sinus have also been found to be potential foci for AF [58, 96, 97]. In addition to the previously mentioned features of PV_s myocytes, these tissues have shorter refractory periods in patients with AF compared to control patients or other parts of the atria in patients with AF [98, 99]. Furthermore, Decremental conduction in PV is more frequent in AF patients than in controls, and AF is more readily induced during pacing in the PV than in the LA [58]. In addition, electrophysiologic studies of the PVs have identified myocardial tissue that can lead to repetitive firing or even the presence of episodic reentrant activation in the veins [81]. Therefore, catheter ablation of AF depends, in large part, on the electrical isolation of the PV_s from the reminder of the atrium.

When rapid local activation happens in the left Atrium LA from PVs, it extends to the right atrium (RA) but in a less organized way. LA has the dominant fibrillation frequency compared to RA because the fibrillation frequency decreased when the activation progressed to the RA [100]. This left-to-right atrial frequency variation in conduction leads to disorganized atrial activation, which might explain the ECG appearance of a chaotic atrial rhythm [58, 101]. Additionally, stretching of the LA can increase the propensity for rapid firing from the PVs as a result of stretch sensitive ion channels, which may explain the association between AF and mitral regurgitation as well as different types of heart failure [102].

AF may persist even after PV isolation and treatment of the triggers due to the existence of abnormal underlying anatomical substrate modification [58]. These factors that might contribute to the persistence and maintenance of AF can be atrial or electrical remodeling. Regarding atrial remodeling, it is well established that the presence of AF results in remodeling of the atrium over time. This include structural changes such as fibrosis that can predispose to the development and maintenance of AF [78]. Thus, the longer a patient has been in continuous AF, the less likely it is to terminate spontaneously, and the harder to restore sinus rhythm. Similarly, electrical remodeling of the atria can happen as a result of the high rate of electrical activation during AF, which can shorten the

atrial effective refractory period and predispose it to the spontaneous recurrence and maintenance of AF [103].

1.4.3.3 Multiple –Wavelet Hypothesis

The multiple-wavelet hypothesis as the mechanism of reentrant AF was demonstrated in several electrophysiological mapping studies in humans and animals [95, 104]. This concept proposed that fractionation of wavefronts propagating through the atria results in self-perpetuating activity [58, 95]. In other words, the arrhythmia of AF is caused by multiple wandering wavelets, which could be due to the heterogeneity of atrial refractoriness and conduction rather than a focal mechanism [81, 95]. The number of these wavelets depends on the refractory period, mass, and conduction velocity in different parts of the atria [58]. This means a large atrial mass with a short refractory period and delayed conduction increases the number of wavelets and increases the chance of developing sustained AF [58]. In contrast, prolongation of refractoriness, enhancement of conduction velocity, and reduction of the available substrate will reduce the number of wavefronts until the arrhythmia ceases [81].

It has been suggested that the multiple wavelet hypothesis would actually not exclude the coexistence of local sources of AF [105]. However, it is technically challenging to do actual experiment to demonstrate multiple wavelets as the mechanism of sustaining AF. This because mapping technique cannot distinguished between fibrillatory conduction remote from a localized source and multiple wavelets [81]. Thus, the direct demonstration of the multiple wavelets hypothesis would essentially require that other mechanisms potentially sustaining AF are ruled out. This could only be achieved by recording all electrical activity in the entire atrium, which is not possible with the techniques currently available. Since it is not possible to identify all local sources of the arrhythmia in AF patients, the multiple wavelets hypothesis will remain an essential but hypothetical model for the perpetuation of AF [81].

1.4.3.4 Other factors contributing to AF

Several other factors were found to be involved in the induction or maintenance of AF. These factors include autonomic nervous system activity, inflammation, atrial

ischemic or dilatation [106], anisotropic conduction [107], and structural changes associated with aging [58].

It is increasingly well recognized that the autonomic nervous system plays an essential role in the development and the maintenance of AF as the increase in sympathetic or parasympathetic tone has been implicated in the genesis of AF [108-111]. Autonomic ganglia containing parasympathetic and sympathetic fibers are present on the epicardial surface of both the RA and LA, clustered on the posterior wall near the ostia of the PV, SVC, and coronary sinus [58, 112]. Epidemiologic studies suggested that exercise-induced AF might be sympathetically driven, whereas parasympathetic nervous system contributed to AF in young patients with no structural heart disease [109, 113, 114]. In animal studies, vagal (parasympathetic) stimulation contributes to the genesis of AF by shortening the atrial and PV refractory periods and potentiates the initiation and maintenance of AF. Furthermore, vagal stimulation can lead to the emergence of focal triggers in the atrium, while vagal denervation of the atria prevents induction of AF [115-117]. In addition to high sympathetic or vagal tone, fluctuation in autonomic tone can be a major determinant of AF, especially in patients with focal trigger originating from PVs [118]. This autonomic fluctuation has been demonstrated as heart rate variability, which can be seen before the onset of AF secondary to autonomic causes [119].

Several systemic diseases have been found to play an important role as precipitating factors for AF. These include hyperthyroidism, acute pulmonary embolus, acute alcohol ingestion, pneumonia, pericarditis, and electrolyte abnormalities [52]. AF also occurs frequently after cardiac surgery, particularly coronary artery bypass grafting and valvular surgery [52, 120].

1.4.4 Pathophysiology of thrombus formation in AF

Generally, three main factors contribute to the formation of any thrombosis. These three factors, called Virchow's triad, are abnormalities in blood flow (stasis), abnormalities in the blood vessel wall (endothelial dysfunction), and interaction with blood constituents (hypercoagulable state) [121].One of the important causes of thrombus formation in AF is the reduction in LA and LA appendage (LAA)

flow velocity during AF. This can be secondary to dilated LA in addition to the loss of organized mechanical contraction during AF, which can lead to blood stasis (hemostasis) and thrombus formation [122, 123]. Therefore, thrombotic material associated with AF is found most frequently in the LAA and not easily detected by TTE [58, 124]. TEE, on the other hand, is a more sensitive and specific tool to assess LAA function and to detect thrombus formation in patients with AF [124, 125]. LAA/LA hemostasis can be demonstrated by the presence of spontaneous echo contrast or "smoke" on TEE. This increase in echogenicity is thought to represent aggregation of red cells mediated by fibrinogen and, unfortunately, is not resolved by anticoagulation [126, 127].

Another cause for thrombus formation in AF is LAA stunning after cardioversion [128]. This cardioversion to sinus rhythm can be electrical, pharmacological, or spontaneous and is responsible for an increased risk of thromboembolism, particularly if patients are not anticoagulated before, during, and after cardioversion [128]. Thrombus formation in atrial stunning might be caused by the de novo thrombus formation induced by impaired LA systolic function "stunning" as well as the dislodgment of pre-existing thrombi [129]. This may explain why a thromboembolic event occurs during the first 3 days (80%) and almost all occur within 10 days after cardioversion [130]. Full recovery of atrial function after atrial stunning may occur within 24 hours to a few days, but sometimes can take longer (3 to 4 weeks) depending on the duration of AF (longer time to recovery with longer AF duration) [131].

Although endothelial damage/dysfunction has been difficult to establish as distinctly contributing to thrombus formation in AF, a number of studies have indicated that it may, along with stasis, contribute to the development of a hypercoagulable state and thrombus formation [58, 132]. Elevated plasma and endocardial levels of von Willebrand factor, P-selectin, thrombin-antithrombin complex, and D-dimer were found in some AF patients [132-134]. Furthermore, AF has been associated with biochemical markers of coagulation and platelet activation that reflect a systemic hypercoagulable state [58, 134-136]. The level of some these markers of coagulation falls to normal during anticoagulation therapy,

and some normalize after the conversion to sinus rhythm [136, 137]. Therefore, the early detection of AF by knowing the signs and symptoms and understanding the ECG pattern of AF are very important for the early initiation of anticoagulation treatment and the prevention of thrombus formation.

1.4.5 AF Signs and Symptoms

Since up to 90% of AF episodes may not cause symptoms, many patients complain of a wide range of AF symptoms [138]. Taking history from symptomatic patients should focus on obtaining detailed information about these symptoms, including the time of onset, frequency and duration, severity, and qualitative characteristics of the AF symptoms. Typical AF symptoms include irregular palpitation, shortness of breath, light headedness, and poor exercise tolerance [52]. Other symptoms include lack of energy, general ill health, and varied nonspecific symptoms including irritability, poor concentration, and sleep disturbances [52, 139].

While some symptoms of AF may be connected to the atrial arrhythmia, others can be secondary to a rapid ventricular response [52]. The loss of normal atrial systolic function can affect the cardiac performance of some AF patients, as 30-40% of left ventricular end-diastolic volume may be attributable to left atrial contraction, especially in the elderly. Therefore, the loss of the normal atrial contraction can affect the cardiac output, which can lead to reduce exercise tolerance in elderly patients [52, 140].

A complete examination of the cardiovascular system should be conducted in all individuals with suspected AF. This examination may reveal different signs that together can suggest the presence of AF. Typical physical signs include irregular radial pulse, irregular jugular venous pulsations (JVP), or variation in the intensity of the first heart sound or the absence of a fourth heart sound heard previously during sinus rhythm. In addition, a cardiovascular exam may also reveal associated valvular heart disease, myocardial abnormalities, or heart failure [58]. Nevertheless, signs and symptoms of AF must always be accompanied or confirmed with a documentation of an ECG study showing AF pattern in order to make the diagnosis of AF.

1.4.6 ECG pattern of AF

The electrocardiogram of AF usually displays the following features: the absence of discrete P-waves; the presence of fibrillatory or f-waves at a rate that is generally between 350 and 600 beats/minute; irregular intervals between QRS complexes; and narrow QRS complexes unless the AV conduction through the His Purkinje system is abnormal [52, 141]. The diagnosis of AF requires ECG documentation by at least a single-lead recording during the arrhythmia, Holter monitoring, or transtelephonic or telemetric recordings [58]. In patients with implantable pacemaker or defibrillator, the diagnostic and memory functions may allow accurate and automatic detection of AF [142].

Although the above ECG findings usually allow the diagnosis of AF to be made easily, errors in the diagnosis of AF are not uncommon, especially with computerized ECG interpretation [143]. AF sometimes goes unrecognized in patients who are continuously or intermittently paced, as their ECGs have no apparent P-wave. Those patients should be closely examined for the presence of AF and their ECG not misinterpreted [144]. Furthermore, AF with rapid ventricular rates may be misdiagnosed as paroxysmal supraventricular tachycardia (PSVT). In such cases, patients are commonly treated with adenosine, which will not convert the hear rhythm of patients with AF to sinus rhythm [145].

Prolonged or frequent monitoring may be necessary to reveal episodes of paroxysmal or asymptomatic AF. This monitoring can be done by using the 24-48 hours Holter monitor or the new generation of heart monitors like the mobile cardiac outpatient telemetry (MCOT), external loop recorders (ELR), or even minimally invasive devices such as the insertable cardiac monitor (ICM). These different types of monitoring will be discussed in more details later under the PAF section.

1.4.7 AF and the risk of developing stroke

The most common and serious complication of AF is thromboembolism, and the most clinically evident embolic event in AF is ischemic stroke [63]. AF is considered an independent risk factor for stroke, as it increases the risk of ischemic stroke by 4 to 5 times compared to the general population [146, 147]. In

addition, the risk of stroke may further increase in AF patients with the presence of additional risk factors on top of AF. Valvular heart disease like mitral stenosis or prosthetic heart valves is by far the highest identified additional risk factor for ischemic stroke in AF patient. It increases the incidence of stroke in AF patient approximately 17 times that of the general population [52, 148].

Other independent risk factors for stroke in nonvalvular or nonrheumatic AF (NVAF) patients have been identified based on the analysis of pooled data from five randomized controlled trials, in addition to other trials in an attempt to develop a strong risk-stratification scheme [149-151]. These risk factors include age greater than 65 years (women greater than 75 in SPAF III study), history of stroke or TIA, diabetes mellitus, history of systemic hypertension, or impaired LV systolic function [149, 150]. The $CHADS_2$ score, which was derived from the Atrial Fibrillation Investigators (AFI) and Stroke Prevention in Atrial Fibrillation (SPAF) models and has been validated in a large community-based, clinical practice cohort, is the most widely used clinical model for assessment of stroke risk for patients with nonvalvular AF [152, 153]. The $CHADS_2$ score has five independent risk factors (the same as the ones mentioned above) and each risk scores one point, except history of stroke or TIA which score two points (Table 1) [153].

Table 1. $CHADS_2$ score [153].

Clinical Parameter	Score
Congestive Heart Failure	1
Hypertension	1
Age ≥ 75 years	1
DM	1
Prior Stroke, TIA, systemic embolic events	2
Total	

Other risk models, other than the $CHADS_2$ score, have been developed to predict the thromboembolic risk and the likelihood of benefit from treating patients with NVAF [154]. CHA_2DS_2-VAS_c is one of these other risk models,

which has been used widely along with the $CHADS_2$ score (Table 2). It has been developed to improve risk stratification, particularly at the lower end of the risk stratum of $CHADS_2$ [155]. This was made by the inclusion of age 65 to 74 years and age ≥75 as individual risk factors, in addition to female sex and the presence of vascular disease. The predictive ability of $CHADS_2$ and CHA_2DS_2-VAS_c scores have been compared in multiple cohort studies and found to be comparable but modestly able to predict stroke [155-157]. The Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) stroke risk score, on the other hand, includes four risk categories for age (< 65, 65 to 74, 75 to 84, ≥ 85), proteinuria, and estimated glomerular filtration rate (eGFR) < 45 ml/min per 1.73 m^2 (or end stage renal disease) in addition to the other risk factors mention in $CHADS_2$ [158]. Interestingly, the ATRIA risk score was found in a recent study to performed better than either $CHADS_2$ or CHA_2DS_2-VAS_c models, particularly in predicting sever stroke events [158].

