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Routine Screening for Silent Atrial Fibrillation

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Routine Screening for Silent Atrial Fibrillation

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III. Abstract

Atrial fibrillation (AF) is the most common arrhythmia and is particularly prevalent in the elderly population. It is associated with an elevated stroke risk which can be easily minimized with anticoagulation. However, AF detection is often difficult due to infrequent or absent symptoms and the first presentation of AF may be a stroke. Advances in technology have made screening for AF more feasible and accessible. Opportunistic screening with pulse palpation and confirmatory ECG is now strongly supported by the evidence and more recent studies have demonstrated that systematic screening – particularly of those with AF risk factors – may be cost effective.

A systematic review was conducted of the literature pertaining to AF screening guidelines and AF detection methods, including pulse palpation, 12-lead ECG, Holter monitors, wearable loop recorders, patch monitors (e.g. Zio patch), ambulatory telemetry, implantable cardiac monitors, single-lead mobile ECG devices, advanced blood pressure monitors, and smartphone photoplethysmography. The best options for screening were discussed and a screening program was proposed. Additional goals and concerns relevant to the future of AF screening were noted.

IV. Introduction

Atrial fibrillation (AF) is the most common arrhythmia with an estimated prevalence around 2-3% in the general population.[1,2] This already high prevalence increases with age; roughly 9% of people over 65 and 15% of those over 85 have some form of AF.[3,1] Furthermore, with the population becoming older the prevalence of AF is expected to double over the next ~30 years.[1] One in four people over age 40 can expect to develop AF at some point in their life.[4]

Atrial fibrillation can represent a major medical issue in and of itself due to the symptoms it often causes (e.g. palpitations, fatigue, lightheadedness, shortness of breath) which can range in severity from concerning to debilitating.[2,3] However, the primary concern associated with AF is sequelae such as heart failure, tachy-brady syndrome, and thromboembolism (i.e. stroke). It is believed that AF-related stroke occurs largely because of poor blood flow through the left atrium which causes blood to stagnate and clot. However, studies have shown that even brief episodes of AF can cause lasting hypercoagulability due to endothelial dysfunction and increased platelet activation that facilitate thromboembolism without any recent AF.[4,5] Having AF makes a person 4 to 5 times more likely to suffer a stroke and these AF-related strokes are often more severe (both in morbidity and mortality) than strokes of other etiologies.[3] It is also worth noting that this increased risk occurs in patients with both high and low burdens of AF. Research continues to look for a threshold burden of AF under which a patient can safely forgo treatment, but the literature at present suggests a similar stroke risk for patients with paroxysmal AF (which starts/stops spontaneously and lasts <7 days) and persistent AF (which lasts >7 days or only resolves with cardioversion).[5,2]

Unfortunately, symptoms are an inadequate method for detecting AF. None of the previously mentioned AF symptoms are specific to the condition. Moreover, AF patients can

have asymptomatic episodes despite a history of symptomatic AF and at other times experience symptoms while in documented sinus rhythm.[7] Roughly one third of patients with AF never develop any such symptoms (silent AF).[8] In fact, a stroke is the first sign of AF in more than 25% of patients who have an AF-related stroke.[9]

Once AF is detected, however, oral anticoagulants (OAC's) such as warfarin or novel anticoagulants (NOAC) have been shown to reduce stroke risk by two thirds and there are clear guidelines for anticoagulant usage (CHA2DS2–VASc score - Table 1).[10] Since AF-related strokes constitute 13 - 17% of all strokes (15 - 20% of all ischemic strokes) this treatment represents a simple way to reduce morbidity and mortality.[11,3] Estimates suggest that 750,000 hospitalizations and 130,000 deaths occur each year due to AF.[3] Better detection and management of AF could also reduce costs - a 2011 study found that AF directly contributes to at least $6.0 billion in healthcare costs and up to $26.0 billion indirectly.[12]

These characteristics make AF a good condition for which to screen according to the World Health Organization's guidelines (Table 2). Until recently, however, there were relatively few options for atrial fibrillation screening (pulse palpation, 12-lead ECG, Holter monitors, and event monitors) and only opportunistic screening (pulse palpation with follow-up ECG if irregular) was found to be cost-effective.[13] Advances in technology over the last several years may have changed this by introducing inexpensive yet sophisticated options, such as simplified mobile-ECG's, smartphone apps and BP cuffs capable of detecting AF, and improved long-term monitoring devices (patches and subcutaneous monitors). These refined methods may bring about cost effective programs to systematically screen for AF in moderate/high risk populations.[6]

<center>V. Background</center>

A. Guidelines

Currently, there are few recommendations from major cardiology organization guidelines which advocate AF screening.

1. European Society of Cardiology

The European Society of Cardiology (ESC) 2016 guidelines most directly address the issue.[14] Their guidelines state that opportunistic screening of AF by pulse palpation with confirmatory ECG seems cost effective and recommend doing so during regular appointments with patients over 65 years old (Class I, Level B). However, their statement on systematic screening where all patients with risk factors undergo electrocardiography only says that the literature appears promising for high risk patients (e.g. patients s/p stroke, elderly patients, etc.) and further evaluation of such programs is encouraged. They recommend systematic ECG screening be *considered* in patients over 75 or at high risk for stroke (Class IIb, Level B). Importantly, the ESC defines a diagnosis of AF as ECG documentation of "absolutely irregular RR intervals and no discernible, distinct P waves" lasting at least 30 seconds.[14] This precludes novel devices from diagnosing AF and no recommendations are made regarding their use. The ESC states these "have been validated for the detection of paroxysmal AF" and that such devices may be useful for detecting infrequent silent AF, but they conclude that further studies are needed to determine what "constitutes a mandate for therapy."[14]

2. Other Major Organizations

Guidelines from other cardiology organizations regarding AF screening are somewhat less thorough. The American Heart Association (AHA) published a statement with the American Stroke Association in 2014 about stroke prevention in women, suggesting that women over 75 undergo opportunistic screening (Class I, Level B).[15] However, they do not mention other

groups to screen and they do not describe any systematic screening nor novel methods of detection. Aside from this single recommendation, the only other statement related to AF screening by the AHA, American College of Cardiology (ACC), or Heart Rhythm Society (HRS) is in a publication regarding gaps in elderly cardiovascular care, in which they state that "Novel biomarkers or monitoring devices aimed at primary prevention or early detection of AF in the older population should be sought" given the stroke risk in subclinical AF.[16] The joint 2014 AHA/ACC/HRS guidelines for AF management make no mention whatsoever of opportunistic screening, systematic screening, or any of the novel methods for AF detection previously described.

B. Methods for Detection

There are numerous methods available for the detection of atrial fibrillation, all of which have their own advantages and disadvantages. This section will provide a discussion of the most common methods currently in use, including their sensitivities/specificities for AF detection, ease of use, practicality, estimated cost (per physicians fee schedule or device-specific sources), and other details pertinent to AF screening. The methods with the longest history of use will be described first followed by more recent developments.

