2023

Screening for undiagnosed atrial fibrillation to prevent stroke

BOSTON UNIVERSITY

ARAM V. CHOBANIAN & EDWARD AVEDISIAN SCHOOL OF MEDICINE

Thesis

SCREENING FOR UNDIAGNOSED ATRIAL FIBRILLATION TO PREVENT STROKE

by

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B.S., Boston University, 2019

Submitted in partial fulfillment of the

requirements for the degree of

Master of Science

2023

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ACKNOWLEDGMENTS

I would like to thank my thesis advisor Dr. DiPetrillo for all her guidance and teaching throughout my thesis writing and throughout my time at BU. I would also like to thank all my friends, family and PA friends who supported me immensely throughout my time in PA school.

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ABSTRACT

Background

AF is a growing epidemic in the United States that will continue to worsen as risk factors become more prevalent in the population. The arrhythmia often persists asymptomatically before presenting as a stroke or when the disease has progressed to cause permanent cardiac restructuring. The gold standard for diagnosis is ECG. The current treatment consists of rate control, rate control, and stroke prevention with anticoagulation.

Literature Review

Recent studies have shown that screening for AF does result in an increase in AF diagnosis. A current gap in literature remains regarding if that increase in AF diagnosis leads to a stroke reduction in the screened population.

Proposed Project

The proposed project is a randomized control trial that will compare AF diagnosis in a control group to a group that is screened for AF using a 30-day cardiac monitor. The statistical analysis will reveal if there is a reduction in stroke and other cardiac sequelae in the screened group compared to the control group.

Conclusion/Significance

Should the study reveal that screening for AF in an at-risk population reduces the risk of stroke, it could assist the USTF in addressing the gap in literature required to either recommend for or against AF screening in the United States.

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LIST OF ABBREVIATIONS

AF ..... Atrial Fibrillation

CHA_2DS_2-VASc.....Congestive heart failure, hypertension, age, diabetes, stroke, vascular

CHF.....Congestive Heart Failure

CRP.....C-Reactive Protein

ECG.....Electrocardiogram

EUR.....Euro

HF.....Heart Failure

INR.....International Normalized Ratio

IRB.....Institaional Review Board

MI.....Myocardial Infarction

QALY.....Quality Adjusted Life Year

RAS.....Reticular Activating System

TIA.....Transient Ischemic Attack

TTE.....Transthoracic Echocardiogram

USD.....United States Dollar

INTRODUCTION

Background

Atrial fibrillation is the most common arrhythmia amongst adults. [1] It is defined as an irregular rhythm with no discernible pattern of p waves on an ECG and abnormal R-R intervals. Due to uncoordinated electrical activity in the atria, there are insufficient atrial contractions at an irregular rate.[1] Currently, diagnosis for clinical AF requires the arrhythmia to be present on an ECG for at least 30 seconds.[1] Symptoms of AF include dyspnea, dizziness, chest pain, fatigue, and disordered sleep.[1] Treatment for the disease includes pharmacologic rate control, rhythm control, and stroke prevention with anticoagulation.[1] Catheter ablations and cardioversions are alternative options to pharmacological therapy.[1]

The prevalence of AF is increasing with many cases going undiagnosed because they are asymptomatic or episodic.[2] In many cases, stroke is the first clinical presentation of undiagnosed AF.[2] Stroke that is caused by AF presents a major preventable disease burden in the United States.[2] If oral anticoagulation is started after an AF diagnosis, 66% of strokes can prevented.[2] Compared to other causes of strokes, emboli due to AF tend to be more fatal.[2] The concept of screening asymptomatic individuals in primary care for AF is controversial due to concerns about healthcare utilization and costs.[2] However, there is increased attention towards the possibility with the development of new AF monitoring tools other than the gold standard ECG.[2]

Statement of the Problem

The United States Preventive Services Task Force currently does not recommend for or against screening of AF due to lack of sufficient evidence.[3] However, the European Society of Cardiology already recommends opportunistic screening for patients older than 65.[1] The literature is mixed, and more randomized control trials are emerging due to new AF detection tools.[2] More research is require to determine whether screening for AF in primary care provides beneficial clinical outcomes compared to usual clinical practice.[2] Similarly, if screening were to be clinically beneficial, the population to be screened and method would need to be determined.[2]

Hypothesis

In patients with a CHA_2DS_2-VASc of 2 or greater who are older than 65, screening for AF in primary care will be clinically beneficial in stroke prevention and reduced mortality. Similarly, earlier detection of AF will reduce the incidence of AF sequelae such as heart failure and stroke.