Table 2. CHA_2DS_2-VAS_c score [155].

Risk Factor	Score
Congestive Heart Failure	1
Hypertension	1
Age ≥ 75 years	2
DM	1
Prior Stroke, TIA, systemic embolic events	2
Vascular Disease	1
Age 65 to 74	1
Female	1
Total	

In general, we can observe that these models agreed on or shared at least three risk factors as important predictors of stroke: older age, hypertension, and prior embolic event. Therefore, understanding these risk models is very important in order to predict the chance of developing stroke in AF patient and to initiate the necessary treatment to prevent embolic events.

1.4.8 Antithrombotic treatment in AF

Several trials have demonstrated that cardioembolic stroke events occurred with equal frequency regardless of whether a rhythm-control or rate-control strategy was being used. Furthermore, most embolic events in these trials occurred after stopping anticoagulation treatment (Warfarin) [159-161]. For that reason, our focus in this section will be more on the antithrombotic treatment for AF. Currently, there are two different antithrombotic treatments, anticoagulation (mostly used is vitamin K antagonist) and antiplatelet (mainly Aspirin).

The efficacy of vitamin K antagonists such as Warfarin for primary and secondary prevention of thromboembolism in patients with NVAF was established more than a decade ago [162-164]. However, this efficacy coexists with the potential of major bleeding such as ICH, especially in elderly patients and high-intensity oral anticoagulation with an international normalized ratio (INR) of 3.5-4.5 [165, 166]. Therefore, targeting the optimal intensity of Warfarin requires the balance between prevention of ischemic stroke and avoidance of hemorrhagic complication [58]. This usually can be achieved by adjusting the Warfarin dose, in addition to monitoring the prothrombin time (PT), or more specifically the INR blood level, in order to reach the optimal intensity of Warfarin. Maximum protection against ischemic stroke in AF is probably achieved at an INR range of 2.0 to 2.5 [167, 168]. Whereas, the absolute increase in ICH during anticoagulation remains relatively small if the INR is 3.5 or less in elderly patients who have AF [166, 167, 169].

Antiplatelet agents such as Aspirin offer only modest protection against stroke compared to anticoagulation for patients with AF [58, 163, 170, 171]. Meta- analysis of 8 randomized trials showed a stroke reduction of 22% for antiplatelet agents compared to 6 randomized trials that showed a stroke risk reduction of 64% for adjusted dose warfarin [167]. Aspirin seems to have a greater effect on nondisabling, noncardioembolic strokes than on cardioembolic infarction but is less protective for disabling cardioembolic stroke [167, 172]. Most guidelines recommend aspirin therapy only in patients with NVAF who are considered at low risk of stroke, or in whom anticoagulation is contraindicated

[58, 173]. However, one recent guideline includes a role for clopidogrel use in combination with aspirin (dual-antiplatelet), which might be considered for stroke prevention in patients for whom oral anticoagulation therapy may be unsuitable [174, 175].

1.4.9 Risk Stratification Models and AF Treatment

Despite the limitations of all risk stratification models, the initiation and guidance of anticoagulation/antiplatelet treatment in NVAF patients should be based on these models to prevent embolization [157]. These models were constructed to recommend antithrombotic treatment when the benefits of treatment outweigh the side effects. Historically, the $CHADS_2$ risk score has been the most popular risk model due its simplicity and validation in different patient populations [152, 153]. Other experts recommend the use of the more detailed CHA_2DS_2-VAS_c model among patients with $CHADS_2$ scores of 0 or 1 to improve the accuracy of their risk stratification [176].

$CHADS_2$ scores of ≥ 2 are considered a high-risk situation for embolism in AF patients (at least 4% per year), and anticoagulation treatment is the recommended treatment in this case. This is because the use of anticoagulation in patients with CHADS2 scores of ≥ 2 shows a significant reduction in the risk of clinical stroke compared to placebo and, in addition, the risk of bleeding is less than the absolute reductions in stroke [167, 177]. Aspirin, on the other hand, did not show superiority compared to placebo in high-risk situations, and warfarin was found to be approximately three times as effective as aspirin [163, 178].

When an AF patient has an intermediate-risk of stroke or a $CHADS_2$ of 1 ($\leq$ 2% per year), either oral anticoagulation or aspirin can be used to prevent stroke. The choice between anticoagulation and antiplatelet in this case depend on many factors, including the clinician's assessment of risk, the ability to provide high quality monitoring of oral anticoagulation, regimen compliance, patient's risk of bleeding on anticoagulation, and patient preference [179].

A $CHADS_2$ score of 0 carries a low risk of stroke (0.5 to 1.7% per year) and the benefit of treatment with anticoagulation or antiplatelet has not been conclusively shown in this category; additionally, the risk of bleeding outweighs

the benefit [152, 153]. However, the European Society of Cardiology guidelines strongly recommend the use of CHA_2DS_2-VAS_c rather than $CHADS_2$ scores, especially when the risk of stroke in an AF patient is low ($CHADS_2 = 0$), and the patient has additional risks like age 65 to 74 years, female gender, or coronary artery disease [180]. In this case, they weakly recommend oral anticoagulation treatment but not aspirin, whereas other guidelines recommend making the decision of treatment with anticoagulation based on the factors that we have mentioned above for a $CHADS_2$ of 1 [174].

The combination of anticoagulation and antiplatelet treatments (warfarin plus aspirin) in patients with nonvalvular AF did not reduce the rate of stroke or systemic embolism. In fact, this combination was associated with an incremental rate of major bleeding [181]. As mentioned before, dual antiplatelet with aspirin and clopidogrel in patients for whom vitamin K-antagonist therapy was unsuitable showed reduction in the risk of major vascular events, especially stroke; however, it also showed an increase in the risk of major hemorrhage [182].

In recent years, several new oral anticoagulants have been introduced for prevention of stroke and systemic embolism in NVAF. These new agents, including dabigatran, rivaroxaban, apixaban, and edoxaban, have been shown in large clinical trials to be equal or, in the case 150 mg of dabigatran twice daily, superior to dose-adjusted warfarin for prevention of stroke and systemic embolism [183-186]. In addition, the rates of ICH were significantly lower with these new anticoagulants compared to warfarin, but there was increased gastrointestinal bleeding [187]. However, there is currently no conclusive evidence to determine which new anticoagulants are more effective and safe for long-term treatment as head-to-head comparison of the different new anticoagulants have not yet been performed [188].

1.5 Paroxysmal Atrial Fibrillation (PAF)

As we discussed previously, PAF is defined as recurrent ($2 \geq$ episodes) AF that terminates spontaneously in less than seven days, usually in less than 24 hours [58, 69]. In addition, PAF episodes should not be related to reversible causes mentioned above [58]. The frequency of PAF is uncertain, because the majority

(up to 90%) of PAF episodes are asymptomatic, including some that last ≥ 48 hours [138, 189]. Furthermore, in patients with symptomatic PAF, there is a 12:1 ratio of asymptomatic versus symptomatic episodes [138]. Therefore, there is a strong likelihood that the incidence and prevalence of AF, including PAF, may be substantially underestimated secondary to the potential under detection of PAF [190].

Several studies have investigated the prevalence of subclinical PAF, However, this estimation is usually influenced by the duration, sensitivity, and specificity of the screening techniques and does not reflect a consistent number [191-193]. For example, in ASSERT study, dual chamber pacemaker or implantable cardioverter defibrillation were used to detect PAF event, and after 2.5 years of monitoring, PAF was detected in 35% of participants [191]. On the other hand, in Tayal et al.'s study, MCOT was used for a mean of 21 days to detect PAF events. At the end of the study, 23% of participants were found to be positive for PAF [192]. Another older study used event-loop recording device for 7 days and found only 11% of that study's participants have PAF [193].

The detection of PAF is as important as any other type of AF because frequent PAF may progress to a more chronic (persistent or permanent) form of AF and higher risk of embolic events [194]. In addition, some experts believe that patients with PAF carry the same risk of systemic embolism and stroke as those with persistent AF [195]. Silent cerebral ischemia (SCI), which is a condition occurring in a patient who has specific lesions on cerebral magnetic resonance imaging or other imaging in the absence of clinical complaints or findings, was found to be associated with PAF as well as persistent AF [196, 197]. In addition, cognitive performance was found to be significantly worse in patients with PAF than in controls [196]. Cryptogenic stroke accounts for up to 40% of ischemic stroke and has been a big dilemma for physicians and patients for a long time with respect to identifying the underlying etiology; recent studies started to show a high rate of undiagnosed PAF in cryptogenic stroke patients by using the new prolonged heart monitoring devices [192, 198]. This finding should stimulate the expertise to develop new investigational tools that can help us to detect more

asymptomatic PAF, in order to initiate the antithrombotic therapy at an early stage and reduce the incidence of embolic stroke.

The mechanism of PAF is somewhat similar to the other types of AF. In addition to the previously discussed factors such as autonomic dysfunction, the precipitating factors of PAF, particularly in patients without structural heart disease, are thought to be secondary to the presence of atrial premature beats (APB), [199, 200]. Several studies have shown that the majority of PAF episodes are usually triggered by APBs, and treating the source of the foci of APB may eliminate the triggering of PAF [200, 201]. Additionally, frequent APBs in patients without AF or structural heart disease were associated with greater risk of new occurrence of AF, and adverse cardiovascular events [202]. APBs most often originate near the ostia of pulmonary veins and less commonly from the right or left atria, the vein of Marshall, and the SVC [200, 203, 204]. Therefore, treating these APBs foci by catheter ablation has been used in many cases to treat recurrent symptomatic PAF [205].

The approach to treat PAF is similar to that for the general population of patients with other types of AF [58]. This approach includes two principal goals: 1) symptom control, 2) and the prevention of embolic event. For symptom control, rate- and rhythm-control medications improve symptoms, but neither has been conclusively shown to improve survival in PAF/AF patients compared to antithrombotic treatment [161, 206]. Patients with frequent symptomatic PAF may require pharmacological or non-pharmacological treatment to prevent recurrence [58, 174]. Catheter-based pulmonary vein isolation (PVI) is viewed by some experts as being more effective than antiarrhythmic therapy [207]. However, recent studies showed no significant difference between catheter-based PVI as a first-line of treatment of PAF and antiarrhythmic drug [208, 209]. Current guidelines for the treatment of symptomatic PAF recommend catheter-based PVI as second-line therapy when antiarrhythmic drugs fail [69]. Catheter-based PVI most commonly performed with radiofrequency as well as other alternative energy sources like cryoballoon and balloon-based laser ablation have also been used [210, 211]. Similarly, rate control agents such as beta blocker,

calcium channel blocker, or digoxin are not generally required for PAF patients, unless the patients are suffering from a highly symptomatic episode or during an acute episode [58, 69].

Antithrombotic therapy, on the other hand, has also been shown to significantly reduce the risk of all stroke and other embolic events in NVAF [167, 177, 212]. This risk reduction usually includes PAF, because as a group, patients with PAF have a risk of embolic events that appears to be similar to that in patients with persistent AF, although the data are not conclusive [173, 195, 212]. Thus, the approach to antithrombotic therapy in patients with PAF is felt by some experts to be similar to that in patients with persistent or permanent AF [58, 174]. This means that the use of antithrombotic therapy in patients with PAF should be guided by the risk stratification approach, such as calculating the risk of stroke by using $CHADS_2$ or CHA_2DS_2-VAS_c scores for PAF patients to determine which patients require antithrombotic treatment.

In contrast, it is still not clear whether infrequent asymptomatic brief ($\leq$ 30 seconds) episodes of PAF are at the same level of risk of embolism as those with longer and more frequent episodes [198, 213]. In other words, there are no solid data to establish a threshold of duration or frequency of AF for the initiation of antithrombotic therapy. This issue emerged and has been discussed more in recent studies after the development and wide use of new extended ambulatory ECG devices or ambulatory event monitors (AEMs) that started to pick up more brief PAF episodes than what the Holter monitor detected in the past [214]. In addition, this new technology started to reveal many occult AF as the underlying etiology in patients suffering from cryptogenic stroke [198].

1.6 Ambulatory event monitors (AEMs)

AEMs are ambulatory ECG recordings able to continuously examine the patient's heart rhythm over an extended period of time and during a normal period of activity. In contrast to the standard ECG, which provides the myocardial electrical activity from 12 leads, AEMs usually provide a view of two or three leads over an extended duration that varies between different AEMs. In addition, AEMs provide

longer monitoring duration than the Holter monitor (24-48 hours), which can last up to 30 days in some monitors. This extended duration has increased the sensitivity to detect abnormal rhythm like AF.

AEMs has evolved rapidly over the last decade to different functionally monitors that serve different clinical situations [215]. These different monitors can be classified as follows [216]:

1- External non-continuous devices with memory.

   These devices are carried by the patients and applied to the precordium area when the symptoms are occurring [217, 218]. These devices have obvious limitation in recording asymptomatic episodes; because the patient likely will miss them.

2- External continuous memory loop with patient-triggered capability.

   These devices are able to continuously store a single channel of ECG data in refreshed memory. When the patient activated the devices, the ECG is recorded from the memory loop preceding 30-90 seconds and for the next minute or so (depending on the programmed algorithm). These devices have to be worn continuously for weeks (2-4 weeks). The limitation of this type of device is again missing asymptomatic episode because these devices require patient's activation to record the arrhythmia. In addition, these devices have monitoring capacity that last less than one month.

3- External continuous memory loop with auto-triggered capability.