1. Pulse Palpation

Pulse palpation is the simplest way to detect atrial fibrillation as no technology is required. This method can be performed in virtually any environment and can be done by healthcare providers, allied health personnel, and potentially even the patients themselves depending on their medical competence. Cooke et al. conducted a systematic review investigating pulse palpation as a method for single time-point AF screening using a standard 12-lead ECG as a reference test. They found that the pulse palpation had a high sensitivity between

91 - 100% (pooled sensitivity of 94%) when performed by a nurse.[17] However, the specificity was somewhat lower with a range of 70 - 77% (pooled specificity of 72%). It was felt this was due to the other conditions which can produce an irregular pulse such as sinus arrhythmia, atrial/ventricular ectopic beats, atrial tachycardia, and second degree heart block. They also calculated likelihood ratios and found that the pooled PLR was 3.4 and the NLR was 0.11. The team concluded that pulse palpation could be used confidently to rule out AF, but positive results would require further workup with an ECG. If we consider pulse palpation to be essentially cost free, it represents a good first step in what would need to be at least a two-step screening procedure. The majority of providers do not consistently check for irregular pulses on exam so this simple change could potentially diagnose a large number of patients with unknown AF. [6]

2. 12-Lead ECG

Some concept of atrial fibrillation had been known for hundreds of years, but its pathophysiology wasn't well understood until it was first documented on ECG over 100 years ago.[18] Because other conditions like sinus arrhythmia, atrial/ventricular ectopic beats, atrial tachycardia, and second degree heart block can cause irregular rhythms, an ECG in some form is required in order to diagnose AF. The advances in detection methods discussed in this paper have not changed that fact and a 12-lead ECG interpreted by a specialist remains the gold standard for AF diagnosis. That being said, 12-lead ECG's are often *not* interpreted by an electrophysiologist specialized in AF. The sensitivity and specificity of a 12-lead ECG varies depending on the method used for interpreting it. Taggar et al. performed a systematic review and meta-analysis comparing the accuracy of software/algorithms and healthcare professionals (general practitioners and nurses) when interpreting ECG's with AF.[19] For software, the pooled data showed a sensitivity of 89%, specificity of 99%, PLR of 96.6, and NLR of 0.11. For

healthcare professionals, the same measures were 92%, 93%, 13.9, and 0.09, respectively, with subgroup analysis showing significantly lower specificity in nurses (88% compared to 96% in GP's). This suggests that the software we use to find AF on ECG's may miss a substantial number of cases and that human interpretation can certainly improve as well.

It is also worth noting that 12-lead ECG's, while being the reference standard, are impractical in most environments other than a hospital. Clinics may have ECG machines available, staff capable of obtaining an ECG, and providers competent in evaluating that ECG, but primary clinic schedules do not often lend themselves to this process for every patient with AF risk factors. Simplified ECG's with fewer leads have been proposed which offer greater convenience, faster use, and allow patients to remain clothed while maintaining good accuracy (sensitivity ≥90%, specificity ≥94%).[20] However, these results were based on interpretation by cardiologists rather than software or other healthcare providers and this method may still be too impractical for systematic screening. Furthermore, a standard 12-lead ECG performed at a single time-point is not ideal for catching the large proportion of AF that is paroxysmal. Still, the 12-lead ECG has the greatest potential to accurately capture AF and with a cost of around $17.23 per ECG with interpretation it is also a relatively inexpensive method for doing so.[21]

The SAFE study - one of only a few large studies organized to investigate AF screening programs - compared standard patient evaluations (the control, n =4,936), opportunistic screening (pulse palpation at ordinary appointments and subsequent ECG for irregular rhythms, n = 4,933), and systematic screening (all patients completed a 12-lead ECG, n = 4,933) of UK patients ≥65 years old to determine which was most effective in detecting undiagnosed AF.[13] It was found that standard evaluations in the control group detected 47 new cases (incidence of 1.04%), the opportunistic screening group detected 31 new cases (incidence of 0.69%) plus an

additional 44 cases outside of the program (total incidence of 1.64%), and the systematic screening group detected 52 new cases (incidence of 1.1%) plus 22 cases outside the program (total incidence of 1.62%). These results showed that both opportunistic and systematic screening were more effective in detecting unknown AF than standard practice, but there was no significant difference in effectiveness between the two. Their analysis suggested that opportunistic screening would likely be cost effective with an incremental cost effectiveness ratio of £337 ($442) per case detected.[13]

3. Wearable Monitors

a. Holter Monitor

The Holter monitor (figure 1) is essentially a simplified ECG which can be worn by the patient. It was developed in the 1940's and remains widely used today.[22] Patients are typically fitted with the device and its 3-5 electrode patches in clinic before leaving their appointment. They then wear it for 24 - 48 hours while it continuously monitors and records their rhythm on 2-3 channels. Afterwards, the patient returns the device and its data is transmitted to a technician who creates a report of pertinent information for the provider to review and interpret. The benefit of Holter monitors is that they provide a wealth of detailed information comparable to a 12-lead but over a longer duration. Patients can note any episodes of symptoms in a diary for review. All of the data is reviewed to check for asymptomatic arrhythmias a patient wouldn't have mentioned. The burden of an arrhythmia can be calculated and the patient's heart rate can be evaluated. Additionally, their heart's response to medications can be closely monitored. For these reasons, Holter monitors have been treated as the standard method for ambulatory arrhythmia detection.

However, the 24-48 hour window that the Holter monitor captures may not be long enough to detect many cases of AF. One study comparing wearable cardiac monitors found that patients diagnosed with AF did not have a detectable episode until an average of 1.4 days into the monitoring period.[23] Cases of low-burden, silent AF may go undetected during Holter monitoring while cases with high burdens or symptomatic AF would likely be detected by opportunistic screening. Another disadvantage of Holter monitors is their inconvenience for the patient. Patients may have trouble using them, the device can feel awkward, and Holters sometimes interfere with a patient's lifestyle (e.g. uncomfortable at work, difficulty when exercising, unable to use device in water, etc.).   As one might expect, Holter monitors are also more expensive than a 12-lead at $92.59 for one monitoring period and its interpretation.[21] These factors make Holter monitors a good tool for further evaluation of AF but an imperfect option for AF screening.

b. Loop Recorder

Loop recorders (figure 1) are similar to Holter monitors in that they are a cardiac monitoring device with a few electrode patches which are worn by the patient.[22] However, loop recorders are worn for much longer durations, usually between 2 to 4 weeks at a time. Loop recorders are also different from Holter monitors in that they do not record every moment during the monitoring period. Instead, they keep a record of only the last few minutes and continuously delete the previous data. Portions of the monitoring period are only saved when the patient activates the monitor or - in some models - when the loop recorder's software detects an arrhythmia. This prompts the device to save the preceding ~60 seconds as well as the next ~60 seconds. The device is able to store between 10 and 20 minutes of data at a time which can be transmitted for review over a phone line.[22]

Loop recorders have a better monitoring duration than the Holter monitor's relatively short window. Wearing a monitor for a longer period of time means that paroxysmal AF is more likely to be captured, although little information is provided about the burden since not all data is kept. In the EMBRACE study of patients with cryptogenic stroke where an etiology remained undetermined after 6 months of standard workup, participants were given either a repeat 24-hour Holter monitor (n = 277) or a 30 day automated loop recorder (n = 280) and the rates for AF detection were compared.[24] The Holter monitors only resulted in 9 (3.2%) new cases being diagnosed compared to 45 (16.1%) new cases with the loop recorders. While loop recorders cost more than Holter monitors per monitoring period at $206.72, a later study which performed a cost analysis using the EMBRACE study's data found that ≤30 days of loop recorder use was likely cost effective for cryptogenic stroke patients.[25] Additional studies would be needed to determine if this were also true for patients with other AF risk factors.

c. Ambulatory Telemetry

Another option called ambulatory telemetry (figure 1) combines the continuous data collection of Holter monitors with the extended duration provided by loop recorders. These devices have a similar patch/device setup but can continuously record the patient's rhythm for up to 30 days.[22] Nearly all such devices have automatic detection software for arrhythmias which, depending on the arrhythmia, prompts immediate transmission of a report by a cellular network. This constant monitoring would make ambulatory telemetry a strong tool for detecting atrial fibrillation whether it be symptomatic or not. There have not been any studies directly comparing ambulatory telemetry devices and loop recorders in terms of diagnostic ability – let alone as AF screening tools – but Kabali et al. conducted a meta-analysis indirectly comparing the two options against Holter monitors.[26] Their study found that both options were significantly

more effective than Holter monitors in detection of arrhythmias but they found no evidence that one option was more effective than the other. With long-term ambulatory telemetry monitoring costing much more than an external loop recorder at a price of $728.90, ambulatory telemetry does not offer any significant, unique advantages as an AF screening tool.[21]

d. Zio Patch

The Zio patch is a device from the company iRhythm which has been proposed as an alternative to Holter monitors and ambulatory telemetry (figure 1). The device is a single, small, adhesive patch (34 grams - 12.3 cm x 5.3 cm x 1.1 cm) which is less bulky than other monitors, is water resistant, and records up to 14 days of a continuous single-lead ECG with a trigger that patients can push to note symptoms.[23] It has been approved by the FDA for cardiac monitoring. The patch is self-applied by the patient then shipped back to a facility for review after the monitoring period and a report is then sent to the patient's provider.