Objectives and specific aims

Based on the gaps in literature cited by the United State Preventive Services Task Force, the purpose of this study is to add to the growing literature regarding the possible clinical benefits or drawbacks of AF screening in primary care. The study will be a randomized

controlled trial that follows patients screened for AF by a 30-day event monitor compared to a matched group of controls who receive routine care. Both groups will have a CHA_2DS_2-VASc of 2 or greater who are older than 65. Specific aims of the study include:

- Determining the incidence of new diagnosed AF in the control group compared to the intervention screening group
- Determining the percentage of new AF diagnoses started on oral anticoagulation
- Monitoring each group for five years and record hospitalizations for AF sequelae and associated conditions such as stroke, TIA, AF exacerbation, or heart failure

REVIEW OF THE LITERATURE

Overview

AF is considered an epidemic in the United States.[2] The overall prevalence of this atrial arrythmia is about 1-2% of the population, or 3-6 million people in the United States.[4] By 2050, the numbers are estimated to reach about 6-16 million.[4] The overall burden of the arrhythmia is significantly underestimated however, because 30% of AF cases are asymptomatic.[4] Additionally, 130,000 people die due to AF yearly, with 750,000 hospitalizations having been attributed to AF and 15% of all strokes can be attributed to AF as the source of the emboli.[4] A higher incidence of AF is reported in males in North American and European populations.[5] Although historical data is lacking in the racial differences, recent data has suggested that there is a higher prevalence of AF in white compared to black individuals.[5]

Many of the risk factors for AF are modifiable as they are lifestyle related.[6] High baseline cardiovascular fitness has been associated with a 6-fold greater AF free survival in comparison to those with lower baseline fitness levels.[6] Similarly, improvement in cardiovascular fitness is correlated with a lower rate of AF recurrence.[6] Some independent risk factors include diseases such as coronary artery disease, congestive heart failure, diabetes mellitus, hyperlipidemia and hypertension, although age is recognized as the most prominent risk factor for development of AF.[6] Obesity plays a role in structural and electrical remodeling through left ventricular hypertrophy, increased

left atrial volume and fibrosis, and reduced left atrial conduction velocity.[6] Obstructive sleep apnea causes a negative intrathoracic pressure which leads to increased blood pressure, increased activity of the ganglionic plexus and reduced refractory period of the left atria.[6]

Understanding the risk factors for AF is crucial for the future prevention and management of the arrhythmia.[6] AF can be classified as paroxysmal, persistent, or permanent.[7] If AF lasts less than 7 days it is considered paroxysmal, and any longer period is considered persistent AF.[7] When the duration is longer than 12 months, it is classified as permanent AF.[7] The defining features of AF include absence of P waves on an ECG, irregular R-R intervals, and dysregulated electrical activity of the atria.[8] The two primary mechanisms in which the arrhythmia arises are reentry circuits and focal ectopic activity.[6] Increased left atrial pressure and size due to irregular activity leads to connective tissue damage and interstitial fibrosis.[8] The condition is a product of many pathological pathways, and the causes are multifactorial, making it difficult to pinpoint a single mechanism as the cause.[8]

The initiation of AF is often due to focal "triggers".[8] These triggers are characterized by atrial myocytes that spread to the pulmonary veins.[8] If there are transient tachycardias from the pulmonary veins, the refractory period of the atrial electrical circuit is decreased.[8] The "multiple wavelet hypothesis" is a major theory in how AF persists once it has been initiated.[8] This theory suggests that there are multiple reentrant waves that perpetuate the arrhythmia.[8] However, another competing theory suggests that the persistence can be attributed to the ganglionic plexi.[8] The ganglionic plexi is a group of

autonomic tissue that this theory proposes is a collection of focal dysregulated electrical activity.[8] When AF is paroxysmal, it is often attributed to focal triggers while persistent AF is due to a more complicated pathogenesis because of more severe atrial electrical remodeling, making persistent AF more difficult to treat.[8] When the myocytes are more frequently depolarized in the atria, the chambers try to compensate by downregulating the L-type calcium channels.[8] This causes the action potential to shorten, reducing the refractory period of the atria and CRP levels are higher in patients with persistent AF than paroxysmal.[8] CRP levels are higher in patients who relapse after cardioversion, showing that inflammation plays a role in progression of the arrhythmia.[8] Increased CRP also reflects an increased risk of an embolic event.[8]

A high clinical index for suspicion of AF is crucial to its diagnosis.[9] Patients with symptoms of an arrhythmia, such as shortness of breath, dizziness or syncope, chest tightness or discomfort, should have an EKG performed and wear a cardiac monitor for further work up.[9] Similarly, patients who present with a transient ischemic attack or stroke should be monitored for AF as the source of the clot.[9] The "gold standard" for AF diagnosis is the ECG, which will show an irregularly irregular rhythm with an absence of discernable P waves.[9] Patients who do not have AF detected on an ECG should use a 24-hour ambulatory ECG monitor if there is suspicion of asymptomatic episodes or if there are symptomatic episodes that are less than 24 hours apart.[9] If episodes are greater than 24 hours apart, another event recorder, other portable ECG technology, or ECG monitoring longer than 24 hours is recommended.[9]

The three main components for treatment of AF are rate control, rhythm control and stroke prevention.[10] Atrioventricular nodal blockers are important for reducing the rate of the ventricular rhythm.[10] The first line therapy are beta-blockers and non-dihydropyridine calcium channel blockers, namely verapamil and diltiazem.[10] A resting heart rate of 80 is the typical target for beta blockers, but the goal can be higher depending on the degree of symptoms and ventricular function.[10] If rate control is not adequate with a beta-blocker, a calcium channel blocker may be added.[10] In patients with heart failure, a low dose of digoxin may be added to improve ventricular rate.[10]