   These devices have the ability to initiate recording continuous ECG from loop memory based on preset parameters of the ECG rhythm or heart rate. For example, R-R interval changes, a heart rate greater than 165 beat per minute, bradycardia, or asystole for greater than 3 minutes. Some devices have both auto-triggered or patient-triggered activation event recording. These devices have the advantage of recording asymptomatic and brief episodes of arrhythmia; however, its duration is still limited to a less than one-month period of monitoring.

4- External real-time continuous monitoring devices.

These devices are also called MCOT. Their function is the same as the continuous memory loop, auto-triggered devices; however, it provides continuous real-time outpatient ECG monitoring by automatically recording and transmitting the arrhythmic event data from an ambulatory patient transtelephonically to an attended monitoring station [219, 220]. These transmitted data are interpreted immediately by a certified monitoring specialist and then send to the referring physician [219]. These devices are considered the most advanced type of the external loop recorders developed by different companies. The duration of the monitoring varies between these different companies with a maximum duration of 30 days.

5- Implantable continuous memory loop with auto-triggered capability.

These are invasive devices that are inserted just under the patient's skin in the chest area. These devices are inserted during an outpatient surgical procedure. Despite the need for an invasive procedure, these devices have all the features mentioned above, in addition, it could be used for more than one year that covers a longer period of monitoring than the non-implantable devices.

Nevertheless, the current standard of care for the diagnosis of AF is still a 12-lead ECG or 24 hour Holter monitor [213, 221]. With these technological advances in the AEM, many institutes started to utilize this new technology to detect AF, particularly in patients with cryptogenic stroke who have gone through thorough investigations and yet no clear underlying etiologies of stroke have been found [51, 192]. Consequently, several studies have been published recently using these new AEMs in patients with cryptogenic stroke and, interestingly, concluded that many of those stroke patients were found to have AF/PAF detected by different types of AEMs [49, 51, 191, 192, 198]. This again confirms the

previously mentioned conclusion that the estimated incidence and prevalence of AF (including PAF) is likely underestimated [190].

Most of the epidemiological studies have used ECG during an office visit rather than ambulatory monitoring to estimate the prevalence of AF in these studies' populations [59, 61, 190]. These methods most likely led to missing many AF episodes, particularly the one with asymptomatic and brief duration and consequently underestimated the true prevalence and incidence of AF in these communities. There is no clear optimum duration so far for monitoring in order to get the best estimate of the prevalence and incidence of AF in the community. Some experts believe that 2 weeks of monitoring is the most cost-effective period of monitoring as the diagnostic yield of AEM usually decreases dramatically after 2 weeks of monitoring [222]. However, this opinion was made based on the use of continuous loop event, patient-triggered recorders only. In addition, several recent studies illustrated many first PAF are detected after 2 weeks of monitoring [192, 223].

It would be interesting to know the frequency of asymptomatic AF in the community by using auto-triggered loop recorder. Any population or community with asymptomatic AF is at risk of stroke and screening this population with new non-invasive prolonged monitors may be important in the field of stroke prevention. Several recent published and ongoing studies using AEMs have revealed a high rate of detection of AF in patients with ischemic stroke or TIA [198, 224].

1.7 Pulse Palpation

Arterial pulse palpation is considered one of the oldest methods to assess the cardiovascular system and volume status of the human body. With regard to AF, radial pulse palpation is usually done as a first step assessment of the presence of irregular pulse rhythm. The suspicion for heart arrhythmia, especially AF, is usually raised whenever irregular pulse rhythm is encountered during pulse palpation and further investigation, such as 12- lead ECG, is usually requested to rule out any abnormal arrhythmia.

Pulse palpation is a cost-effective and easy method to assess for AF. In fact, it can be done by any health professional personnel, like physicians, nurses, or even by the patients themselves in some cases. Furthermore, a systematic review study has compared the sensitivity and specificity of pulse palpation and ECG to detect AF, and its investigators concluded that pulse palpation has a high sensitivity (91% - 100%) for detecting AF, even though the specificity is relatively low (70% - 77%) [225]. Their pooled negative likelihood ratio was 11%, showing that when no pulse irregularity is detected, the diagnosis of AF can be excluded with reasonable confidence [225]. This likely applies for persistent AF more than PAF; nevertheless, pulse palpation still can be used as an initial screening assessment for AF, especially in a setting where other assessment tools are not available.

1.8 Study Aims and Hypothesis

As has been shown previously, asymptomatic PAF was found to account for many events of cryptogenic stroke. This observation was demonstrated in several recent studies by the use of new internal and external loop recorders in the diagnostic workup for patients with cryptogenic stroke. It would be challenging to demonstrate this observation in the past by using 12-lead ECG or Holter monitor as these diagnostic tools have low yield to detect brief infrequent PAF. The incidence and the prevalence of AF, including PAF, were measured in most of the epidemiological studies in the past by calculating the number of cases diagnosed by one of these diagnostic tools (12-lead ECG or Holter monitor). This led to raise a question by many authors about the real frequency of AF, in light of the new results from the recent studies that used ELRs and IRLs to diagnose PAF.

The work of this thesis is to evaluate the diagnostic yield of a new generation of 21-day ELR with auto-trigger function to detect asymptomatic PAF compared to pulse palpation and ELR's ECG rhythm. Little is known about the frequency of brief PAF in the general population, in addition to the long-term stroke risk and the progression to persistent AF. In this thesis, I have utilized these new 21-day ELRs to estimate the frequency of AF and PAF in a population that previously has not been diagnosed with AF or stroke, and compare the effectiveness of this new technology with the manual pulse palpation and baseline ECG rhythm.

I hypothesize that the continuous 21-day ELRs will show a higher frequency of AF and PAF than what has been previously reported. Furthermore, 21-day ELRs will have a higher yield to detect AF and PAF, particularly brief PAF, than manual pulse palpation and baseline ECG. To the best of our knowledge, this is the first time that continuous ELRs have been used to estimate the frequency of AF in the community.

Chapter 2: Materials and Methods

2.1 Study Design

This is an observational, cross-sectional community based study. It was designed to measure the efficacy of an external ELR to detect AF or Atrial Flutter (AFL) compared to manual pulse palpation and baseline ECG rhythm in participants with no previous history of AF or stroke. In addition, this design aimed to measure the frequency of AF in order to estimate the prevalence of AF in Edmonton. Therefore, this study design was preferred (cross-sectional) to measure the prevalence of our desired outcome in a sample of the general population, and by this way make our results generalizable. Furthermore, a cross-sectional study carries low cost compared to other designs, and this advantage was required, as our study has limited funding.

2.2 Participant Population

From July 2013 to May 2014, participants from the community of Edmonton were recruited via four different recruiting sites. These four sites include three retirement/assisted living facilities and one community clinic. The names of these three retirement/assisted living facilities are Devonshire Village, Glastonbury Village, and Citadel Village. Regarding the community clinics, it belongs to the Misericordia Hospital and is called Misericordia Family Medicine Center.

Our inclusion criteria in this study were as follows:

1) Age: 40 years or older.
2) The ability to report the medical history by the participant him/herself or any family members or nursing staff at the facility during the index visit. The medical history includes the past medical or surgical history, drug history, and demographics of the participant.
3) The participant is expected to survive at least 6 months.
4) The participant agrees to sign the consent sheet and allow the investigators to check his/her medical records if needed.

The exclusion criteria were as follows:

1) Previously documented history of AF or AFL, i.e. past history of AF or atrial flutter detected on previous investigations such as ECG, Holter monitor, or telemetry. In addition, any past medical documentation stating that the participant was diagnosed with AF or atrial flutter. Remote history of transient perioperative atrial fibrillation is not exclusionary.
2) Previously documented event of Stroke or TIA.
3) Participant has a pacemaker or ICD device.
4) Participant has skin reaction to synthetic polymers or silver.
5) Participant is still enrolled in other clinical trials at the time of index visit. This includes clinical trial for medication or medical devices.

These inclusion and exclusion criteria have been verified verbally with the participant or one of his/her family members or nursing staff at the time of index visit.

2.2.1 Enrolment & Data collection

Prior to the index visit, invitation letters to participate in our study have been distributed to the mailboxes of all residents at the three retirement facilities. Furthermore, oral presentations about our study have been conducted in these facilities and all residents were invited to attend these presentations. Participants who were interested in this study voluntarily replied to the invitation letter by calling the manager office of the facility to register their names and contact numbers on the participant list. Regarding the community clinics, invitation letters were given by the front desk clerk to all patients coming to visit their physicians. The letters were usually given to the patients during their waiting time to see their physicians. When the patient agreed to participate in the study, his/her name and contact numbers were registered on the participant list before leaving the clinic.

2.2.2 Index Visit

An index visit was arranged with each participant who lives at the retirement home depending on his or her availability. The index visit took place at the participant's place (apartment/condominium). For the community clinic, appointment was arranged for each participant to see the investigator, and the index visit took place at one of the exam rooms. The inclusion and exclusion criteria were verified with the participant either prior to the index visit (through phone call) or during the index visit.

At the index visit, all participants had to sign an informed consent and were asked to report their demographic data and medical history including stroke and AF risk factors, cardiac history, relevant past surgical history and drug history. If possible, the date and indication of any previous CT or MRI of the head were collected from the participants, in addition to any previous ECG or Echocardiography. $CHADS_2$ and $CHA_2DS_2VAS_c$ scores were calculated during the index visit. Missing information from the self-reported medical history during the index visit was crosschecked later against electronic medical records. Two of the 50 participants denied any past history of AF during the index visit, but later their extended monitoring revealed a chronic AF result. In spite of that, the remaining 48 participants reported their medical history correctly.

Single pulse palpation of both arms (Radial pulse) was done for participants for one minute during the index visit. This includes documenting the heart rate and the rhythm for each participant. In addition, a baseline ECG rhythm by the ELR was reviewed for a 30 seconds and a snap shot picture was taken for the baseline ECG after attaching the ELR to the participant's chest, but before starting the real recording for the study (Figure 1). This baseline ECG rhythm will be compared to the extended ECG monitoring after the ELR monitoring is done. The baseline ECG rhythm was interpreted by a study investigator (neurology resident) and certified electrophysiology nurse. The ELR study (extended ECG monitoring) was interpreted by an electrophysiology nurse practitioner and electrophysiologist who were blinded to participant's age and medical history.

Figure 1. Baseline ECG Rhythm. A snap shot of the baseline ECG rhythm was taken from one of the participant during the index visit.

Follow up visits occurred for only the retirement facility participants in order to collect the ELR and the participant's diary sheet after the recording ended. No further data obtained or assessment was done during the follow up visit.

2.3 Study Outcomes

The primary outcome of this study is as follows:

1) Detection of one or more episodes of AF/AFL ≥ 30 seconds by the ELR.

The secondary outcomes are as follows:

1) Detection of one or more episodes of AF < 30 seconds, but > 3 seconds.
2) Detection of one or more episodes of AFL < 30 seconds, but > 3 seconds.
3) Detection of one or more episodes of Atrial tachycardia (AT)/ paroxysmal atrial tachycardia (PAT) > 3 seconds.
4) Any adverse effects from the ELR at the end of the recording.

2.3.1 ELR Data (21 day monitoring report)

ELR monitoring data included the duration of ELR monitoring and total numbers of AF/AFL and atrial tachycardia events detected. The detection of other significant dysrhythmias was indicated under comments/additional narrative by the electrophysiologist. AF/AFL episodes were then sub-classified to 1) episodes > 3 and < 30 seconds or 2) episodes ≥ 30 seconds. The longest event duration and the date of the first event were recorded for AF, AFL, and AT.

An AF event was defined by the absence of p wave activity and RR interval variability in the extended ECG monitoring for > 3 seconds. An AFL event was defined by the presence of flutter waves (F waves) at a rate of about 250-350 beats/min with variable ventricular response (R-R intervals). Atrial tachycardia usually documented whenever the atrial rate (P waves) was between 130-350 beats/min.

All new-onset AF/AFL or AT episodes detected by the ELR via the arrhythmia detection algorithm had to be confirmed by manual review by expert personnel (see above). Additional information of the ELR monitoring, such as premature battery failure or device malfunctioning was stated under the comment/ additional narrative section of the ELR monitoring report. If the duration of the ELR monitoring was less than two weeks due to one of the two reasons mentioned above, the technical issue was fixed and the participant was asked to have the study repeated.

2.3.2 Recording Technique

We utilize SpiderFlash-T® (SFT®) digital ELRs manufactured by the SORIN Group. The ELR is storing one- or two-lead ECG tracings on a high-capacity removable secure digital card (which can store a vast number of events), with looping memory capabilities, intended for long-term ECG monitoring up to 30 days. This is true when only one-lead ECG tracing is used during the monitoring study. However, we have noticed when two-lead ECG tracing are used during the monitoring study, the duration of the monitoring is reduced to an average of 14 days. With the use of lithium battery instead of alkaline one, we were able to extend the monitoring duration to up to 21 days.

SFT® recorders are programed by Hook-up2® (v2.00) software provided by the SORIN Group. This software allows the choice of several recording and pre-analysis parameters, such as pre- and post-event recording duration, timetable for predefined recordings, and type and characteristics of arrhythmia for auto-trigger functions. This software was upgraded recently to a newer version (v2.1), also provided by SORIN Group. The upgrade fixed some technical issues related to the speed of programming, but it did not affect or change the already available parameters or our programming protocol.

The SFT® recorder has been available since 2009, and it has three recording modalities: 1) patient-activated, 2) programmable timetable recordings, and 3) auto-triggered capability which automatically detects and records predefined and programmable rhythm disturbances such as pauses, bradycardia, or supraventricular and ventricular arrhythmias. In our study we utilized only the auto-triggered recording feature to automatically detect asymptomatic AF/AFL events.