Multiple studies have been conducted comparing their efficacy with Holter monitors and the Zio patch seems to be better in terms of both diagnostic ability and patient preference. One study conducted by Barrett et al. had all patients (n = 146) referred for possible arrhythmias simultaneously wear a Holter and a Zio patch for 24 hours and 14 days, respectively.[27] The Holter detected significantly more arrhythmias than the patch during the first 24 hours (61 with Holter vs 52 with Zio) but the patch outperformed the Holter monitor when considering its entire monitoring period (61 with Holter vs 96 with Zio). Additionally, surveys about the devices showed that patients found the Zio patch more comfortable/convenient and that 81% would prefer it over standard Holter monitors.

Another study by Rosenberg et al. also had patients (n = 74) wear a 24 hour Holter and the 14 day Zio patch simultaneously but specifically to find and quantify suspected AF.[7] In this

study, all episodes of AF found by the Holter in the first 24 hours were also detected by the Zio patch (25 episodes from 21 patients). The Zio patch then detected additional episodes of AF in many of the same participants as well as AF episodes in a significant number of new participants (18) over the remainder of its monitoring period. Furthermore, the Zio patch was able to calculate the patients' AF burdens more accurately than the Holter which prompted changes in therapy for 21 of the participants. The team concluded that the Zio patch represented an easier, more efficient method for AF detection than Holters, loop recorders, or ambulatory telemetry but studies of cost effectiveness would need to be done.

More recently - and most relevantly - a study conducted by Turakhia et al. used the Zio patch specifically to screen high-risk, asymptomatic patients (≥55 years old with ≥2 AF risk factors) with no prior history of AF or recent arrhythmia workup.[28] Their program detected new AF in 4 (5.3%) of the 75 participants, all of whom were eligible for anticoagulation therapy due to their high CHADS scores. Once again, however, the authors concluded that more research would need to be done before claims about cost-effectiveness could be made. With the price of $995 quoted by iRhythm for a Zio patch with interpretation (oral communication, July 2017), it is a relatively costly option but one which could be outweighed by the savings from stroke prevention.

e. Other Wearable Monitors

There are a number of other devices currently being tested for cardiac monitoring purposes, among other things. One example, the NUVANT by Corventis (figure 2), is similar to the Zio patch in that it continuously monitors a patient's heart rate and rhythm.[29] However, it also senses a number of other things such as posture, sleep, and activity duration/intensity. It is also different from the Zio patch in that it can transmit data like ambulatory telemetry rather than

needing to be physically returned for interpretation. Unfortunately, there is relatively little literature published about the NUVANT. One study conducted by Engel et al. reviewed the data pertaining to any arrhythmias detected in 951 patients given the device after completing a negative Holter.[29] They found that the NUVANT detected a relatively high prevalence of AF, as some amount was captured in 20% of the subjects. No comparisons with other devices were made and the study was retrospective with no emphasis on screening, but it still offers some potential for situations where long term monitoring for AF might be warranted. Obviously additional research would be needed.

Other devices are also being developed which have been discussed in the literature, such as the Sensium by Toumaz and the Discover by Proteus.[29] The Sensium is another small patch worn on the chest which is able to monitor a patient's heart rate, respiratory rate, and temperature every couple minutes.[30] The Discover also involves applying a patch to monitor vitals but includes an ingestible, pill-like sensor as well which can track medication adherence.[31] These devices offer more features than would be necessary to simply screen for AF and would likely be better suited for other roles. Additionally, there is no literature available describing their ability to detect AF or other arrhythmias at this time.

4. Implantable Monitors

a. Implantable Loop Recorders

Small loop recorders which can be placed subcutaneously have been developed which allow for increasingly long term cardiac monitoring (roughly 3 years per device). The downside, as mentioned by Dr. Michael Peterson of United Heart and Vascular Electrophysiology in his 8/1/2017 interview, is the $4,000 price tag. These also require a minimally invasive procedure for placement, but they remove the burden of constantly wearing a standard external

monitor. One of the more studied examples of these ILR's is the Reveal LINQ by Medtronic (figure 3) which is a small (0.7 cm x 4.5 cm x 0.4 cm) device inserted under the skin of the chest. It can store up to 14 episodes of AF and is capable of automated remote transmissions.[32,33] Patients can perform all their normal activities of daily living and it is also MRI compatible.[34] Many patients receive a LINQ device due to infrequent syncopal episodes which are unlikely to be captured on a 24 hour Holter or even 30 day telemetry but also cannot be captured with a patient activated device.[32] The other main indication for LINQ placement is for monitoring AF, whether it be to better guide management or accurate detection following cryptogenic stroke or AF ablation. A study investigating the LINQ algorithm's performance for AF detection when compared with Holter monitors found that the LINQ had a sensitivity of 98.4%, specificity of 99.5%, PPV of 97.2%, and NPV of 99.7% making it a very accurate tool.[32] Additionally, the AF burden calculated by the LINQ monitor was 98.4% sensitive compared to the burden calculated by Holter monitoring.

No studies have been completed using the LINQ monitor as a method for AF screening, but there are a few underway. The largest such study by Diederichsen et al. started enrollment for the LOOP study in January 2014 in which participants (n $\cong$ 6,000) are selected if they are ≥70 years old, have at least one AF risk factor (specifically, HTN, DM, HF, or stroke), and have no history of AF or current anticoagulation.[33] They are then allocated to either a control group or an ILR group in which they have a LINQ placed with regular follow-up and monitoring over the next ~4 years. The team hopes to determine how helpful an ILR is in detecting AF, what benefits this early detection might have for patients, and also any clear markers that one might develop AF in the future. They plan to complete a cost effectiveness analysis using their data as well. The team anticipates that their study will wrap up in May 2020. Other similar but smaller

studies have by now reached their endpoints but have yet to be published. The REVEAL-AF study also utilized the LINQ (n ≅ 400, duration 18 - 30 months) while the ASSERT-II (n ≅ 250, duration 18 months) and ASSERT-III (n = 129, duration 60 days) used the St. Jude Confirm ILR.[35-37] According to initial reports from the ASSERT-II trial, subclinical AF was detected in 34% of patients with left atrial enlargement per year.[6] However, conclusions about using ILR for AF screening will have to wait until the rest of these results are available.

b. Pacemakers and Implantable Cardioverter Defibrillators (ICD's)

Pacemakers and ICD's represent another method available to detect AF. These devices would not be implanted for the sake of AF screening given the more complicated procedure necessary to place them. Furthermore, while many of these devices are capable of detecting atrial high-rate episodes it is unclear to what extent these should be treated as AF.[6] Studies have shown that the many patients who had atrial high-rate episodes detected by a pacemaker or ICD do have increased rates of stroke, but not to the same degree as similar patients with clinical AF.[6] In fact, analysis of the first ASSERT study which investigated AF detected by pacemakers/ICD's found that stroke risk was only increased when the atrial high-rate episodes lasted longer than 24 hours.[38] Ongoing studies (e.g. ARTESiA, NOAH) are looking at the effect that anticoagulation has on stroke risk in patients whose pacemaker/ICD detected these episodes.[6] Tables 3 and 4 demonstrate the complexities of diagnosing AF by these methods. Suffice it to say, pacemakers and ICD's are unlikely to be the best AF screening method for patients who already have them and they are not an option whatsoever for patients who do not.