Patients may also need a detailed assessment of cardiac function through a transthoracic echocardiography if their long-term management would be affected by the results.[9] Similarly, a rhythm control strategy such as a pharmacologic or electric cardioversion may be considered for patients who need acute rhythm control.[9] If there is a suspicion of heart failure or a heart murmur, a patient may benefit from a TTE to detect a problem with cardiac structure.[9] To aid in determining the cause of AF, patients should have a complete blood count, electrolytes, thyroid function, and renal function evaluated.[11]

The major sequela of this arrhythmia is embolism, so the risk of and consequently bleeding risk, must be identified for each individual patient with diagnosed paroxysmal, persistent, or permanent AF must be identified.[9] The major predictor for stroke risk is the CHA_2DS_2-VASc that categorizes age, sex, history of CHF, hypertension, stroke/TIA/thromboembolism, vascular disease and diabetes into a point system.[9] The numeric score can then be used to identify a need for anticoagulation.[9] For bleeding risk,

it is recommended to monitor and modify risk factors that increase chances for bleeding such as uncontrolled hypertension, poor control of INR and alcohol consumption.[9] The assessment of stroke and bleeding risk must then be applied to individual comorbidities and the patient's preferences for their own anticoagulation.[9] For most patients, the benefit of anticoagulation in preventing of stroke far outweighs the risk of bleeding.[9]

Stroke risk, as determined by the CHA_2DS_2-VASc score ,and subsequent anticoagulation is crucial to AF treatment and reduction of mortality.[10] Anticoagulation is indicated in individuals who have greater than a 2.2% stroke risk per year, as defined by having at least two risk factors.[10] However, anticoagulation should also be considered in patients who have one risk factor other than female sex.[10] Antiplatelet therapy by itself is not adequate treatment for stroke prevention in AF patients.[10] Direct oral anticoagulation options include the factor Xa inhibitors apixaban and rivaroxaban, and the direct thrombin inhibitor dabigatran.[11] With long term warfarin therapy, patients with an estimated stroke risk of 4.0% per year decreased to 1.4%, however randomized trials have affirmed that direct oral anticoagulants are not inferior to long term warfarin.[10] In a meta-analysis, the risk of embolic events was 11% lower in the direct oral anticoagulation group compared to warfarin with lower risks for major bleeding and intracranial hemorrhage.[10] However, for patients with mitral stenosis or mechanical heart valves, warfarin is still recommended.[10]

There are many comorbidities that interplay with the progression of AF, some that cause progression and others that are a sequela of the arrhythmia.[4] These comorbidities include heart failure, stroke, chronic kidney disease, venous thromboembolism, and

dementia.[4] There is a large interdependence between AF and these comorbidities and establishing a direct causal relationship is difficult.[4] For heart failure, the main pathologic mechanism is left atrial remodeling and the upregulation of the reticular activating system which can contribute to the progression of AF.[4] Heart failure eventually manifests in 50% of patients in AF.[4] Some of the clinical consequences of AF that can lead to HF include irregular heart rhythm, a shorter diastole and a lower cardiac output.[4] Figure 1 demonstrates how risk factors and comorbidities lead to cardiac sequelae.

Myocardial infarctions can lead to AF through left ventricular dysfunction and hypertrophy. Conversely, AF can cause an MI through a coronary thromboembolism, accounting for 3% of all MI cases.[4] A major adverse prognosis for AF is co-occurrence with chronic kidney disease.[4] The reticular activating system plays a major role in progression of both conditions.[4] AF may contribute to kidney disease through lower cardiac output, leading to increased RAS activation.[4] Renal failure is also a significant risk factor for stroke risk.[4] AF results in a 4-5-fold increased stroke risk, which is significant considering the burden of AF.[4] There is also a clinical correlation between AF and dementia with AF as the predisposition.[4] AF is associated with cognitive impairment at a younger age and a 30% increased risk of dementia overall.[4]

AF is a major cause of disease in the US and has been recently described as an epidemic.[12] It affects quality of life and has substantial effects on morbidity and mortality as well as on the economic burden of the healthcare system.[12] The cost to the United States healthcare system annually is $6-26 billion-with 50-70% of those costs attributable to hospitalizations.[12] Most of the increased cost of AF is due to hospitalization, stroke,

and heart failure care.[8] AF is a chronic disease and requires long term outpatient management.[12] Many individuals with AF (20%) do not have adequate stroke prophylaxis, which is a major cause for concern as stroke is a major cause of disability.[12] One-fifth of patients who suffered from a stroke due to AF had AF diagnosed after the event.[3] Undiagnosed AF is associated with 3.8%-6.1% of all strokes.[13] Screening measures may alleviate the cost by preventing sequelae that lead to hospitalization, which accounts for most healthcare costs related to atrial fibrillation.[12] Additionally, those with asymptomatic AF have been shown to be a greater risk for stroke than those with symptoms.[14] Stroke is the third leading cause of global disease burden.[13] With the high burden of disease and the importance of stroke prevention, there is an argument for screening for undiagnosed AF.[13]