During the index visit, SFT® recorders were programmed to identify different rhythm disturbances (including AF algorithm) according to the parameters listed in (Table 3) [226]. With respect to AF algorithm, ELR uses RR interval variability and QRS morphology analysis to detect all possible AF/AFL events. The AF events are then transmitted and stored in a removable secured data

card (memory card) inside the ELR, which will be used by the electrophysiologist to analyze the extended ECG recording for each participant.

Table 3. Rhythm disturbances programmed for auto-triggered detection.

Rhythm disturbances	Recorder parameters	Programmed thresholds
Supraventricular tachycardia	Prematurity Rate Rate Minimum duration	<75% >150 b.p.m. >3 s
Ventricular tachycardia	Prematurity Rate Minimum duration	<80% >120 b.p.m. >1 s
Atrial fibrillation	Irregular RR* duration	>30 s
Bradycardia	Rate Minimum duration	<40 b.p.m. >10 s
Pauses	Duration	>3000 ms
Missed beat	Duration	>1500 ms

Adopted from *Locati et al.* (2013). * Irregular RR is SORIN algorithm for the detection of AF.(b.p.m., beats pre minute. s, seconds. ms, millisecond).

SFT® recorder was carried by the participant in a disposable bag hung around the neck (necklace position). It weighted around 60g including the inside battery and was sized around 75×50×19 mm without the disposable bag. The recorders were connected to the thorax by three lead wires and disposable adhesive electrodes. The participants were trained and instructed to change these electrodes on a daily basis for personal hygiene. They were also asked to annotate on a diary sheet the times when the recorder was removed and why, any concerning symptoms like palpitations or dizziness or any history of physical exercise during the monitoring period. Retirement facility participants were instructed to phone the investigator to collect the recorder when the recording ended (shown by a status light-emitting diode on the device) or when they decided to stop wearing the recorder and not to continue participating in the study. In

contrast, the community clinics' participants were instructed to return the recorders to the clinic directly. Participants were always encouraged to complete a minimum 21 days of monitoring. However, they had the right to withdraw at any time from our study. If they agree to do so, participants whose recorders stopped prematurely before completing the two weeks were asked to repeat the study after fixing the technical issue.

Figure 2. SpiderFlash-T® (SFT®), the size is around 75×50×19 mm. (SORIN Group)

2.3.3 ELR Analysis Technique

Analyses were performed by EventScope2® (v2.00) software provided by the SORIN Group and dedicated for analysis of SFT® recorders. As Hookup2® software, EventScope2® was recently upgraded to a new version that has the same features as EventScope2® (2.1v). The auto-triggered detection algorithm was validated in a dedicated study, and Sensitivity and specificity were estimated to be 100% and 83%, respectively [227]. At the beginning, the recordings were screened for quality of the tracing and real use by the participant by means of the analysis of the lead impedance. No recording had to be excluded due to insufficient quality, since in most recordings at least one tracing from one of the

two leads was adequate for arrhythmia analysis. However, some tracings had to be excluded due to motion artifacts. Then, all auto-triggered tracings were examined first by an electrophysiology nurse practitioner and then by an electrophysiologist. In addition, the tracings were matched, as possible, against the symptoms annotated in the participant's diary.

2.4 Ethics approval and Funding

The study consent form, recruitment sites, and the methodology were approved by the Health Research Ethics Board at the University of Alberta. The SFT® recorders were provided free of cost by the SORIN Group and there was no dedicated outside funding for this study.

2.5 Statistical Analysis

Descriptive and frequency statistical analysis were performed and comparisons were made with Statistical Package for the Social Sciences (SPSS) version 22. Continuous variables are reported as mean with standard deviation (SD) or median with interquartile range (IQR). Categorical variables reported as frequency and proportion. Comparison of categorical data of the baseline characteristics for detection vs. non-detection of AF by ELR was performed by the Fisher exact test. For continuous variables, Student *t* test was performed for normally distributed data and Mann-Whitney *U* test for non-parametric data. Two-tailed tests were applied. In all comparisons, *P* value < 0.05 was considered significant. An asterisk above datum denotes a *p* value < 0.05.

Chapter 3:Results

3.1 Study Participants

During the period from July 2013 through April 2014, a total of 50 participants were enrolled from our enrollment sites (see above) after they met the inclusion and exclusion criteria of this study. Of the three-retirement/assisted living facilities, 60% (n = 30) of the participants were enrolled from the Devonshire facility, whereas 8% (n = 4) and 16% (n = 8) were enrolled from the Glastonbury and Citadel facilities, respectively. In regards to the community clinic, we enrolled 16% (n = 8) from the family center at Misericordia hospital. Two participants were excluded from the study because they were found to have chronic AF after the recording was done, although both participants had denied any history of AF or being on treatment for AF.

3.1.1 Baseline Characteristics

Demographics and baseline characteristics are illustrated in (Table 4). The mean age of the participants was 78 years (SD ± 14) and the female gender was prevalent (68.8%). 46 of 48 (95.8%) participants were not on anticoagulation at the time of monitoring, and 38 of 48 (79.2%) were not on an antiplatelet. 64.6% (31/48) have a $CHADS_2$ of two or more. The median ELR monitoring duration was 19 days (IQR 15.5-20). 87.5% (42/48) completed at least 7 days of monitoring, while 75% (36/48) completed at least 14 days and 18.8% (9/48) completed at least 21 days (Figure 3). 8.3% (4/48) of the participants completed ≤ 7 days of monitoring and their recordings were prematurely terminated (Figure 4). This was due to skin reaction to the electrodes or patient lack of compliance.

Table 4.
Baseline characteristics of study population

Baseline Characteristics	All participants (N=48)
Age, y	78 ±14
Male	15 (31.3)
Female	33 (68.8)
Race	
Caucasian	47 (97.9)
South Asian	1 (2.1)
Body mass index (BMI)	26.4 ±3.3
Hypertension (HTN)	30 (62.5)
Diabetes Mellitus (DM)	4 (8.3)
Hyperlipidemia	18 (37.5)
Tobacco use	3 (6.3)
History of palpitation	8 (16.7)
Family history of AF	4 (8.3)
History of Syncope	8 (16.7)
Hyperthyroidism	2 (4.2)
Peripheral vascular disease (PVD)	7 (14.6)
Coronary artery disease (CAD)	8 (16.7)
Angina	5 (10.4)
Congestive heart failure (CHF)	1 (2.1)
Myocardial infarction (MI)	5 (10.4)
Coronary artery bypass graft (CABG)	2 (4.2)
Pulmonary embolism (PE)	6 (12.5)
Chronic pulmonary disease	5 (10.4)
Chronic kidney disease (CKD)	2 (4.2)
Alcohol consumption (Mild-moderate)	13 (27.1)
Antiplatelet (Aspirin)	10 (20.8)
Anticoagulation (Warfarin)	2 (4.2)
$CHADS_2$ score	1.8 ±1.2

Values are reported as n (%) or mean ± SD. Chronic pulmonary disease indicates chronic obstructive pulmonary disease (COPD) or obstructive sleep apnea (OSA). Chronic kidney disease is equivalent to chronic renal failure. $CHADS_2$: CHF, HTN, age ≥ 75, DM and stroke × 2.

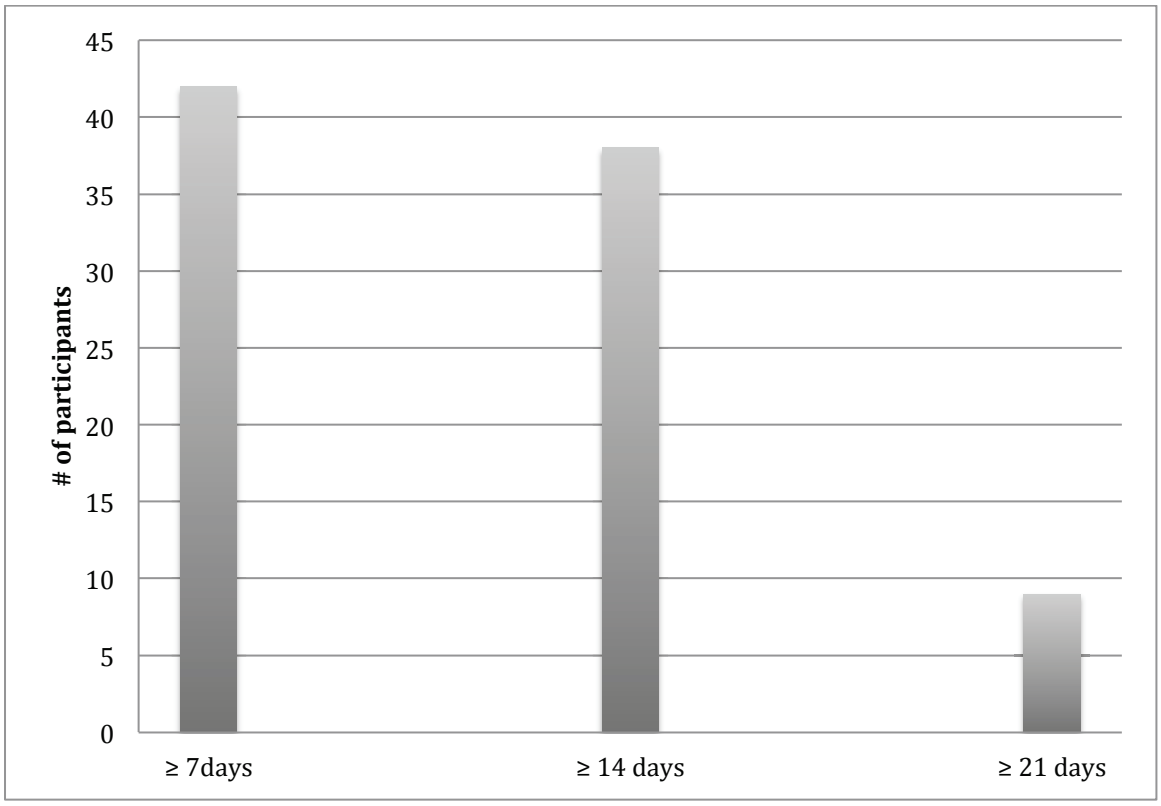

Figure 3. Days of monitoring completed by the participants. Distribution of the monitoring duration stratified by completing ≥ 7 days, ≥ 14 days, or ≥ 21 days.

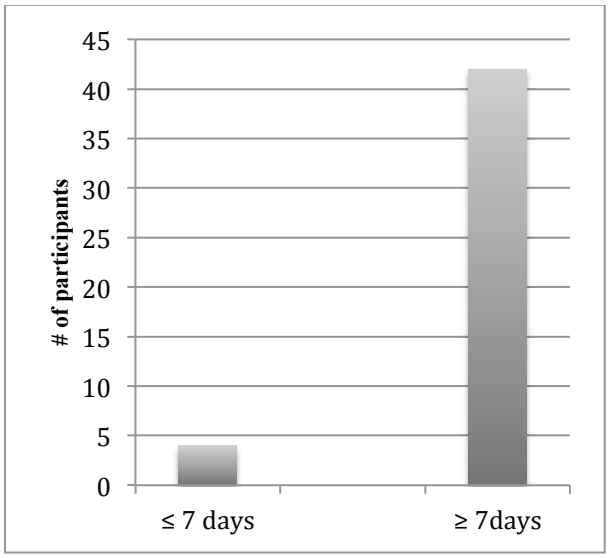

Figure 4. Days of monitoring completed by the participants. Distribution of the monitoring duration stratified by completing ≤ 7 days (monitoring terminated prematurely) or ≥ 7 days.

3.2 Manual pulse palpation and baseline ECG rhythm

Radial pulse palpation was checked manually in all participants. Irregular pulse rhythm was found in 6% (3/48) of the participants. Baseline ECG rhythm was taken by the ELR in 81% (39/48) of the participants and the remaining 19% (9/48) had their ECG's results obtained from their electronic medical records. 12.5% (6/48) of the ECG rhythm revealed non-sinus rhythm and 87.5% (42/48) revealed normal sinus rhythm (Table 5). 6.3% (3/48) of participants had irregular pulse palpation, and 93.8% (45/48) had regular pulse palpation.

Table 5. Frequency of pulse palpation and baseline ECG rhythm.

Pulse palpation * Baseline ECG rhythm Crosstabulation

			Baseline ECG rhythm		
			sinus rhythm	non-sinus rhythm	Total
Pulse palpation	Regular	Count	42	3	45
		% of Total	87.5%	6.3%	93.8%
	Irregular	Count	0	3	3
		% of Total	0.0%	6.3%	6.3%
Total		Count	42	6	48
		% of Total	87.5%	12.5%	100.0%

3.3 Extended Loop Recording Results

Positive results (AF/PAF) were detected in 13 cases (27%; 95% confidence interval [CI] 14%-40.1%). Of those, 23% (3/13) of the AF events were ≥ 30 and 77% (10/13) were < 30 but > 3 seconds (Figure 5). The duration of monitoring was not significantly different between patients with or without detected PAF (19 versus 18 days; $p = 0.31$). The characteristics of the groups with and without AF are displayed in (Table 6). Significant difference has been noticed in female gender and history of palpitation between participants with and without AF.

Table 6.
Baseline characteristics based on the presence of AF by the ELR.