5. Novel Devices

a. Mobile ECG's

A variety of new event-monitor-like devices have been developed in the last several years which act as simplified ECG machines. Most of these devices produce a single lead (typically Lead I) by having the patient hold one electrode with each hand.[39] While this does not produce an ECG with the same amount of detail as a standard 12-lead, it is often enough to detect most abnormalities. The Alivecor, for example, has been successfully used in studies for several purposes: evaluating QRS/PR morphology; measuring QRS delay; checking for ST-elevation (with additional sticker electrodes); monitoring QT intervals in patients receiving QT-prolonging drugs; performing pediatric ECG's; and screening high-level athletes.[39] Compared to these purposes, determining whether a patient is in sinus rhythm versus AF is quite feasible.

The mobile ECG device used in the greatest number of studies seems to be the Alivecor which was developed by Kardia (figure 4). It consists of two dry electrodes which can be attached to a smartphone by a case. When in use, the electrodes transmit a signal to the smartphone which creates the 30-second, single-lead ECG in real time using the associated Kardia app. The device also produces an interpretation in most cases, including sinus rhythm, AF, or "unreadable"/"unclassified" if not clear. The device is FDA approved and costs $99 to purchase, plus $9.99/month after the first 30 days for data storage and other features (although single ECG's can be emailed to oneself).[39,40]

The device's validation study conducted by Lau et al. compared Alivecor reports to a reference 12-lead ECG in patients with and without AF and the results demonstrated a sensitivity of 98% and specificity of 97%.[41] Subsequent studies utilizing the Alivecor have found similar levels of accuracy regardless of the situation. The previously mentioned study in which the Alivecor was used to screen high-level athletes (n = 123) also included screening of medical students (n = 128) and patients from a cardiology clinic (n = 130).[42] The device was used to

create an ECG which was then followed by a 12-lead for comparison. For some conditions the

sensitivity was fairly low, like the 72.4% sensitivity for QRS delay. However, the sensitivity for

AF was high at 94.4% and the specificity for all conditions was >94%. Additionally, when

surveyed over 95% of these participants had "no problems" with the Alivecor and over 75%

stated they preferred it to a standard ECG. The second of the three largest AF screening program

studies, SEARCH-AF, used the Alivecor device to screen participants ≥65 (n = 1,000) visiting

several Australian pharmacies.[43] They found new AF in 1.5% of the population after

confirmatory 12-lead and all of these participants were eligible for anticoagulation. Their

subsequent cost analysis found that screening with this procedure would likely be cost effective

with an incremental cost effectiveness ratio of $4,066 per QALY gained.[43]

Other models of mobile ECG devices have been used in similar studies. In fact, the most

recent of the few large published studies investigating AF screening programs utilized the

Zenicor device (figure 5).[44] The Zenicor is another handheld which uses two thumb electrodes to

produce an ECG transmitted by cellular data to a database where it is reviewed.[45] The

STROKESTOP study in Sweden - while ongoing - has published preliminary results after

inviting patients aged 75-76 with AF risk factors (n = 7,173) to use a Zenicor device twice daily

for two weeks after a preliminary 12-lead. Previous studies had shown good sensitivity and

specificity with the Zenicor (96% and 92%, respectively)[46] and multiple other studies had shown

that extended, intermittent ECG use was more effective for arrhythmia detection than shorter,

continuous monitoring (i.e. Holter monitors).[47,48] STROKESTOP showed that using this method

for AF screening detected 218 (3.0%) new cases of AF.[44] Of these cases, only 37 (0.5%) were

found by the initial 12-lead while 140 (2.0%) were detected using Zenicor. A cost analysis of

this data found that the program would also likely be cost effective, concluding that for every

1,000 people screened an estimated 8 strokes would be prevented and 12 QALY's saved at

€4,313 ($5,067) per QALY.[49] The study aims to continue until 2019 and will publish additional

data on patient outcomes at that time.

The MyDiagnostick device (figure 6) is another mobile ECG which has been studied as

an AF screening tool, albeit to a lesser degree. The device is essentially a stick with a dry

electrode on either end which the user can grip to produce a single lead ECG. It also has the

advantage of using USB for transmission so Wi-Fi and/or Bluetooth are not necessary.[50]

Tieleman et al. measured the device's diagnostic ability in a validation study (n = 192) which

found it had a 100% sensitivity while still maintaining a specificity of 95.9%. They completed a

screening program for AF in a second, larger group (n = 676) which found new AF in 11 people

(1.6%) but cost analysis was not performed.[50]

Other devices include the Omron HCG-801, which has one apply an electrode to their

bare chest and another to their index finger, and the Merlin, a watch-like device with one

electrode on the inside band and a second on the "watch face" for the palm of their other hand.[51]

Kearley et al. found that the Omron's autoanalysis had a sensitivity of 98.7% and specificity of

76.2% while the Merlin (which must be manually interpreted) had a sensitivity of 93.9% and

specificity of 90.1%.[51] These devices have been less thoroughly investigated and have poorer

measures of accuracy, so for now the three previously mentioned tools would be preferable for

screening programs.

b. Smartphone Photoplethysmography (PPG)

Plethysmography is the measurement of changes in volume of a substance (typically

blood) in the body. Photoplethysmography (PPG) essentially uses changes in light associated

with these changes in volume to quantify certain processes, like a person's pulse. Technology

utilizing this method has been developed as a method of screening for irregular rhythms by monitoring the time between R waves. One early study by Lewis et al. (n = 594) aimed to validate the method by comparing a finger-tip probe using PPG with cardiologist-interpreted 12-lead ECG's performed at the same time.[52] They modified the parameters of the PPG device until its sensitivity for irregular rhythms was at 100% and found that the specificity of the device remained fairly good at 91.1%.

Since then, PPG has been developed and adapted so that it can be performed using apps on a standard iPhone. One app called PULSESMART (figure 7) was tested by McManus et al. in patients before and after cardioversion (n = 98) as well as patients with other arrhythmias (n = 30) expected to "trick" the sensor.[53] Use of their app involved applying the participants 2nd or 3rd finger to the phone's light and camera for 2 minutes while the app's software used different methods to measure irregularity (specifically, "Root Mean Square of Successive Difference of RR intervals [RMSSD], Poincare plot [or Turning Point Ratio], and Shannon Entropy [ShE]").[53] The study found that the PPG app was 97.0% sensitive and 93.5% specific for AF. A similar app called Cardiio Rhythm was evaluated by Chan et al., who had participants (n = 1,013) take 3 separate 17.1-second readings and defined a positive result as 2 of 3 readings being irregular.[54] Their results suggested the app had a sensitivity of 92.9% and a specificity of 97.7%, although their study design only referenced the app against a 12-lead ECG for positive readings.

These apps represent a very accessible tool with which to screen for AF. According to the Pew Research Center, 64% of Americans own a smartphone and that number continues to rise.[55] Only 27% of Americans ≥65 years old own a smartphone but this number is increasing as well. Furthermore, with 54% of people owning a smartphone between the ages of 50-64, soon the majority of people with a CHADS-VASc score of ≥1 will have access to PPG. The accuracy

of these apps is not perfect and their ability to detect abnormalities can worsen depending on the environment, the patient's skin, and other sources of noise/artifact. However, screening targeted towards those at risk could minimize false positives while helping detect silent AF.

c. Advanced Blood Pressure Monitors

There are several models of BP cuffs which are capable of simultaneously checking a person's BP and their rhythm for AF. All of the models discussed in the literature are developed by Microlife and Omron. The devices all also use an algorithm for AF detection which only prompts the monitor to flash for positive readings, so manual interpretation is not possible. However, these devices would be convenient as they check for AF while measuring a standard vital sign that is regularly taken. The most accurate devices were found to have sensitivities and specificities on par with other novel methods for AF detection.[56] Marazzi et al. compared the AF detection ability of the Omron M6 device and the Microlife BP A200 Plus device to a 12-lead ECG in patients referred to a HTN clinic (n = 503). Their results showed a sensitivity of 100% and specificity of 92% for the Omron M6 while the Microlife BP A200 Plus had a sensitivity of 100% and specificity of 95%. Additionally, their study diagnosed 47 (9.3%) new cases of AF by using the Omron and 42 (8.3%) new cases using the Microlife. The prevalence of AF in the group was somewhat high at 101 (20%) so the incidence of new AF might be higher than expected.[56] However, the results still show that using advanced BP cuffs such as these could be a viable option for AF screening. Another device, the Microlife Watch BP was found to have a sensitivity of 94.9% and a specificity of 89.7% by Kearley et al.[51] The same device was used by Omboni et al. in a screening program for a less selected community (n = 220) and found that 4 (1.8%) were diagnosed with previously unknown AF.[57] A systematic review on the topic of AF screening with BP cuffs was performed by Kane et al. who concluded

that additional studies would be needed to clarify the accuracy of such methods.[58] Studies on

cost-effectiveness would also be required for these devices before implementation with clinics,

let alone with home BP monitors.