There are a wide range of potential device modalities for screening for AF that involve either continuous or intermittent monitoring.[15] The main methods, those that have persisted in standard of care the longest include manual pulse palpation and 12 lead ECG.[15] With new technologic advancements, several different screening devices have been evaluated for continuous arrhythmia detection.[15] Some of these devices have very high sensitivities such as patches or implantable monitors, but require longer recording times and are typically more expensive than the usual modalities.[15] Non-invasive devices have been developed to detect irregular rhythms while oscillating blood pressure.[15] These methods are practical in that they can be performed at a primary care visit and do not require patient at home participation.[15] Advancements in smartphones have made it possible for patients to have watches that perform photoplethysmography, and more

recently, a single lead ECG.[15] Choosing the correct modality involves balancing costs, convenience, and risk of AF for the individual patient.[15]

The American Heart Association recommends finding a way to detect AF more effectively in a way that is cost beneficial.[13] Superior sensitivity may come at the cost of time and resources.[15] One point ECG testing or opportunistic screening by pulse detection is cheaper, but many cases of paroxysmal AF can be missed if the patient is not currently in the rhythm at the time of screening.[16] Holter monitoring or continuous ECGs are more expensive but will have a higher detection rate.[16] The benefits of different types of screening tests must be weighed against the cost effectiveness.[16] For patients who are at higher risk for AF, more intermittent monitoring may be a better screening measurement for diagnostic yield than patients who are at lower risk.[15]

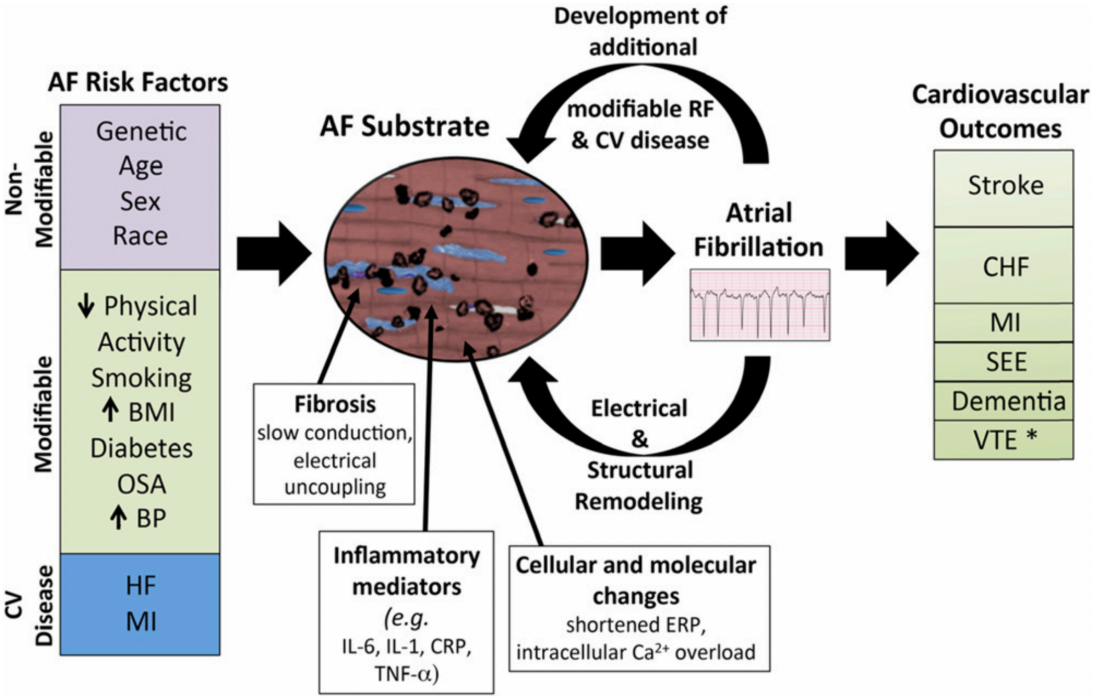

Figure 1:Risk Factors for Atrial Fibrillation (adapted from Staerk, et al, 2017)[5]

Existing Research

Potential Screening Tools

Several studies looked at the accuracy of different types of screening tools. A study by *Himmelreich et al* compared a smartphone single lead electrocardiography test and compared it to the sensitivity and specificity of the gold standard 12 lead ECG in a one-time screening.[17] The study recruited patients who underwent 12 lead ECG for an indication that was not due to an acute episode of symptoms.[17] Patients (N=214) were included from 10 Dutch practices.[17] Patients held the smartphone tool while a

cardiologist simultaneously performed and analyzed the ECG.[17] The smartphone tool had a sensitivity and sensitivity of 87% and a specificity of 97.9%, while the cardiologist reading the electrocardiogram had 100% sensitivity and specificity in detection of AF. [17] This tool proves that it can be clinically useful in primary care for immediately detecting episodes of AF.[17]