Baseline Characteristics	AF (n = 13)	No AF (n = 35)	*p* Value
Age, y	79±13.4	78±13.4	0.429[+]
Female	12 (92.3)	21 (60)	0.040[*]
Race Caucasian (versus South Asian)	13 (100)	34 (97.1)	1.000
Body mass index (BMI)	26.5±3.9	26.4±3.1	0.963[•]
Hypertension (HTN)	9 (69.2)	21 (60)	0.740
Diabetes Mellitus (DM)	1 (7.7)	3 (8.6)	1.000
Hyperlipidemia	3 (23.1)	15 (42.9)	0.317
Tobacco use	1 (7.7)	2 (5.7)	1.000
History of palpitation	6 (46.2)	2 (5.7)	0.003[*]
Family history of AF	2 (15.4)	2 (5.7)	0.294
History of Syncope	2 (15.4)	6 (17.1)	1.000
Hyperthyroidism	0 (0.0)	2 (5.7)	1.000
Peripheral vascular disease (PVD)	0 (0.0)	7 (20)	0.166
Coronary artery disease (CAD)	0 (0.0)	8 (22.9)	0.088
Angina	0 (0.0)	5 (14.3)	0.304
Congestive heart failure (CHF)	0 (0.0)	1 (2.1)	1.000
Myocardial infarction (MI)	0 (0.0)	5 (14.3)	0.304

Coronary artery bypass graft (CABG)	0 (0.0)	2 (5.7)	1.000
Pulmonary embolism (PE)	1 (7.7)	5 (14.3)	1.000
Chronic pulmonary disease	2 (15.4)	3 (6.3)	0.602
Chronic kidney disease (CKD)	0 (0.0)	2 (5.7)	1.000
Alcohol consumption (Mild-moderate)	6 (46.2)	7 (20)	0.140
Antiplatelet (Aspirin)	1 (7.7)	9 (25.7)	0.248
Anticoagulation (Warfarin)	0 (0.0)	2 (5.7)	1.000
$CHADS_2$ score	1.7±1.1	1.8±1.3	0.806[+]
Duration of monitoring	19 (16-22)	18 (13-23)	0.310[+]

Continuous measures are presented as mean ± SD or median (interquartile range) with *p* values from the Mann-Whitney *U* test or Student *t* test. Categorical measures are presented as percent of total in each category with *p* values from Fisher exact test. Chronic pulmonary disease indicates chronic obstructive pulmonary disease (COPD) or obstructive sleep apnea (OSA). Chronic kidney disease is equivalent to chronic renal failure. $CHADS_2$: CHF, HTN, age ≥ 75, DM and stroke × 2. Duration of monitoring reported as days (range).

[+] Mann-Whitney test.

[•] Student *t* test.

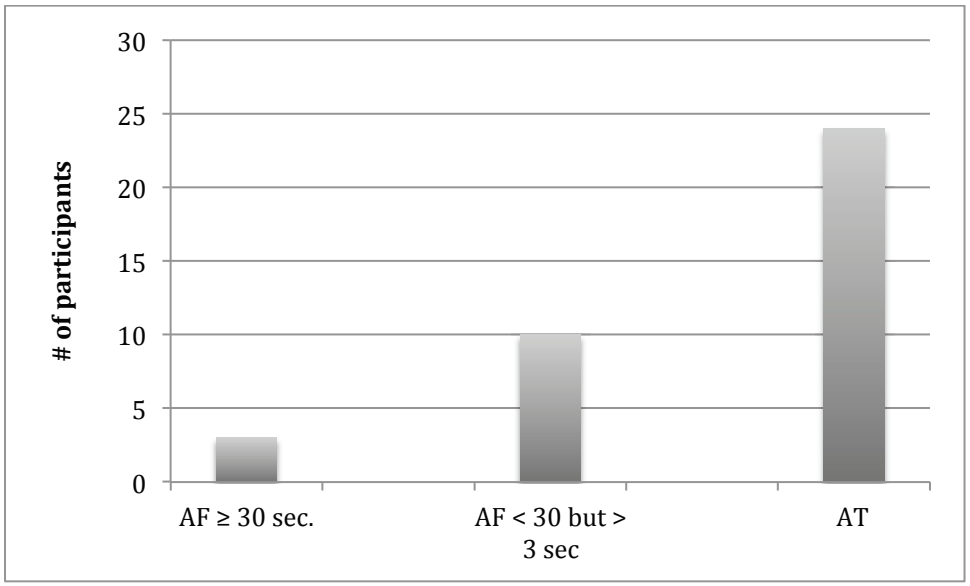

Figure 5. Frequency AF > 30 seconds, AF < 30 but > 3 seconds, and AT events detected by ELR. Sec. = seconds.

The median total numbers of AF events for each positive recording is 3 events (IQR 2-7). AFL has never been detected clearly in any ELR monitoring; however, our study cardiologist has encountered several times brief episodes of abnormal rhythms that could be AFL, but are not clear enough to be labeled as AFL rhythm. Instead, these unclear abnormal rhythms were labeled and added to the AT category. AT events were found in 50% (24/48) of the participants, of those 62.5% (15/24) of AT results occurred without the presence of AF events and more frequently than occurring concomitantly with AF (37.5%) in the same recording (Table 7). With respect to AF results, 69.2% (9/13) of these results occurred concomitantly with AT, and 30.8% (4/13) occurred without AT in the same recording (p = 0.19) (Figure 6). A picture of ELR tracings of AF > 30 seconds (Figure 7), AF ≤ 30 seconds (Figure 8), and AT (Figure 9) were attached below.

Table 7. Frequency of AT with or without AF events.

Rhythm * AF Crosstabulation

			AF		
			Negative	Positive	Total
Rhythm	AT	Count	15	9	24
		% within Rhythm	62.5%	37.5%	100.0%
		% within AF	42.9%	69.2%	50.0%
		% of Total	31.3%	18.8%	50.0%
	No AT	Count	20	4	24
		% within Rhythm	83.3%	16.7%	100.0%
		% within AF	57.1%	30.8%	50.0%
		% of Total	41.7%	8.3%	50.0%
Total		Count	35	13	48
		% within Rhythm	72.9%	27.1%	100.0%
		% within AF	100.0%	100.0%	100.0%
		% of Total	72.9%	27.1%	100.0%

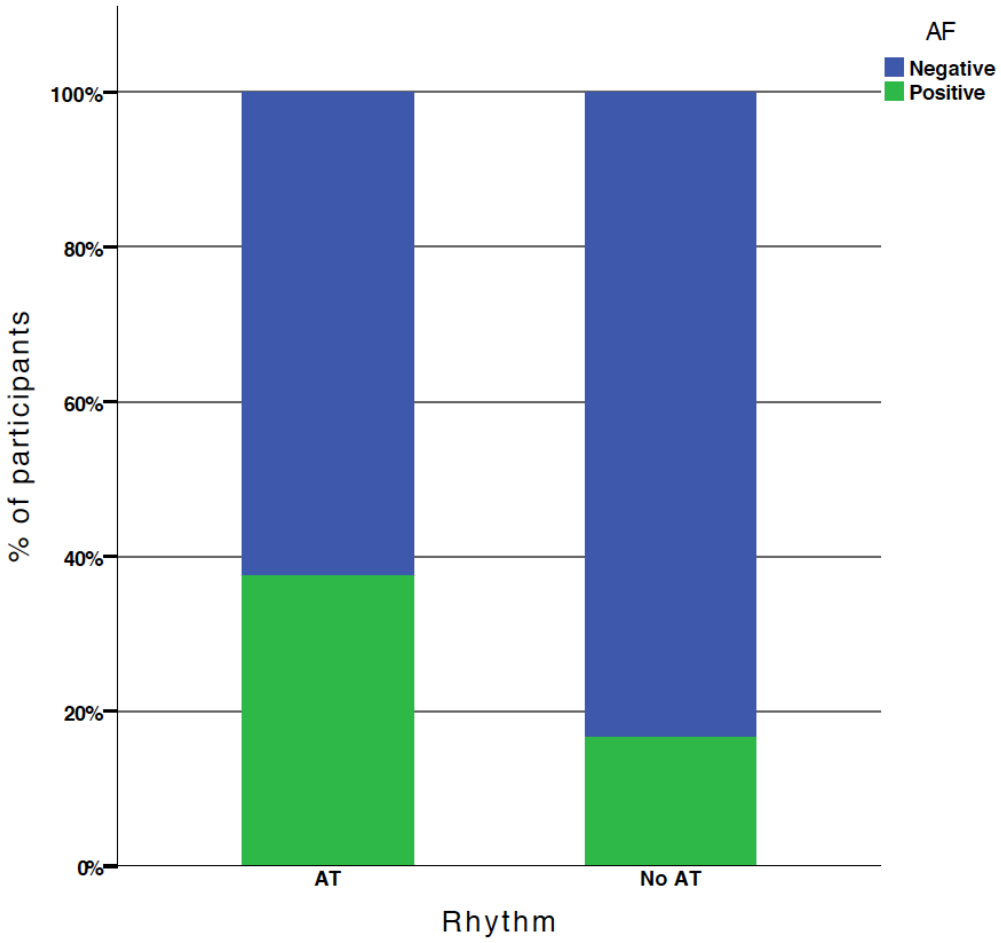

Figure 6. Frequency of AT with and without AF event.

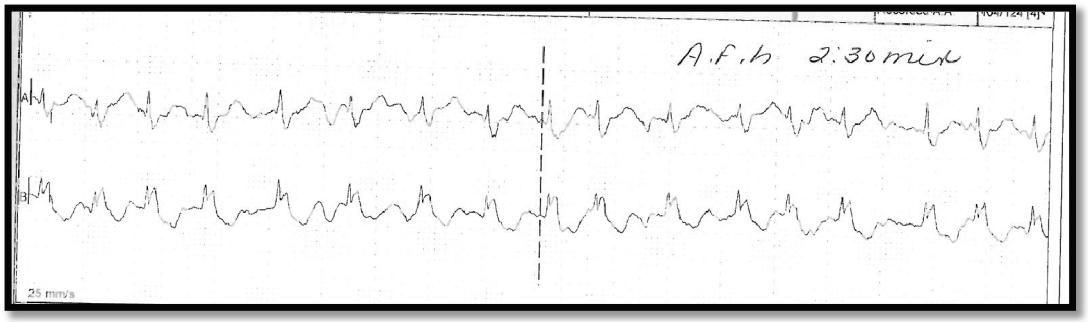

Figure 7. AF ≥ 30 seconds

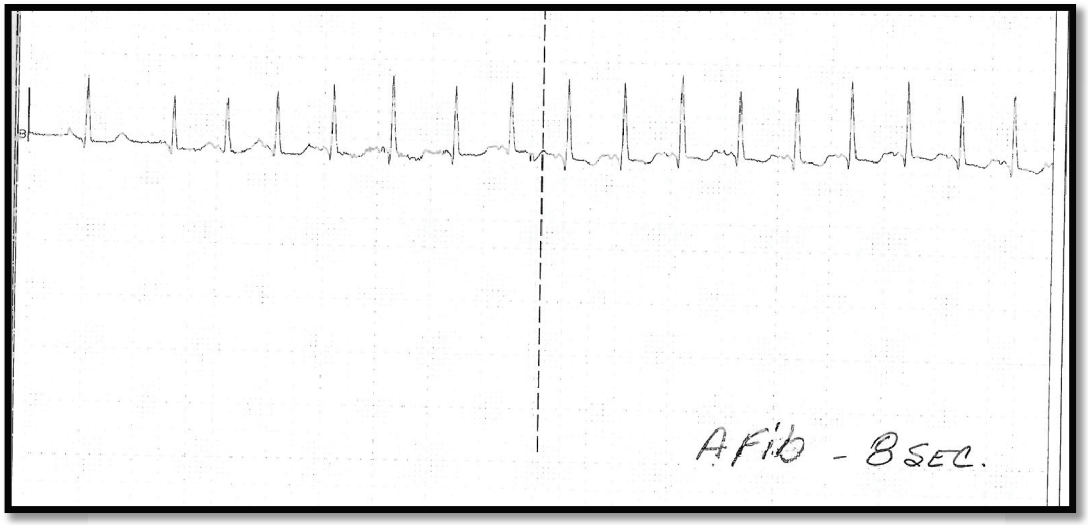

Figure 8. AF < 30 seconds

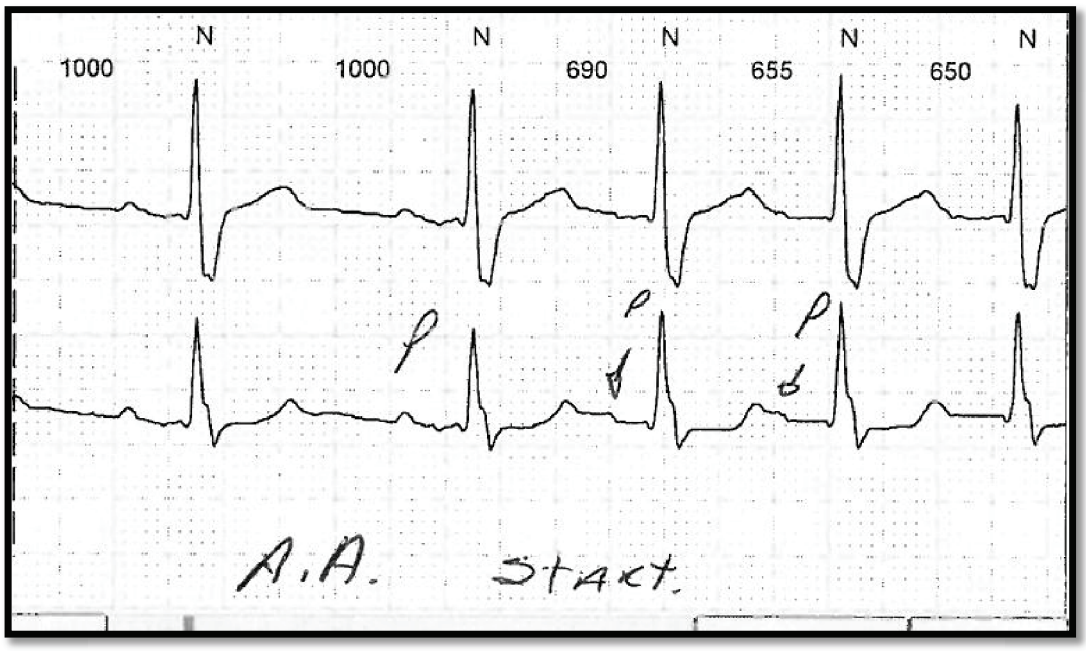

Figure 9. AT

3.3.1 Duration of AF and AT Events

The median duration of recording prior to the first episode of AF was 5 days (IQR 2-8) (Figure 10). The median longest duration of an AF event ≥ 30 seconds was 44 minutes (IQR 22-61.5 minutes), while the median longest duration of AF < 30 but > 3 seconds was 7.5 seconds (IQR 6-11). Regarding AT events, the median longest duration was found to be 8 seconds (IQR 6-25).