VI. Methods

Pubmed and the Joanna Briggs Institute EBP Database were searched through June 2017. The terms "ATRIAL FIBRILLATION SCREENING" with and without "OPPORTUNISTIC" or "SYSTEMATIC" were included in the search strategy. The references of these studies were also reviewed and any relevant publications were included. Specific information about individual screening methods was found using Pubmed. The search strategies in these situations included the terms "METHOD NAME" (e.g. "12 LEAD ECG", "PULSE PALPATION," "ALIVECOR", etc.) and "SENSITIVITY" or "SPECIFICITY" or "COST" or "COST EFFECTIVE". Clinical trials, observational studies, systematic reviews, and meta-analyses were reviewed. All languages of publication were accepted.

Current guidelines were reviewed using the organization websites for the European Society of Cardiology, the American Heart Association, the American College of Cardiology, and the American Heart Rhythm Society. Additional publications relevant to AF screening were searched using the terms "ATRIAL FIBRILLATION" with and without "SCREENING".

The professional interview with Dr. Michael Peterson was performed after completing the literature review as described above. Dr. Peterson is a cardiac electrophysiologist who works at United Heart and Vascular Clinic in St. Paul, MN. The interview was conducted over the phone on August 1st, 2017 using the predetermined questions as written out in the excerpts included in the Appendix.

VII. Discussion

A. Assessment of Detection Methods

Review of the literature regarding AF screening clearly demonstrates that there are a variety of methods available for screening programs. Furthermore, the way in which a method is applied (opportunistic vs systematic) allows for an even greater number of possibilities for screening. It would therefore be useful to make a few conclusions about which method is best in various regards.

1. Most Sensitive/Specific

The most sensitive and specific test would be the gold-standard, the 12-lead ECG. However, screening programs obviously cannot hook patients up for a 12-lead ECG and monitor them for months at a time in order to detect all cases of paroxysmal, silent AF. With that being said, the next best option to accurately and reliably detect AF seems to be the implantable loop recorders. With a sensitivity and specificity of 98.4% and 99.5%, respectively, for automatic detection software as well as the option for review of any concerning/ambiguous arrhythmias, the LINQ monitor is very close to a standard 12-lead in accuracy.[32] Furthermore, the device's battery lasts roughly 3 years once implanted. Since studies have shown that a longer duration of monitoring improves the chance of detecting AF[24,32,47,48] and 3 years is the longest duration available, implantable loop recorders obviously have an advantage over all other methods. A wearable option such as the Zio patch would provide a shorter alternative for patients unwilling or unable to have an implantable device.

2. Most Practical

The most practical choice for AF screening is debatable depending on context. One option would be advanced BP cuffs. Blood pressure is a fairly ubiquitous measurement in

healthcare whether it be an inpatient or outpatient setting. Simply replacing current BP monitors in settings where patients with multiple AF risk factors are seen would constitute the bulk of an AF screening program. The only other planning which would be necessary would be protocols for 12-lead confirmation and referral for patients who screen positively. Such protocols were already established for STROKESTOP and SEARCH-AF.[44,43] Clinics and hospitals wishing to establish similar protocols with advanced BP monitors could likely do so with minimal effort. Another option available for screening with advanced BP cuffs would be in ambulatory monitoring. Patients who use BP monitors at home to track their BP could be given a model which detects AF as well. This program would require more elaborate planning so that confirmatory ECG's could be done and to ensure patient follow up. However, this method would be comparable to the intermittent ECG checks used in STROKESTOP and would likely increase AF detection rates while minimizing additional testing.

The other highly practical option for screening would be with smartphone photoplethysmography. Since the majority of people own a smartphone and the vast majority of people at least have some access to one, an app which can screen for AF would arguably be more practical than an advanced BP cuff.[55] Depending on the cost of these apps once released to the public, such apps could also be the cheapest option available aside from pulse palpation which would require training. Still, smartphone PPG screening would need even more complete screening protocols than screening with ambulatory BP monitoring. Patients performing ambulatory BP checks typically do so at the recommendation of their provider with whom they in theory have good communication. A tool downloaded from the app store on a whim without consulting a healthcare provider may not result in the same follow-up which is necessary for both rate or rhythm therapy and anticoagulation therapy.

3. Most Cost Effective

Because there have been relatively few studies analyzing the cost effectiveness of AF screening methods it is somewhat difficult to conclude which screening method would be best in this regard. Furthermore, not all studies made the same cost comparisons. The SAFE study found that opportunistic screening with pulse palpation had an incremental cost of $442 per case detected.[13] The STROKESTOP study - which is also ongoing - found an incremental cost effectiveness ratio of $5,067/QALY with intermittent mobile ECG use, and the SEARCH-AF study found an ICER of $4,066/QALY.[44,43] The startup cost for screening with these methods also needs to be taken into account. While certain methods may detect more cases of AF, purchasing new BP monitors, mobile ECG machines, or even standard 12-lead machines may not be feasible for all healthcare facilities. With that being said, the evidence suggests that screening with pulse palpation and confirmatory ECG's would be the most cost effective method. In their extensive review on the economic aspects of the topic, Welton et al. made the same conclusion.[59] In contrast to the SAFE study's conclusion favoring opportunistic screening, however, they go on to suggest a more systematic approach with opportunistic screens every 5 years in patients ages 65 - 80. Welton et al. do add that new devices "may be of relevance to a screening programme when their diagnostic performance is better understood" but do not make further recommendations about their use.

B. Proposal for Screening

Multiple studies will be concluding in the next few years which will have significant input regarding AF screening strategies, particularly systematic ones. The LOOP study should tell us a great deal about the prevalence and incidence of AF while hopefully elucidating some new methods for predicting who will develop AF.[33] Along with the LOOP study, the remainder

of the STROKESTOP study should provide some insight regarding patient outcomes resulting from these screening procedures.[44] As such, it would be prudent to wait until these studies are done before putting into place any widespread screening programs.

With that being said, there is already evidence that a systematic, opportunistic screening of all patients over 65 years old with pulse palpation would be cost effective and likely reduce strokes. All patients in this category would have a CHADS-VASc score of at least 1, making them eligible for anticoagulation therapy. Stratification of additional patients could result in more people being added to the screening pool, such as those with CHF, HTN, DM, and/or CVD/PVD (females without other risk factors could be excluded, as anticoagulation is recommended in females with CHADS-VASc ≥2).[60] A program like this would require flagging systems to be prepared to ensure screening is done but this could be easily arranged using the electronic medical record system. Similar programs are already in place to screen for various types of cancer. If diagnosed, patients could then be removed from the screening pool after establishing care with a cardiologist. This screening program would reflect the most up-to-date recommendations from the ESC which suggest opportunistic screening be performed. It is also supported by the 2017 recommendations from the AF-SCREEN group, an international collaboration dedicated to AF prevention and management.[6]