Although one time screening tests may be more feasible than continuous monitoring, there are studies that suggest that many diagnoses of paroxysmal AF may be missed for patients who are at high risk.[18] A prospective multicenter study by *Reiffel at al* examined the incidence of AF detected by implantable monitors.[18] The study was very generalizable as it included over 57 centers across Europe and the United States.[18] The recruited patients had a CHA_2DS_2-VASc score of 3 or greater and had no diagnosed AF.[18] The patients were then monitored with an implantable cardiac monitor.[18] About one-third of patients (29.3%) had an episode of AF lasting longer than 6 minutes at 18 months, and at 30 months, the incidence increased to 40%.[18] Over half (56%) of the patients were prescribed oral anticoagulation.[18] The study is limited in that it does not compare those that had AF detected by the implanted device compared to usual care, however, it does show the high incidence and yield of AF diagnosis amongst those patients who are at risk.[18] The type of screening test used for AF must be balanced between feasibility and economic resources with the diagnostic yield and clinical implications.[18]

The cost effectiveness of screening depends on the method of AF detection used.[16] One point ECG testing or opportunistic screening by pulse detection is cheaper,

but many cases of paroxysmal AF can be missed if the patient is not currently in the rhythm at the time of screening.[16] Holter monitoring or continuous ECGs are more expensive but will have a higher detection rate, so the benefits of different types of screening tests must be weighed against the cost effectiveness.[16]

Yield Of Atrial Fibrillation Diagnosis through Screening

The REHEARSE-AF study by *Halcox et al* (2017) was a randomized control trial that used an iPod attached Kardia monitor which was able to obtain ECGs and compared the new detection of AF to usual care.[14] Unique to this study was a CHA_2DS_2-VASc score greater than or equal to two was required for the patients to participate.[14] Patients (N=500) from the UK were assigned to the Kardia Monitor, while 501 were assigned to usual care.[14] The study was 12 months long and required the monitoring group to submit twice-weekly EKGs.[14] They found that 19 patients in the Kardia Monitor group were diagnosed with new AF compared to 5 in the routine care group.[14] Nearly half (42%) of the Kardia Monitor patients did not have symptoms when they were diagnosed with AF.[14] Over half (53%) of patients with newly detected AF patients were started on oral anticoagulation, which the study estimated that would result in a net economic benefit.[14] However, future studies are needed to fully determine the morbidity and cost benefits of starting oral anticoagulation in patients who were previously diagnosed with AF.[14]

The SCREEN-AF study was a randomized clinical trial performed by *Gladstone et al (2021)* evaluated if screening in older participants would detect a high rate of AF

and lead to anticoagulation for most patients.[2] The inclusion criteria required the patient to be older than 75 with a diagnosis of hypertension. Patients (N=856) were recruited from 48 different practices.[2] The control group received usual care while the intervention group underwent 2-week continuous ECG monitoring.[2] AF was detected in 5.3% in the screening group and only 0.5% of the control group.[2] The mean detected time in AF was 6.3 hours in the screening group. Anticoagulation was subsequently initiated in 75% of the group whose AF was detected by continuous ECG.[2] AF was asymptomatic in 85% of the screened group.[2] This study showed the advantages of continuous ambulatory monitoring in detecting subclinical AF.[2] Limitations of the study include the lack of cost effective analysis, as well as concern regarding overdiagnosis and overtreatment of AF for lower risk patients.[2] The study recognized that more trials will be needed to evaluate stroke prevention in these patients.[2]

The mSToPS trial by *Steinhubl et al (2018)* used a randomized control trial and prospective matched observational cohort study to evaluate whether ECG patch monitoring detected more AF than usual care.[19] Patients were randomized to either home monitoring that started immediately or to delayed monitoring that began four months later.[20] The study consisted of 1,738 actively monitored individuals.[20] The primary endpoint was newly detected AF at onset versus delayed monitoring.[20] Monitored patients underwent two weeks of continuous patch monitoring.[20] New AF was identified in 3.9% of the immediately screened group in four months and 0.9% in the delayed monitoring group. Active monitoring also increased initiation of anticoagulation in the actively monitored group.[20] A limitation of this study is that only 2.6% of eligible

individuals were successfully enrolled- and, of those enrolled, 38% ended up deciding to discontinue their participation, which significantly decreased the sample size.[20]

Morbidity and Mortality after Screen Detected Atrial Fibrillation

The STROKESTOP study was an unmasked, randomized control trial performed in Halland and Stockholm, Sweden.[21] All 75- and 76-year-olds in a particular region were randomized 1:1 in an intervention and a control group.[21] One group underwent screening for AF while the other was a control group.[21] There were no exclusion criteria.[21] Patients in the intervention group were instructed to perform an initial index ECG, and if the index ECG did not reveal AF, they recorded twice daily ECGs for two weeks.[21] The primary initial endpoint was stroke, but after new data revealed that treatment with direct oral anticoagulants lowered mortality in patients with AF, the primary endpoint was changed to include all-cause mortality as well.[21] Additional primary endpoints include ischemic or hemorrhagic stroke, systemic embolism, and all cause death.[21] There were 7,165 participants in the screening group and 14,382 in the control group.[21]

They estimated that the annual risk of stroke in untreated patients with AF was 7% and the protective effect of anticoagulants would be 70%.[21] According to these estimates, the risk of AF in the population treated with anticoagulants would be reduced to 2%.[21] The study revealed that 5.1% of the population in the intervention group had AF undiagnosed prior to the initiation of the study, increasing the prevalence of AF by 33%.[21] After a 5.9 year follow up, significantly fewer endpoints occurred in the intervention group that was screened compared to the control group.[21]