69.2% (8/13) of the first AF events occurred during the first week of monitoring, and 23.1% (3/13) and 7.7% (1/13) occurred during the second and third week, respectively (Figure 11).

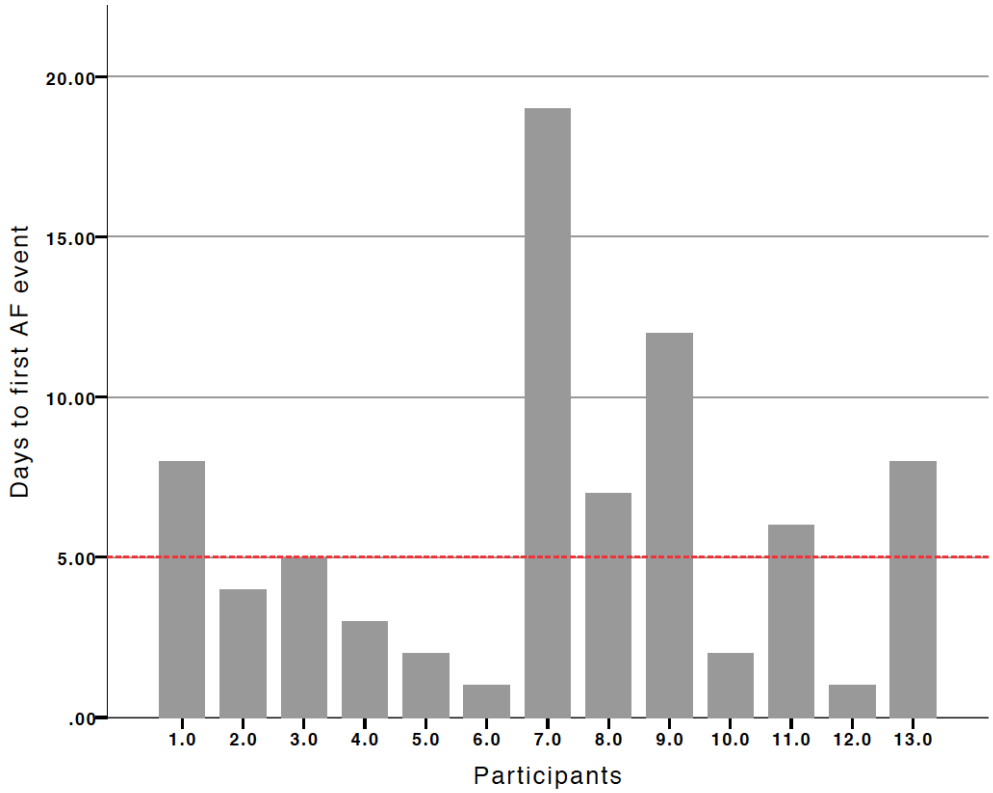

Figure 10. Time to first AF event for each participant with positive ELR result. Red interrupted line represents the median.

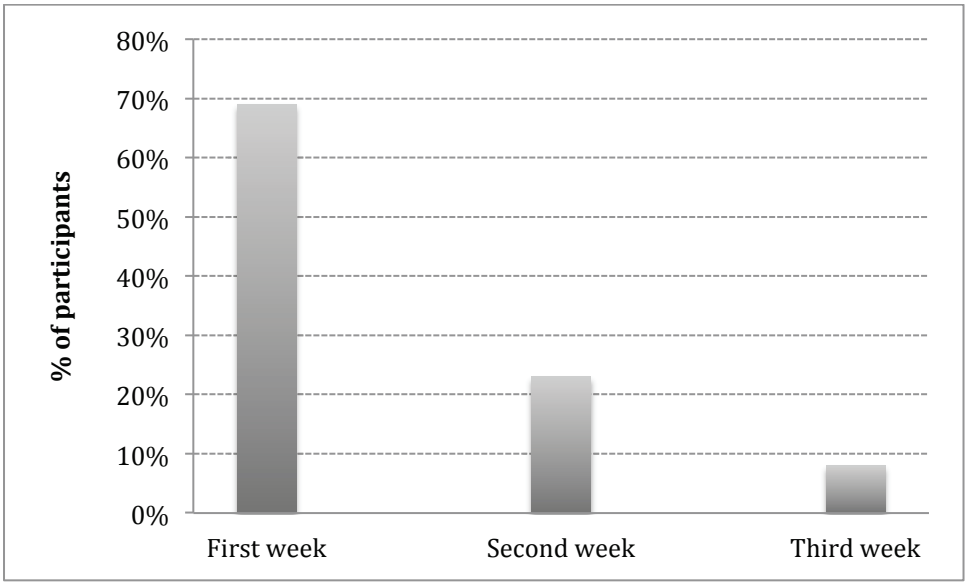

Figure 11. Percentage of first AF event detected per week.

3.3.2 Other Significant Dysrhythmias

ELR monitoring frequently revealed other significant dysrhythmias, including the following: 1) APBs (10.4%; 5/48); 2) nonsustained ventricular tachycardia (NSVT) (4.2%; 2/48); 3) PSVT (4.2%; 2/48); 4) first degree AV-Block (8.3%; 4/48); and 5) Mobitz II second-degree AV block (2.1%; 1/48) (Figure 12).

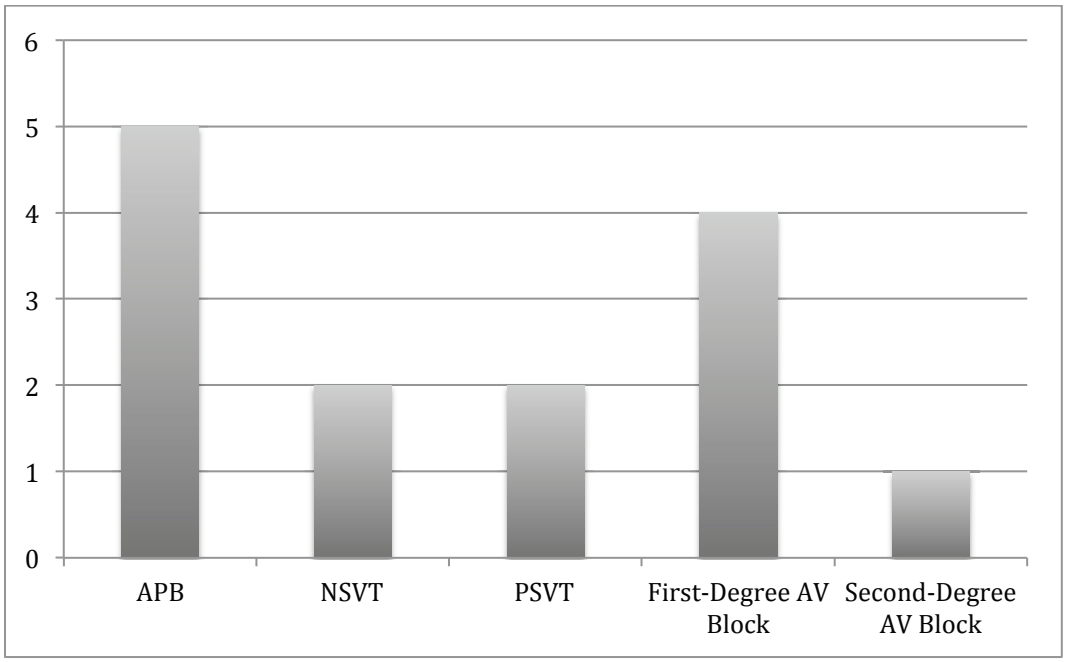

Figure 12. Frequency of other significant dysrhythmias detected by ELR. APB= Atrial premature beat, NSVT = nonsustained supraventricular tachycardia, PSVT = paroxysmal supraventricular tachycardia.

3.4 ELR Result and Pulse Palpation

ELR was able to detect AF in 13 participants, while pulse palpation was able to detect irregular pulse in 3 participants. Only 15% (2/13) of the participants with positive ELR results had irregular pulse palpation (p = 0.004) (Figure 13).

84.6% (11/13) of the participants who had an ELR result showing AF had regular pulse palpation at the time of the index visit, while only 15.4% (2/13) had both an ELR result showing AF and irregular pulse palpation. On the other hand, 97.1% (34/35) of participants with a normal ELR result had regular pulse palpation, and 2.9% (1/35) had a normal ELR result but irregular pulse palpation. Give us a Sensitivity = 15.4% (95% CI 2.7% - 46.3%); Specificity = 97.1% (95% CI 83.4% - 99.9%); positive predictive value (PPV) = 66.7% (95% CI 12.5% - 98.2%); negative predictive value (NPV) = 75.6% (95% CI 60.1% - 86.6%) for pulse palpation (Table 8).

Table 8. Numbers of participants with regular or irregular pulse palpation compared to ELR result.

	ELR		
	No AF	**AF**	**Totals**
Irregular pulse (+)	1	2	3
Normal pulse (-)	34	11	45
Totals	35	13	48

Sensitivity = 15.4% (95% CI 2.7% - 46.3%); Specificity = 97.1% (95% CI 83.4% - 99.9%); PPV = 66.7% (95% CI 12.5% - 98.2%); NPV = 75.6% (95% CI 60.1% - 86.6%).

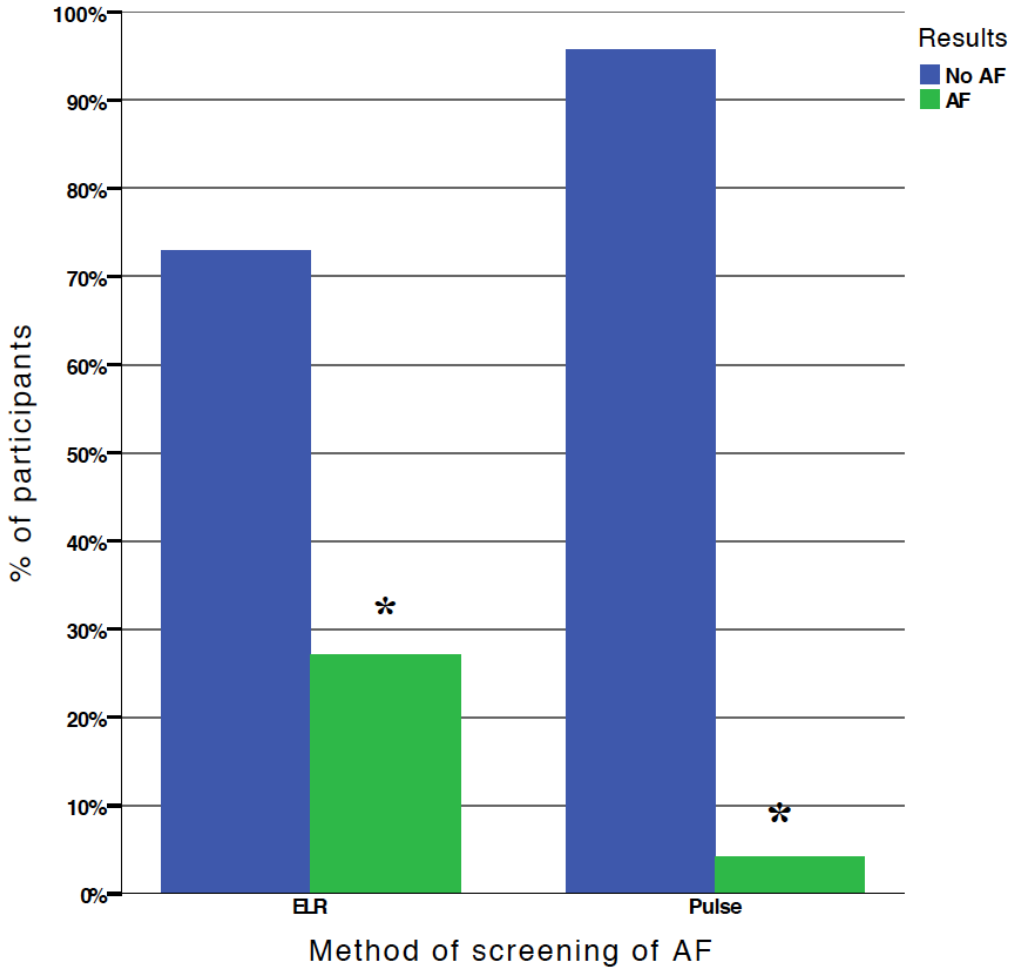

Figure 13. Frequency of AF event detected by ELR versus pulse palpation. (*) indicates a significant difference.

3.5 ELR Result and Baseline ECG Rhythm

ECG baseline rhythm detected non-sinus rhythm in 6 participants (versus 13 participants by ELR). However, only 3 participants with non-sinus baseline ECG have positive ELR result (p = 0.01) (Figure 14).