Other components could be added to the screening program as additional information is published. Elderly patients at the highest risk of AF could be flagged for additional systematic targeted screening procedures at routine intervals. For example, patients could be offered two weeks of mobile ECG or advanced BP monitor use in order to optimize detection rates. Alternatively, patients could be offered an ILR at a certain age such as 75. This would have the added benefit of continuous monitoring for other conditions (e.g. VT in patients with

cardiomyopathies, precipitating conditions in falls, etc.). If we assume that monitoring for extended durations nearly doubles AF detection in patients ≥75 as seen thus far in STROKESTOP (where detection was 3.0% compared to ~1.6% in SAFE), then either of these options could be very effective for diagnosing AF undetected by the standard screening procedure.[44,13]

Another arm that could be added to the screening program would be having mobile ECG devices on-site at pharmacies. Many pharmacies already have BP cuffs available for patients and adding an ECG device which patients could also use would likely boost detection rates. Having this option available for patients would increase access as well. Many patients may be unwilling or unable to purchase such a device for themselves, but for many pharmacies the cost of single device would be a negligible fee. Having this setup at a pharmacy would also facilitate follow-up where other ambulatory screening methods might not. Furthermore, this method already has some support from the results of the SEARCH-AF study.[43]

VIII. Conclusion

More research needs to be performed to ensure that any systematic screening program put into place would be cost effective. It seems there has been sufficient research done with several methods to say with good confidence that they could detect greater numbers of AF cases. However, other methods like smartphone PPG and certain mobile ECG devices have been studied relatively little. Additionally, the exact cost of a screening program is poorly defined for most methods currently available. Furthermore, studies regarding the outcomes of patients who are screened and subsequently treated for AF need to show that the expected benefit (i.e. stroke prevention) actually occurs. The role of AF burden, associated symptoms, and AF etiology (cardiogenic vs post-stroke neurogenic) need to be clarified as all AF may not confer the same stroke risk. Dr. Michael Peterson of United Heart and Vascular Clinic Electrophysiology voiced similar concerns in his 8/1/2017 interview, suggesting that stroke risk likely exists on "a gradient based on burden of arrhythmia and other risk factors like diabetes, advanced age, low EF, HTN," etc. Many studies are currently investigating these issues and should publish their results in the next few years. Continually assessing this new information as it is released will be vital for developing a strong, effective AF screening program. A goal of all such programs must be to understand AF and diagnose it accurately. AF screening could clearly prevent strokes and reduce expenses, but over-diagnosis and unnecessary anticoagulation would inevitably result in unnecessary hemorrhagic strokes, other complications, and increased costs.

A separate issue which was somewhat surprising when reviewing the literature was the undertreatment of diagnosed AF with anticoagulation therapy. Multiple studies reported that a large proportion of their participants with known AF (22-43%) did not have any contraindications to anticoagulation but were not being treated.[6] Excluding patients who declined anticoagulation with informed consent, it seemed that this was most commonly due to a

combination of OAC therapy not being offered or some confusion about anticoagulation guidelines (e.g. stopping the medication following failed cardioversion). Since the main goal of an AF screening program would be to reduce stroke risk through anticoagulation, ensuring patient adherence would be key. Dr. Michael Peterson of UHVC added in his 8/1/2017 interview that specialized AF clinics could minimize this undertreatment and improve patient care.

The developments in AF screening options in just the last few years have made a significant impact on AF detection and management. The new devices available to document AF represent a move towards more patient-friendly medicine. It is easy to understand why a patient might prefer a smartphone app or an ECG built into their phone case over an intimidating 12-lead ECG machine with its several patches. These newer options provide patients with a greater degree of control over their own healthcare. This independence will hopefully facilitate better patient understanding and regimen adherence. Additionally, any steps which are cost-effective and allow for a greater degree of primary prevention are desirable from both a patient and provider standpoint.

IX. References

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X. Appendices

Table 1 – CHA$_2$DS$_2$-VASc Score Guide with Stroke Risk Estimation[61]

KNOW YOUR STROKE RISK			
CHA2DS2-VASc Risk	Score	CHA2DS2-VASc Score	Adjusted stroke rate (% / year)
		0	0
CHF or LVEF <40%	1	1	1.3
Hypertension	1	2	2.2
Age > 75	2	3	3.2
Diabetes	1	4	4
Stroke / TIA / Thromboembolism	2	5	6.7
Vascular Disease	1	6	9.8
Age 65-74	1	7	9.6
Female	1	8	6.7
		9	15.2
CHF = congestive heart failure; TIA - transient ischemic attack; LVEF = left ventricular ejection fraction.			

Table 2 – Wilson's Criteria for Screening[62]

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

Table 3 – Incidence of Cardiac Implanted Electronic Device-Detected Atrial High-Rate Episodes in the Population with Cardiac-Implanted Devices[6]

Year	Trial	Device Indication	Clinical Profile of Patients	Mean Age	% Male	% LVEF	Mean CHADS$_2$	Follow-Up	AF Burden Threshold	Incidence of AF
2002	Gillis et al.[8]	PPMs for sinus node disease	All	70±12	52%	NA	NA	718±383 days	>1 min	157/231 (68%)
2003	Ancillary MOST[10]	PPMs for sinus node disease	All	Median 73 (68,81) for no AHRE Median 75 (68,79) for AHRE detected	45%	NA	NA	Median 27 mo	>5 min	156/312 (50%)
2010	TRENDS[15]	PPMs and ICDs All indications	History of prior stroke No history of AF No oral anticoagulant use ≥1 stroke risk factor	72.8±9.9 for no AHRE 74.0±9.1 for AHRE detected	63% for no AHRE 71% for AHRE detected	NA	4.1±0.8 for no AHRE 4.2±0.8 for AHRE detected	Mean 1.4 y	>5 min	45/163 (28%)
2012	TRENDS[14]	PPMs and ICDs All indications	No history of prior stroke No history of AF No oral anticoagulant use ≥1 stroke risk factor	70.2±11.8	66%	NA	≥2 in 70%	1.1±0.7 y	>5 min	416/1368 (30%)
2012	ASSERT[11]	PPMs and ICDs All indications	History of hypertension No history of AF No oral anticoagulant use	76±7 for no AHRE 77±7 for AHRE detected	59% for no AHRE 56% for AHRE detected	NA	2.3±1.0 for no AHRE 2.2±1.1 for AHRE detected	2.5 y	>6 min	895/2580 (34.7%)
2012	Home monitor CRT[18]	CRTDs and CRTPs Congestive heart failure	Heart failure No history of AF	66±10	77%	25 (20–30)	≥2 in 64%	370 days (253–290)	≥14 min	126/560 (23%)
2013	Healey et al.[12]	PPMs All indications	All	71.7±14.4 for no AHRE 74.3±13.7 for AHRE detected	59% for no AHRE 58% for AHRE detected	NA	2.02±1.30 for no AHRE 2.23±1.47 for AHRE detected	Single center Retrospective	>5 min	246/445 (55.3%)
2015	IMPACT[19]	ICDs and CRTDs All indications	No permanent AF No contraindications for oral anticoagulant	64.2+11.5 for control 64.7+10.8 for intervention	73% for control 74% for intervention	29.4+11.3 for control 29.9+10.8 for intervention	2 (median)	701 days	>4–12 sec	945/2718 (34.8%)
2016	RATE Registry[13]	PPMs and ICDs	All No permanent AF	73.6±11.8 for PPMs, 64.5±12.6 for ICDs	54% in PPM 72% in ICDs	57.8±10.5 for PPM 29.2±11.3 for ICDs	1.8±1.0 for PPM 2.0±0.8 for ICDs	22.9 mo (median)	> 3 atrial premature complexes	145/300 (48%) of PPM patients 155/300 (52%) of ICD patients of the representative samples studied

Table 4 – Summary of Studies Regarding Cardiac Implanted Electronic Device-Detected Atrial