A study by Oguz *et al* performed in the US compared the costs of one-time systematic screening and continuous systematic screening to no screening for asymptomatic AF in patients 75 or older.[22] They used a hypothetical population of 10,000 patients with epidemiologic and effectiveness data from the STROKESTOP study and stroke events and other clinical outcomes from the ARISTOTLE study.[22] Both screening tests (one time screening and continuous ECG monitoring) led to lower morbidity compared to the group that was not screened and increased the number of quality adjusted life years, 9.8 ischemic strokes were avoided in the groups that received single ECGs and 42.2 ischemic strokes were avoided in the group that used the handheld ECG monitor.[22] One limitation of this study is that in estimation of stroke risk, continuous ECG monitoring may detect patients with AF at a lower burden (paroxysmal vs persistent) which may underestimate the stroke risk compared to patients who have AF detected by a one-time ECG.[22] This may imply that the stroke risk of the patients in this study may be underestimated.[22]

A study by *Waalen et al (2021)* tracked healthcare resource use after AF was detected by screening and compared that to healthcare utilization following usual care.[20] The screened population was asymptomatic and at moderate risk.[20] The patients (N=1718) were tracked with an ECG sensor twice a week over the course of four months, were matched with 3,371 patients by age, sex, CHA_2DS_2-VASc score, and by health plan.[20] The group that was actively screened with an ECG patch and found to have newly diagnosed AF had lower rates of Emergency Department visits by a mean of four visits per month compared to the control group that was diagnosed with AF by routine care.[20]

The rate of outpatient cardiology visits did increase in the actively monitored group, with most of the visits being AF related.[20] This could be beneficial in terms of cost effectiveness due to the switch of AF management from overnight hospital stays to outpatient settings.[20]

A potential concern of increased AF detection is increase in invasive procedures, however, they found that the rates of ablation and cardioversion were similar between the controls and actively monitored.[20] Among those who had newly diagnosed AF by the ECG patch compared to a clinical diagnosis, there were lower rates of hospitalizations for AF, atrial flutter, strokes, transient ischemic attacks, congestive heart failure, and angina pectoris.[20] In the patients who were diagnosed with AF by usual diagnostic care, most hospitalizations occurred within one month of their diagnosis.[20] 126.6% of those patients endured a stroke, 10.2% were diagnosed with heart failure, 9.2% had a myocardial infarction, and 42.9% were hospitalized compared to no strokes, transient ischemic attacks, and only one diagnosis of heart failure within four months of the patients who were actively monitored.[20]

While this study provides evidence to refute the concern that AF screening could lead to more healthcare utilization, there are some limitations.[20] Because the monitored group had to actively attempt to understand the important effects of the study, the monitored group may be limited to those who are more actively engaged with their health.[20] The most common diagnoses within 5 years of AF detection clinically are heart failure, stroke and death, which are all sequelae of AF.[20] However, more research is

needed in the benefits of early AF detection in the prevention of these cardiac and cardioembolic sequelae.[20]

Cost Effectiveness

A study in the Netherlands by *Jacobs et al* evaluated the cost effectiveness of one-time screening with a handheld ECG device for patients older than 65 at their annual influenza vaccination.[23] The study chose to use seasonal flu vaccination because those who are recommended to get vaccinated above the age of 65 likely have cardiovascular comorbidities that are also risk factors for AF.[23] Silent AF was newly diagnosed in 1.3% of individuals which was clinically significant, with all the patients requiring the initiation of oral anticoagulation.[23] The study included a model based on cost analysis factors such as: cost of the handheld ECG device, primary care resource and provider costs, as well as false positive results.[23] They also included the cost of oral coagulation for apixaban, dabigatran and rivaroxaban.[23] Effects of a new diagnosed AF case by screening and the subsequent costs were analyzed using a decision analytic model.[23] They found that screening for AF in the Netherlands at their seasonal flu influenza vaccination would decrease costs by 796 USD.[23] One major limitation of the study is that to estimate probability of stroke events they used three studies that had a short follow up, in which they then used to extend over a lifetime model.[23] Similarly, the patients in the clinical trials may not have the same baseline characteristics as the population to be screened.[23] For example, the patients in the clinical trials had a younger baseline age than

the patients who were screened for AF while getting the influenza vaccine, but the same stroke event predictors were used for the same population.[23]

To analyze cost effectiveness of screening for AF in a primary care setting, *Ghazal et al* performed a retrospective cohort study based on a cross sectional study at one primary care center in Sweden.[16] The results showed that there was a EUR 2389/quality adjusted life years gained in the screening group compared to the group that was not screened.[16] Adherence to oral coagulation was 92% for patients who were candidates.[16] Mortality did not differ between the group who was diagnosed with AF by screening compared to the group who did not have AF detected by a handheld ECG device.[16] Screening at this primary care center showed a 99% probability of being cost effective, at a willingness to pay of EUR 20,000 per QALY.[16] A limitation is that the sample size was smaller, and the study was based on only one primary care center in Sweden which makes it less generalizable.[16]