76.9% (10/13) of the participants had positive ELR results but their baseline ECG rhythm showed normal sinus rhythm; however, 91.4% (32/35) of the participants with negative ELR had a normal sinus rhythm ECG baseline. 50% (3/6) of the participants with non-sinus ECG rhythm had a positive ELR result, and remaining 50% (3/6) had non-sinus ECG rhythm and positive ELR result. Give us a Sensitivity = 23.1% (95% CI 54% - 61.6%); Specificity = 91.4% (95% CI 75.8% - 97.8%); PPV = 50% (95% CI 13.9% - 86.1%); NPV = 76.2% (95% CI 60.2% - 87.4%) for baseline ECG rhythm (Table 9).

Table 9. Numbers of participants with sinus or non-sinus rhythm compared to ELR result.

	ELR		
	No AF	**AF**	**Totals**
Non-sinus ECG (+)	3	3	6
Sinus ECG (-)	32	10	42
Totals	35	13	48

Sensitivity = 23.1% (95% CI 54% - 61.6%); Specificity = 91.4% (95% CI 75.8% - 97.8%); PPV = 50% (95% CI 13.9% - 86.1%); NPV = 76.2% (95% CI 60.2% - 87.4%).

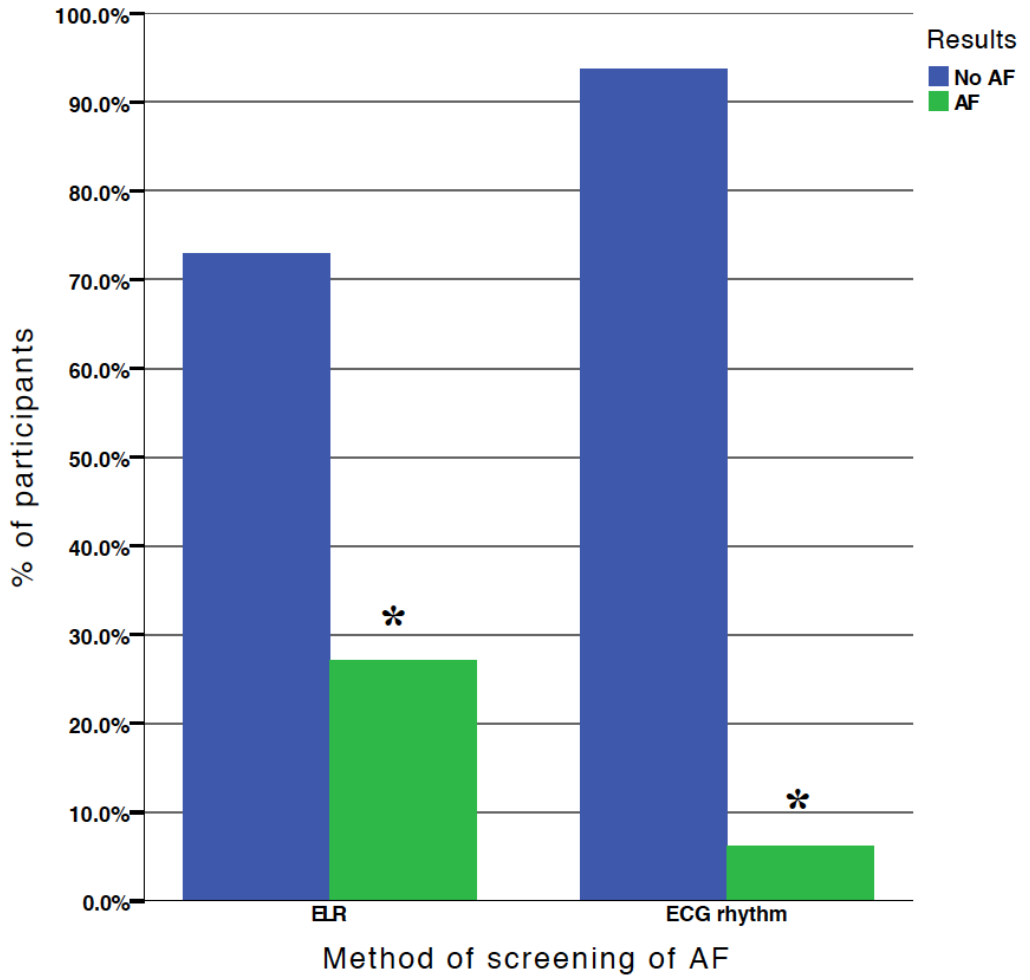

Figure 14. Frequency of AF event detected by ELR versus baseline ECG rhythm.

3.6 The Prevalence of AF

The prevalence of AF in a previously unknown AF population was estimated from our sample to be 27% (95% CI 14%-40.1%). The incidence rate could not be calculated from this study design.

3.7 Documented Symptoms (palpitation) with AF

6.3% (3/48) of the participants complained of at least one event of palpitation during the ELR monitoring. 92.3% (12/13) of participants had positive ELR results but did not report palpitation event duration the same ELR monitoring. On the other hand, participants who had negative ELR results and did not report palpitation event during the same ELR monitoring were also high (94.3%; 33/35). Therefore, palpitation can give us Sensitivity = 7.7% (95% CI 0.4% - 37.9%); Specificity = 94.3% (95% CI 79.5% - 99%); PPV = 33.3% (95% CI 1.8% - 87.5); NPV = 73.3% (95% CI 15.1% - 42.2%) (Table 10).

Table 10. Numbers of participants with or without palpitation compared to ELR result.

	ELR		
	No AF	**AF**	**Totals**
Palpitation (+)	2	1	3
No palpitation (-)	33	12	45
Totals	35	13	48

Sensitivity = 7.7% (95% CI 0.4% - 37.9%); Specificity = 94.3% (95% CI 79.5% - 99%); PPV = 33.3% (95% CI 1.8% - 87.5); NPV = 73.3% (95% CI 15.1% - 42.2%).

3.8 ELR and Adverse Effects

Skin irritation and redness were the most common adverse effects for ELR, resulting from the use of the adhesive electrodes over the chest area for long periods. 12.5% (6/48) of the participants complained of skin irritation and redness during the period of wearing the ELR. The redness of the skin usually disappeared completely after one to two days after ELR monitoring and needed no treatment apart from a moisturizing agent. In addition, participants who changed the lead patches daily and always changed the attachment area encountered fewer problems with skin irritation and redness.

Another adverse effect noticed during this study was participant compliance in continuing to wear the ELR. 8.3% (4/48) of the participants asked to stop wearing the ELR and terminated the monitoring prematurely. 4.2% (2/48) participants had problems with sleeping while they were wearing the ELR, while another 4.2% (2/48) had problems with the ELR hanging pouch scratching their skin (Figure 15).

Almost all the participants complained that the ELR mentoring duration was too long; however, no one asked to terminate the monitoring early because of this reason.

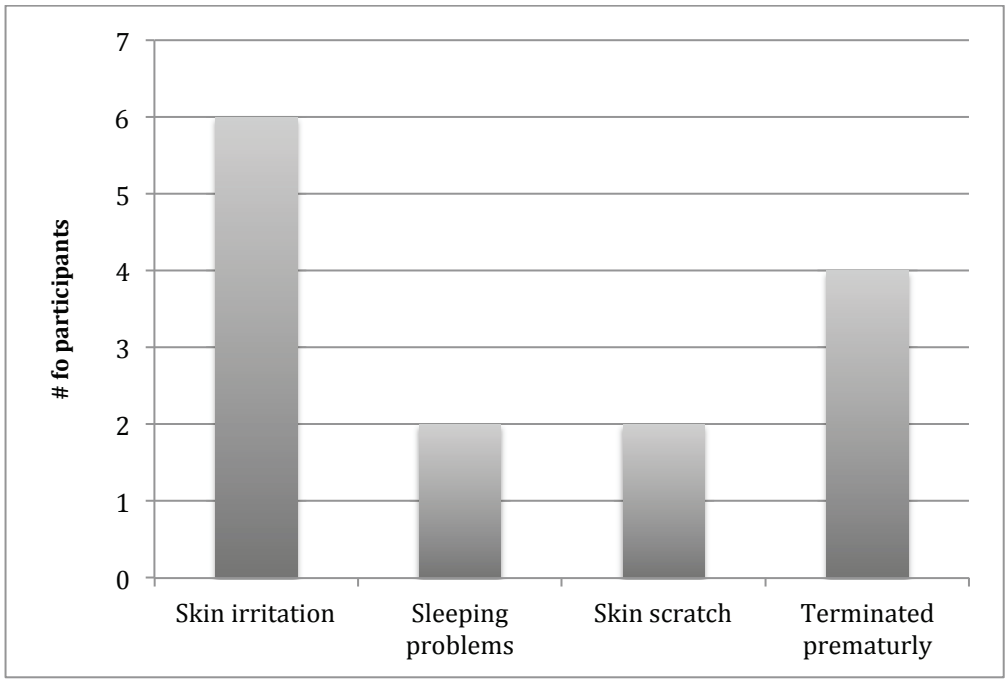

Figure 15. Frequency of the adverse effects of ELR. ELR monitoring that terminated prematurely was secondary to either sleeping problem or skin scratches by the ELR hanging pouch.

3.9 Informing The Family Physicians About the Results

Family physicians of participants with positive results were informed about the ELR results either by faxing the results to their clinics or by contacting them by phone. Recommendation for anticoagulation was made based on $CHADS_2$ and CHA_2DS_2-VASC scores. Cardiology referral was recommended based on our cardiology recommendation. 92% (12/13) of participants with positive results were not on anticoagulants or antiplatelet prior to ELR monitoring.

Chapter 4: Discussion

4.1 Summery of the Results

In this observational community-based study of participants with unknown history of AF or stroke/TIA, ELR was used to detect asymptomatic AF and the yield of this new tool was compared with pulse palpation and baseline ECG rhythm. Pulse palpation and baseline ECG were obtained from most participants at the time of index visit and prior to starting the ELR monitoring. ELR results were received for all participants and there was no missing data.

This study reveals a high detection rate of asymptomatic AF using ELR in participants with no previous history of AF or stroke/TIA. An overall AF detection rate of 27% was found in this community population with ELR monitoring. Moreover, the rate of all abnormal dysrhythmia, including AF or AT was even higher compared to normal ELR results. Other dysrhythmia such as Mobitz type II second-degree AV block and NSVT were encountered in this community population. The median AF event frequency and duration were delineated in this study. The majority of the first AF events detected during the first week of monitoring. However, there are still few numbers of first AF events detected during the third week, which indicates the importance of longer monitoring to detect AF events.

The diagnostic yield of the ELR was found to be significantly higher than pulse palpation in detecting AF. Pulse palpation missed around 84.6% of participants with positive ELR results for AF. Furthermore, the diagnostic yield of ELR was also found to be significantly higher than baseline ECG rhythm. Baseline ECG rhythm missed around 76.9% of participants with positive ELR results for AF. In general, the diagnostic yield of ELR was higher than pulse palpation and baseline ECG, and even higher than both of them combined.

4.2 Frequency of AF in the community

The main finding of this study is a high rate of asymptomatic AF detection (27%) by ELR in a community-based population with participants who have never had a prior history of AF or stroke/TIA. This finding may be related to several factors: 1) longer duration of cardiac monitoring (21 days) compared to prior studies; 2) our outcomes included AF < 30 seconds, which was excluded in several previous studies; 3) AF event detection was based upon a standardized automated arrhythmia detection algorithm, in addition to an ECG tracing review by a cardiologist.

Most previously conducted studies that utilized AEM, including ELR and ILR, were conducted on patients with stroke or TIA, specifically cryptogenic stroke patients. Nevertheless, a single large study conducted in the community of Halmstad in Sweden used an extended hand-held ECG recording for 20-30 seconds twice daily but no continuous cardiac monitoring [228]. In this study, 7.4% (30/403) were diagnosed by the extended hand-held ECG with previously unknown PAF. The low AF frequency in this study, compared to our results, is likely due to the interrupted recording and the absence of continuous automated monitoring [228]. In addition, their initial 12-lead ECG screening prior to using the extended hand-held ECG excluded some participants who showed evidence of AF. In our study, our initial screening included pulse palpation and baseline ECG rhythm. However, we did not exclude any participant with irregular pulse or abnormal baseline ECG rhythm as the aim of this study is to compare the efficacy of the different modalities to detect AF (ELR versus pulse palpation and baseline ECG rhythm). Furthermore, excluding participants based on non-specific irregular pulse or baseline ECG rhythm may lead to excluding participants with no AF and then affect the real estimated frequency of AF. This study (*Engdahl et al.*, 2013) was the only community-based study that used extended (but not continuous) ECG recording in the community. The rest of the studies that used continuous cardiac monitoring were all conducted, as mentioned above, on patients who had stroke/ TIA, or symptomatic patients (syncope or sustained palpitation) who required further evaluation.

Regarding studies used continuous cardiac monitoring, *Flint et al.* used an auto-triggered ELR in cryptogenic stroke patients with a longer monitoring duration (30 days) than our study, and their estimated frequency of PAF ≥ 5 seconds was found to be 12.1% (29/239) [223]. Another study utilized the same monitoring modality (auto-triggered ELR) in cryptogenic stroke and TIA patients but a shorter monitoring duration (7 days) than our study, and their estimated AF frequency using ELR was 5.7% (5/88) [193]. This difference in the AF frequency between these two studies with the difference in monitoring duration confirms the importance of the longer monitoring duration as one of the factors to determine the accurate AF frequency in any cohort.

On the other hand, several recent studies have used MCOT, which has the advantage of continuous review of monitoring ECG tracing data, to estimate the frequency of AF in cryptogenic stroke and TIA patients. Two of these studies used MCOT for up to 21 days and reported a frequency of 23% (13/56) and 17.3% (27/156) of AF in cryptogenic stroke and TIA patients [192, 198]. However, due to the obvious difference between the sample sizes of both studies (56 vs. 156), the one with a larger sample size (156) may reflect more accurate AF frequency than the one with a smaller sample size. In fact, the one with the smaller sample size (56) has a higher AF frequency, and because its sample size is close to our study, it may explain the higher rate of AF in our study, even though our study population (community-based population) is different than this study (cryptogenic stroke/TIA patients).