High-Rate Episodes and Thromboembolic Risk[6]

| Trial (Year)	Number of Patients	Duration of Follow-Up	Atrial Rate Cutoff (bpm)	AF Burden Threshold	Hazard Ratio for TE Event	TE Event Rate (Below vs. Above AF Burden Threshold)
Ancillary MOST[10] (2003)	312	27 mo (median)	>220	5 min	6.7 ($P=0.020$)	3.2% overall (1.3% vs. 5%)
Italian AT500 Registry[7] (2005)	725	22 mo (median)	>174	24 h	3.1 ($P=0.044$) (95% CI, 1.1–10.5)	1.2% annual rate
Botto et al[6] (2009)	568	1 y (mean)	>174	$CHADS_2$+AF burden	n/a	2.5% overall (0.8% vs. 5%)
TRENDS[9] (2009)	2486	1.4 y (mean)	>175	5.5 h	2.2 (95% CI, 0.96–5.05, $P=0.06$)	1.2% overall (1.1% vs. 2.4%)
Home Monitor CRT[18] (2012)	560	370 days (median)	>180	3.8 h	9.4 (95% CI, 1.8–47, $P=0.006$)	2.0% overall
ASSERT[11] (2012)	2580	2.5 y (mean)	>190	6 min	2.5 ($P=0.007$) (95% CI, 1.28–4.85)	(0.69% vs. 1.69%)
SOS[27] (2014)	10016	2 y (median)	>175	1 h	2.11 ($P=0.008$) (95% CI, 1.22–3.64)	0.39% per year overall
RATE Registry[13] (2016)	5379 (3141 with pacemakers and 2238 with ICDs)	22.9 mo (median)	NA	Nonsustained atrial high-rate episodes with a duration from 3 atrial premature complexes to 15–20 s	0.87 (95% CI, 0.58–1.31, $P=0.51$)	For nonsustained atrial high-rate episodes: 0.55% (0.34%–0.76%) per year for pacemakers and 0.81% (0.50%–1.12%) per year for ICDs

Figure 1 – External Electrocardiographic Monitors[22]
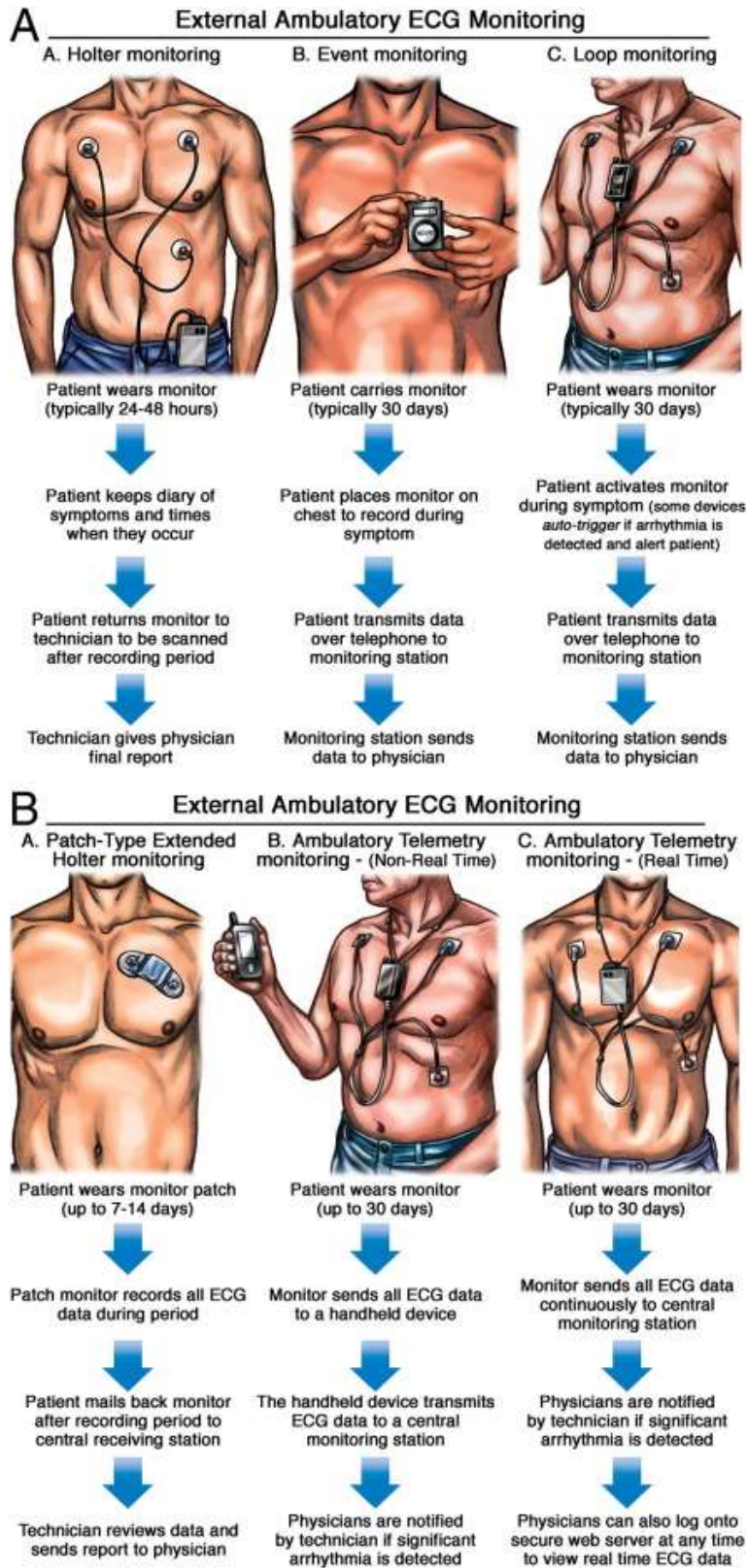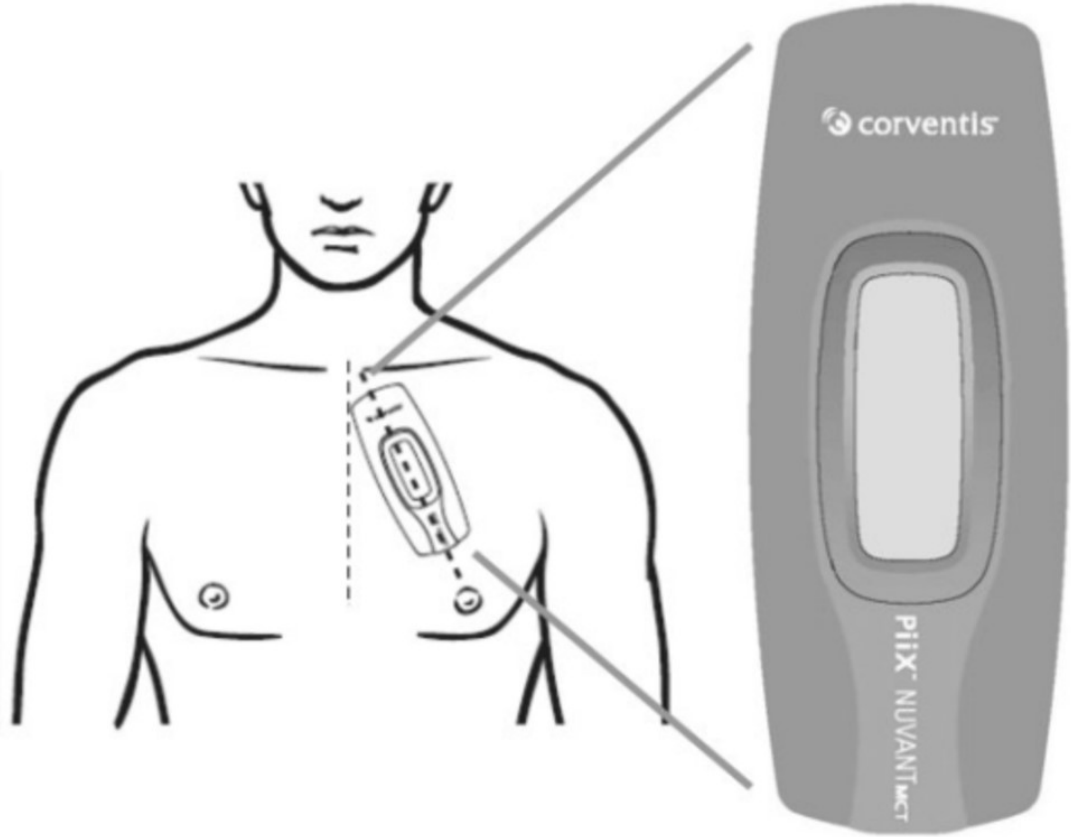
Figure 2 – Nuvant Device[29]
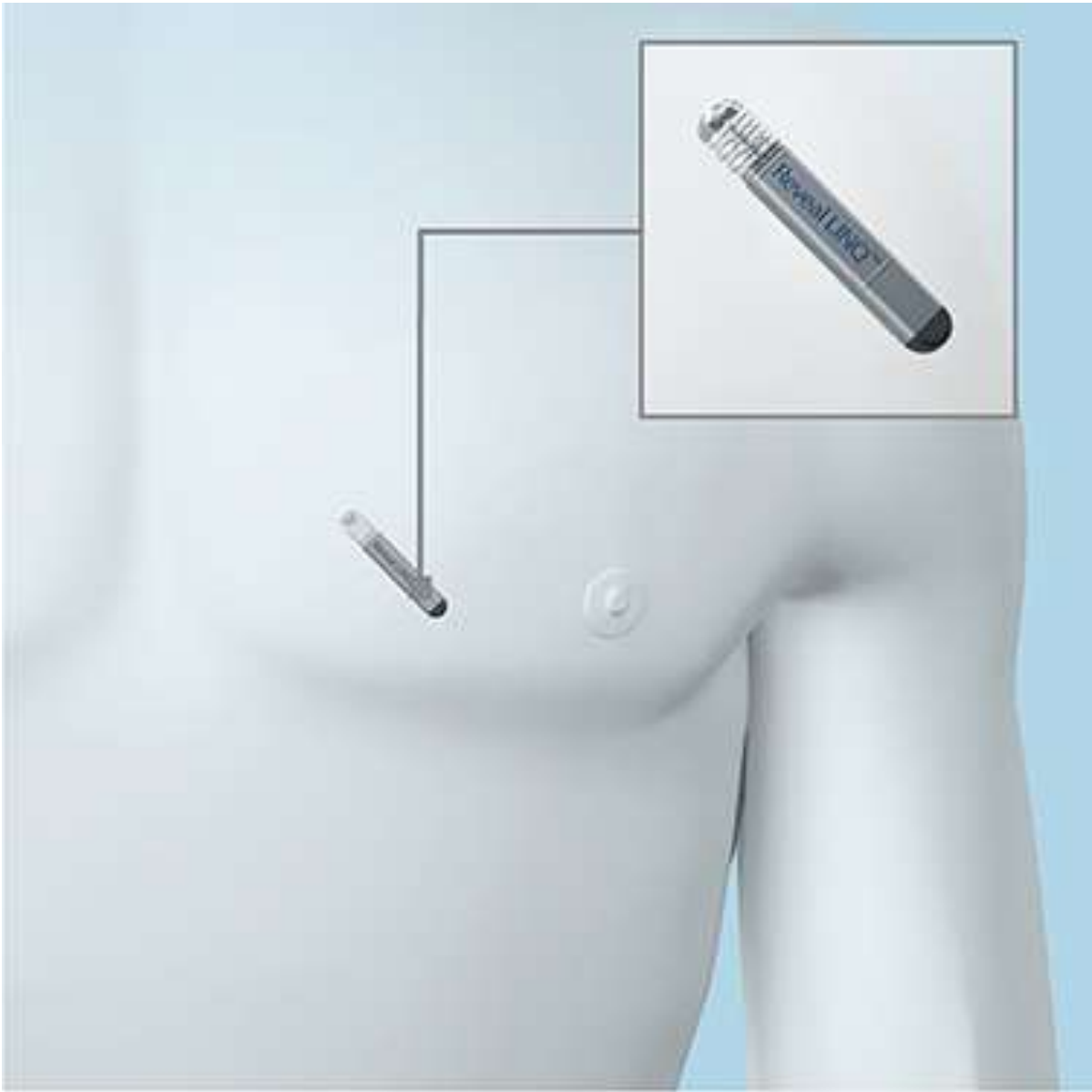
Figure 3 – Medtronic Reveal LINQ[34]