The study by *Oguz et al* analyzed cost effectiveness of one-time electrocardiogram screening compared to the handheld ECG device.[22] Screening was cost effective at a willingness to pay of $58,728 for each QALY for the one-time ECG and $47, 949 for each QALY for the handheld ECG device, which was determined to be cost-effective at that willingness to pay.[22] Similar to the *Ghazal et al* study, the patients in the two referenced randomized trials may not reflect the demographics of the total population.[22]

In summary, screening for AF requires many variables to be addressed to create the greatest net benefit. The type of device, the burden of AF detected that requires

anticoagulation and a cost benefit analysis must be investigated. The literature demonstrated that continuous monitoring would detect more AF than one time screening electrocardiograms. Additionally, in patients who had AF detected by screening mechanisms, there were lower rates of hospitalizations for AF, stroke, atrial flutter, and transient ischemic attacks. Several cost benefit analyses have shown that there may be a cost benefit to screening for the healthcare system as it prevents future hospitalizations.

METHODS

Study design

The proposed study will be a randomized controlled trial with an associated observation to evaluate for the incidence of stroke in a usual care group compared to a group that was screened for atrial fibrillation using a 30-day event monitor. The observational cohort component will involve patients being followed through EMR for stroke and primary endpoints. For one month, participants in the intervention group will undergo continuous cardiac monitoring. The analysis of the ECG recordings will be provided to the patient's general practitioner. If atrial fibrillation is detected on the ECG recordings, the primary care provider will weigh the risks and benefits of initiating oral anticoagulation on the patient. Primary and secondary endpoints will then be analyzed using electronic medical records for five years after the trial starts. The primary endpoint is ischemic stroke. Secondary endpoints will include other cardiovascular events or death.

Study population and sampling

The study population will include patients older than 65 from the New England area without an established diagnosis of atrial fibrillation and a CHA_2DS_2-VASc score greater than 2. The participants will be randomly allocated through an interactive web system to two groups, either to be screened or to a parallel group that participates in usual primary care. The inclusion criteria include established patients in a primary care practice who are

willing and able to participate in the study and consent for assessing their electronic medical record for data about the study's end points. Exclusion criteria includes patients who already have a diagnosis of AF, patients who are already on anticoagulation, patients for whom anticoagulation is contraindicated (severe renal impairment, bleeding disorder or history of severe bleed), presence of implanted cardiac devices, as well as any condition that impedes their ability to wear a patch for 30 days.[24] The goal sample size will be 9,746 using an 80% power and an alpha of 0.05 for a moderate effect of 0.3-0.5.[25]

Study Variables

The main objective is to determine if intermittent AF screening will lead to decreased rates of ischemic or hemorrhagic stroke risk due to the initiation of anticoagulation compared to a patient population who did not undergo any screening. AF will be defined as a 30 second contiguous recording of an irregular rhythm without p waves.[21] Additional variables needed for this analysis include the number of patients who were found to be in AF through both routine care and screening, the number of patients who were initiated on anticoagulation, and the number of patients who suffered from a stroke in the follow up. Follow up records regarding stroke incidence will be collected through the patient's EMR, so after four weeks of wearing the cardiac monitor no further follow up from the patient will be necessary. Stroke is designated as the primary endpoint because this is the disability that screening for atrial fibrillation aims to prevent. The definition of stroke required for the study is either a transient or persistent vascular injury of the nervous system that causes a neurologic deficit. Strokes that are atherosclerotic in nature and not

embolic will not be included in the study. Secondary endpoints will include transient ischemic attacks, heart failure exacerbations, cardiovascular death, and all cause death.[24]

Data Collection and Recruitment

The study will recruit primarily by email for logistical convenience of both the patient and the general practitioner. The practice will send out approximately 15,000 patients an invitation to participate from both rural and primary care offices in New England. The invitation will include an information pamphlet and a consent form that they can fill out online. Half the patients will be in the intervention arm and half will be in a control group who will not require an at home cardiac monitor. The intervention arm will receive a video and written tutorial on how to use the cardiac monitor with an optional telephone line of support during business hours if needed. A phone call with one of the investigators will then facilitate delivery of the advice and answer any outstanding questions from the patient. The patient will then wear the monitor for one month and then subsequently returned by mail to the research coordinators. The ECG recordings will then be sent to the patient's primary care provider. The study does not have specific guidelines on who should be started on anticoagulation based on the ECG findings. The initiation of anticoagulation for newly diagnosed AF found through screening should be a discussion with their primary care provider based on the individual patient's comorbidities and CHA_2DS_2-VASc score.

Data Analysis

Incidences of stroke that meets the study criteria and requires hospitalizations will be collected after five years. Primary analysis of strokes will be further subdivided into the following subgroups: Age >75 versus younger, gender, race, body mass index, heart failure, hypertension, atherosclerotic disease, and diabetes. To analyze the data endpoints, a risk ratio will be calculated between the exposure and control group. A Kaplan Meier survival curve will be generated to evaluate time to first stroke between the population of patients that have been screened versus the patients who received usual care. A cox regression analysis will be used to evaluate primary endpoints.[14]

Timeline and Resources

Pending approval from the IRB, the study will begin in 2024 until conclusion of the five year follow up. The general practitioners in the primary care offices that include the patients that are participating in the study will need to be aware of the study protocol and be prepared to initiate anticoagulation in patients whose atrial fibrillation is discovered upon screening. Research coordinators will be required to identify the eligible participants and be available for phone call consultations regarding use of the device and any potential questions that the patients may have regarding the use of the device. The tutorial videos with instructions will be constructed by research assistants prior to the start of the study. Heart monitor results will be reviewed by the patient's primary care provider. The patient and the primary care provider will then make an informed decision

regarding initiation of anticoagulation. Following the completion of the heart monitor data collection, research assistants will sequentially follow the patient's chart periodically for five years, identifying and recording any hospital admissions for stroke, transient ischemic attack, heart failure exacerbations, cardiovascular events, or death. The only materials required for the study are the heart monitors that will be provided to each participant.