Furthermore, ILR has also been used to estimate the frequency of AF in cryptogenic stroke and TIA. In a recent study, the frequency of AF > 2 minutes was found to be 25.5% (13/51) after a median of 50 days of monitoring [51]. This high rate of AF in that study is again close to our AF rate. In addition, their sample size is also close to our sample size (51 versus 49). However, there is difference in the mean age (78 years old vs. 51 years old), monitoring duration, and study population between our study population and that study. Interestingly, extended ELR and ILR (both with auto-trigger capability) were reported to have similar diagnostic yields, when considering the same time interval [226].

Overall, we can see that the estimated frequency of AF varies based on different factors like the duration of monitoring, the monitoring modalities, and the study population size and characteristics (Table 11). We could not find a study that utilized the same modality (ELR) as we did to estimate the frequency of AF in community-based population, in order to make an equivalent comparison.

Tables 11. Yield of long-term cardiac rhythm monitoring studies.

Study	Patients population	Duration (days)	Sample size	No. diagnosed	Percentage
Barthélémy et al. 2003	Stroke/TIA	4	28	4	14.3
Jabaudon et al. 2004	Stroke/TIA	7	88	5	5.7
Tayal et al. 2008	Stroke/TIA	21	56	13	23
Elijovich et al. 2009	Stroke/TIA	30	20	4	20
Gaillard et al. 2010	Stroke/TIA	30	98	9	9.2
Ziegler et al. 2010	Stroke/TIA	365	163	45	28
Stahrenberg at al. 2010	Stroke/TIA	7	220	28	12.7
Bhatt et al. 2011	Stroke/ TIA	21	62	15	24
Flint et al. 2012	Stroke	30	239	29	12.1
Sposato et al. 2012	Stroke/TIA	5	155	21	13.5
Miller et al. 2013	Stroke/TIA	21	156	27	17.3
Cotter et al. 2013	Stroke	154	51	13	25.5
Gladstone et al. 2014	Stroke/TIA	30	280	45	16.1%

(Adopted from *Khan et al*., 2013)

4.3 Monitoring duration and diagnostic yield of ELR

The monitoring duration required to detect the first AF episodes was 5 (IQR 2-8) days in our study. This suggests that prolonged cardiac monitoring has to be more than 5 days continuously, even though first AF events were also detected during the third week (day 19) of monitoring in our study. Therefore, prolonged monitoring (> 5 days) may be warranted for patients with cryptogenic stroke/TIA. While 24 hours Holter monitoring is commonly used, the yield is low and less than 5% [229]. Longer monitoring improves the yield, with a doubling of diagnosis by increasing the monitoring duration to 7 days [51, 229]. In addition, prolonged ELR monitoring with auto-triggered capability can even improve the yield more than other ELRs that lack this important feature. ILR, on the other hand, has longer monitoring duration than ELR; however, the early use of ILR is difficult to implement in real clinical practice due to the high cost and invasive implanting procedures [226, 230]. In addition, extended ELR and ILR (both with auto-trigger capability) had similar diagnostic yields when considering the same time interval [226]. Therefore, non-invasive and easy-to-use ELR with prolonged monitoring can be provided in the early phase of the diagnostic workup before moving to more invasive investigation [231, 232].

4.3.1 ELR, pulse palpation, and baseline ECG rhythm

Pulse palpation is an easy method and less time consuming to screen for an abnormal arrhythmia. With respect to AF, the sensitivity of pulse palpation was found to be 91%-100%, while specificity ranged from 70% - 77% [225]. However in our study, the sensitivity of pulse palpation to detect PAF has been found to be low (15.3%), but the specificity was 97%. This great difference in sensitivity between our study and Cooke et al. is likely secondary to the type of AF that has been measured. In our study, the AF events that have been detected were all PAF, while in the one in Cooke et al. were most likely prolonged or persistent AF events. Therefore, pulse palpation is not a reliable method for screening for PAF, as pulse palpation has a high chance of missing asymptomatic brief PAF events that may lead to cardioembolic stroke/TIA.

Baseline ECG rhythm is a convenient way to check the instant ECG rhythm for individuals. However, it only utilizes 1- or 2-lead ECG instead of the regular 12-lead ECG to assess the heart rhythm. A patient-activated single-lead ECG device was evaluated and found to have a sensitivity of 99% and a specificity of 96% to detect AF compared to 12-lead ECG [233]. However in our study, this sensitivity went down to 23.1%, and the specificity was 91%. This drop is likely secondary to the same reason for pulse palpation, which is the lower ability to detect PAF, the only type of AF events detected in our study. This means using baseline ECG rhythm by ELR or any other devices that use 1- or 2-lead ECG is useful as a screening method for longer duration AF events, but not the best modalities for short duration AF that might lead to cardioembolic stroke/TIA.

4.4 Prevalence of AF

AF is an independent risk factor for ischemic stroke, which increases in prevalence with age [192]. The annual risk of stroke secondary to AF was estimated to be 1.5% in patients aged 50-59 years and 23.5% in those aged 80-90 years [147]. The prevalence of AF has been estimated to be between 2%-5% in the general population [61, 62]. In addition, AF risk doubles with each progressive decade of age with a prevalence of 11-18% in patients aged ≥ 85 years [54, 55, 64, 65].

The prevalence of AF in our study population was estimated to be 27% by using ELR. This high prevalence of AF compared to the other epidemiological studies is due to several factors: 1) most of the other epidemiological studies utilized 12-lead ECG, which is prone to miss AF with a short duration (PAF); 2) the mean age of our population was 78 years, which is one of the groups at the highest risks of AF. This high age of participants was because our enrolling sites were mainly from the retirement facilities; 3) epidemiological studies usually require a high number of participant in order to estimate real numbers of the desired disease. In our study, the study population was only 48, which might

reflect an inaccurate estimation of the AF prevalence in the general population of the same age.

4.5 Predictors of AF

Multiple predictors of AF in cryptogenic stroke patients have been proposed by several studies using extended cardiac monitoring. These predictors include older age, female gender, DM, APBs on ECG, left atrial dilation, and multiple acute infarcts [172, 192, 198]. Most of these risk factors have been observed and identified in multiple randomized control trials [149, 150]. In our study, we have detected significant differences in participant characteristics between those with or without AF in females and those with a history of palpitation. Multiple prospective studies of patients with palpitation undergoing extended cardiac monitoring showed a high detection rate of AF in those patients [226, 234].

Some of these predictors make pathophysiological and clinical sense of predicting AF events. Different predictors have been consolidated into risk assessment scoring schemes to provide a predictive model for AF detection [213, 235, 236]. These scores can be useful tools when correlated with clinical judgment in selecting stroke patients for long-term monitoring [213]. For community-based population with no history of AF or stroke/TIA, large size and wide range population samples are necessary to confirm our observations about the female gender and history of palpitation as predictor of AF.

4.6 AF patients and anticoagulation/antiplatelet

92.3% (12/13) of the newly diagnosed AF participants were not on antiplatelet or anticoagulation at the time of the index visit. All the AF participants' family physicians were made aware of their patients' ELR result by an official letter. Only 2 family physicians shared their plan with regard to initiating the necessary treatment; however, we do not have any information about the treatment plan for the rest of the AF participants.

The decision to recommend initiating anticoagulation or not was, generally, made based on the $CHADS_2$ and $CHA2DS_2VAS_c$ scores for the

participant with an AF > 30 seconds. Nevertheless, the information in the literature about initiating anticoagulation for patients with an AF event ≤ 30 was inconclusive, and the decision to recommend initiating anticoagulation to the family physicians of our participants was difficult to make.

4.7 PAF < 30 seconds

The 30 seconds benchmark used to describe AF events mainly comes from the AHA 2006 guidelines [58]. It is unclear how the authors came up with the 30 seconds event as a benchmark, although they do mention that shorter events may be relevant in the right clinical setting [58]. Most of the studies that we have mentioned used this guideline (AHA 2006 guidelines) and defined PAF in their studies as events lasting more than 30 seconds. Nevertheless, they did mention encountering frequent events of PAF that were < 30 seconds. It has been shown that auto-triggered AF algorithm functions do have high false positive rates in detecting AF with short events (PAF < 30 seconds), as these short events can be confused with myopotential artifacts [237]. Likely just to avoid the artifact issue, some of these studies defined their primary AF outcome to be several minutes in order to call it an AF event [51, 191]. However, this problem was overcome in our study by doing a manual review of these recorded events and filtering the artifact events by our cardiologist.

There is no established threshold of AF duration that may lead to stroke or TIA. Furthermore, it is unclear how often short PAF events lead to chronic AF. Healey et al.'s study showed an increase in the frequency of ischemic stroke, as well as verified AF rates in patients with a subclinical AF of > 6 min [191]. However, this study cannot exclude the risk of developing stroke/TIA from AF events that last less than 6 minutes, as another recent study has shown a high rate of PAF < 30 seconds in patients with cryptogenic stroke/TIA [198]. In our study population, most of the AF events were less than 30 seconds, which confirms the same observation in the previous study. However, none of our study participants had a history of stroke or TIA. This brings us to the question of what duration of AF event is predictive of a future stroke. To answer this question, another parallel

study was designed in our center to test the hypothesis of having a silent stroke from these brief PAF events by doing a follow up MRI on our participants with AF ≤ 30, searching for any evidence of silent stroke. This ongoing study will probably help with exploring the burden of PAF < 30 seconds. In addition, another ongoing study (CRYSTAL AF) is investigating the value of longer-term monitoring with ILR in patients with cryptogenic stroke to identify the predictive value of these events [213, 238]. Furthermore, both CRYSTAL AF and another trial (IMPACT) will help us to identify the best candidates for anticoagulation [238, 239].

Until further conclusions about what duration of AF event is predictive of a future stroke, we believe using 30 seconds duration as a benchmark for AF event is not supported by any clinical evidence.

4.8 Study Limitations

Although our study represents a new view about the frequency of AF in people who have never had previous history of AF or stroke/TIA, there are some expected limitations as follows:

1) Although we tried to enroll as great a number of participants from the community as possible, the sample size of the study is still relatively small to make our results generalizable. In addition, the independence of predictive factors could not be assessed, as there were insufficient numbers to allow a meaningful multivariate model to be constructed.
2) Since our study was carried out in a single community, the results may not be reproducible in all populations.
3) Our average population age was high (78 years old), which may explain our finding of high rates of AF in this population. However, this high rate of AF is likely limited to this age group and cannot be generalized to other younger age group in the community.
4) All the ELR results have been reported from a single center, and the majority of AF events recorded were < 30 seconds in duration, which may be more prone to misinterpretation than longer AF events. However, we

have tried to minimize this bias by asking two different experts (electrophysiologist nurse and cardiologist) from the same center to analyze the ELR result independently.

5) Pulse palpation and ECG rhythm are not the best screening tools for PAF. However, in our case they are the most available and cost effective tools that we can compare with in the community.
6) Poor compliance from some participants was a barrier to complete 21 days of monitoring. This poor compliance was usually secondary to the lead wires and adhesive electrodes that are important to insure a standard ECG quality but are poorly tolerated by some of the participants.

Despite these limitations, this study is still unique and these limitations are outweighed by the benefit of understanding the yield of ELR in the community and revealing new information about the frequency of AF detected in the community.

4.9 Improving future studies

Several points have to be considered in order to improve future studies, including this ongoing study, in the community. First, we targeted senior and retirement facilities at the beginning as potential sites to enroll participants for this study. This step was justifiable as elderly people are at higher risk of developing AF and may benefit from early initiation of AF treatment. However focusing only on this age group may not reflect the accurate prevalence of AF in the general population. Therefore, expanding the enrolling process to include different age groups and races would be important to estimate the correct frequency and prevalence of AF in the general population. Second, the sample size of the study is low and needs to be increased, even though this study was the first one to use ELR in the community and a low sample might be acceptable for an initial study. However, enrolling more participants for this study will definitely help improve the results to be more generalizable and provide more meaningful analysis of the collected data. Third, this data, which presents a high frequency of AF in our study, was collected from a single population, and it would be interesting to know the

frequency of stroke/TIA incidence from the same population. Because if the same population revealed a high frequency of stroke secondary to AF, then the high frequency of AF that we found in our study may be explained as it is a geographical or population dependent. Therefore, an age-matched stroke group would be helpful to give us some explanation about this high frequency of AF in this community. Finally, with regard to the compliance issue with our ELR, the use of belt or patch electrode or vest or wireless non-contact ECG electrodes instead of the lead wires and adhesive electrodes may improve participant compliance to complete the required duration for the ELR [226, 240].

Conclusion

This thesis presented a study designed to examine the frequency of AF in a community-based population, and to compare the yield of extended ELR with pulse palpation and baseline ECG rhythm to detect AF. The frequency of AF was found to be high in our study population. The yield of the extended ELR was found to be better than pulse palpation and baseline ECG rhythm for detecting AF in the community. The sensitivity of both pulse palpation and baseline ECG were low and not suitable as screening tools for PAF in the community.

Participants with an AF < 30 seconds constitutes the majority of our study AF population. Cardiac monitoring for at least 5 days is essential in order to detect brief AF events. Other dysrhythmias were detected in our study population with a high frequency of AT. Our sample did reveal two independent risk factors for brief AF, however, further enrollment of more participants and different age groups are recommended to empower the study results and make it more generalizable.

ELR can be used as a first choice tool to search for asymptomatic AF in a group with risk of AF in the community. Further prospective study is required to determine the long-term stroke risk in populations with a high frequency of brief AF that lasts < 30 seconds and the role of anticoagulation as a primary stroke prevention method.

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