Institutional Review Board

The comprised study will include the use of human subjects. Consequently, the study protocol will be submitted for expedited IRB approval to the Boston University Medical Campus IRB.

CONCLUSION

Discussion

The continuing discussion regarding the role of AF screening is becoming increasingly prevalent as the disease burden continues to increase. More studies like this are crucial to assess the benefits and potential difficulties in screening for AF. The study does contain some weaknesses that are crucial to address. First, it requires a larger sample size that may be difficult to recruit. The study will aim for a larger sample size as many patients will be lost in the five year follow up due to switching of practices. The population must be over the age of 65 and have a CHA_2DS_2-VASc score greater than 2. This study is catered to patients who actively participate regularly with their primary care provider. This may require that the patients who choose to participate are more engaged in their healthcare at baseline, which will create a sample that is more likely to be adherent to anticoagulation and screening tools which show a reduction in adverse primary outcomes that is not representative of a random population. While this study may reveal that screening will result in AF, it may not demonstrate that screening for AF results in decreased stroke prevention compared to the control group. Regardless, it is important to determine if screening for AF reduces morbidity, given lack of existing research.

Summary

AF is a large and increasing burden on the United States healthcare system.[26] This arrhythmia is often subclinical, existing asymptomatically while causing permanent damage and changes to the structure of the heart.[26] The changes in heart structure lead to

enlarged atria that cause blood to pool in the chambers, increasing risk for an embolism.[26] Not only does the disease increase morbidity, but the sequelae of the disease also cause a significant economic burden on the healthcare system. For example, 30-50% of patients who are diagnosed with AF either die or are hospitalized within five years of diagnosis.[27] Earlier detection of the arrhythmia could dramatically change the course of the disease through rate control and stroke prevention with anticoagulation. One study by *Healey et al (2020)* found that patients with AF have an attributable 13% risk of ischemic stroke.[28] Screening in the United States is currently not recommended because there are not enough studies to demonstrate a decreased stroke risk through identifying previously undiagnosed AF.[3] However, Europe is more progressive than the United States in the movement for screening.

The main knowledge gap that this study will aim to address is whether screening will result in a decreased risk of stroke through diagnosing previously unknown AF. This study will differ from most of the existing research in that it will track stroke and other causes of morbidity and mortality in both the intervention and control group. While the study will aim to fill that gap in literature, further research will be necessary to identify the most ideal population to screen and the ideal screening device to capture AF. For example, in some elderly patients the risk of bleeding with anticoagulation may outweigh the benefits. The study will reveal what degree AF burden will benefit from anticoagulation. Knowing the degree of AF burden and stroke risk will be crucial clinically if screening becomes an intervention in the future, as the risk of stroke is dependent on the frequency of the arrythmia.

Clinical and/or Public Health Significance

With the trending AF epidemic in the United States, screening the appropriate population for AF could prevent stroke and other cardiac sequelae. Over half of AF patients over the age of 75 who are not anticoagulated would benefit from anticoagulation.[29] AF not only contributes to cardiac functional decline, but cryptogenic and ischemic strokes can lead to cognitive decline.[30] The overall aging of the population will continue to make AF a growing clinical concern for both patients and providers.[30] The incidence of AF has doubled from 1990 to 2017.[31] Additionally, it is approximated that 16 million people in the United States will have AF by 2050.[32] The growth of the disease necessitates further investigation into the risks and benefits of screening.

Despite the significant prevalence, AF is not a well understood or acknowledged disease compared to other conditions that are already commonly screened for. Increased awareness of the arrythmia may create a movement towards education on prevention of risk factors. Reducing the prevalence of AF is slowed not because of lack of treatment but rather due to increase in modifiable risk factors.[33] Patients may not fully understand the benefits as AF can be asymptomatic or mildly symptomatic, but with proper education that may become motivated to prevent disease progression.

With increased awareness of symptoms, patients may be more compelled to be seen by their healthcare provider for palpitations, lightheadedness, or other symptoms of AF that they may have ignored previously. The goal in understanding early detecting of AF is to prevent cardiac sequelae that will lead to increased hospitalizations and overall mortality. While this study aimed to focus on screening for a disease, it is crucial to

emphasize the importance of prevention of cardiac disease. Ideally, future emphasis in cardiac disease will rely heavily on prevention of risk factors. Lifestyle education programs in primary care on nutrition, exercise and smoking and drinking cessation could further reduce the prevalence of hypertension and obesity which are the main risk factors for AF and other cardiac disease.

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