Figure 4 – Alivecor and Kardia App[40]

Figure 5 – Zenicor[45]

Figure 6 – MyDiagnostick[50]

Figure 7 – PULSESMART App[53]

Professional Interview Excerpts – Dr. Michael Peterson, Electrophysiology, United Heart and Vascular (August 1st, 2017)

ZS: Is there anything you feel people should know that they don't know about AF and stroke risk?

MP: AF is the most common heart rhythm problem in western civilization. It accounts for at least 20% of strokes, a third of them are asymptomatic at time of diagnosis. It's a huge expense to modern healthcare.

ZS: How do you feel about some of these novel devices for detecting AF, like the Alivecor?

MP: So it all gets down to sampling frequency - the more you look, the more you see. The ultimate example of that is the pacemakers implanted in the last 12 years. Then the next step up is the Reveal Loop recorder, the LINQ. Those are very, very sensitive in detecting atrial arrhythmias. Then if you go to the non-permanently implantable, there are several patches like Zio, they are all very equivalent. So you get 30 days of continuous monitoring and that adds a lot. (…) It picks up a lot more than the usual symptom activated monitor or Holter monitor. (…) Daily sample checks (…) That's okay, but not as good. Daily pulse checks are better than nothing. As you go down, though, this chain, you see increasing artifact. You get this very difficult distinction between device-detected arrhythmias and clinician diagnosed arrhythmias. (…) [Patients with] Clinically diagnosed [AF] by some physician or care provider are at the same risk as patients with symptomatic AF. They need to be anticoagulated. (…) The question is 16 seconds on a pacemaker. An Alivecor is one snapshot. Are those the same? And no one has the answer to that. How much AF is enough AF? It probably is a gradient based on burden of arrhythmia and other risk factors like diabetes, advanced age, low EF, HTN, all these other

things - the CHADS-VASC score. (…) So someone needs to do a study where we say "How much AF detected by device warrants anticoagulation?" How do you translate that into actual stroke risk? (…)

So this is my problem with the [novel devices]: they generate a lot of phone calls, they generate a lot of anxiety, and we don't always know what to do with the data. The good news is that it does force people to have shared clinical decision making with their patients, so they can think about it and make informed decisions. The problem is we don't know when to shift gears and do something different [with treatment].

As the person who had to review the Reveal implantable loop recorders, I had to read every AF diagnosis at United Heart and Vascular for many months, and there is a lot of artifact, there are a lot of overcalls, there are a lot of problems. And that's with implantable monitors. So you go to the Alivecor and my God there's noise. It's just not a perfect tool. And we often accept imperfect tools if they're non-invasive, but the cost of over-diagnosis and time spent on that and resources is significant, and there's resentment growing in the cardiology community because of this because they don't get paid for it. So now you're getting a phone call, you have to take time to look at the strip, you have to think about a patient, you have to make a recommendation often over the phone (…) There is gonna be some pushback on this at some point on a large scale, of people saying either we need to get paid or we don't want to get involved with these noisy tracing, these difficult to interpret tracings.

ZS: If you are going to start a screening program, what sort of coordination do you think there should be? Should it be a single time point, or should it be intermittent checks with those devices, or should it just go straight to implantable monitors?

MP: So the beautiful thing about the implantable monitors is that they really explode your sensitivity and you get significantly better tracings than the wearable monitors, and there's just so much better information, and they're so much better tolerated by the patient, but they're $4,000 and they only last 3 years. The Alivecor is $110 on Amazon. So the cost is crazy. (…) We'd all like a cheap implantable monitor with a 5 year scope on it, but right now there is no perfect tool. Right now, I think if you wanted to go into a community setting, like a nursing home or something, I think an interesting middle ground starting point would be using an Alivecor and going to all the residents with morning medications or at breakfast and just doing a quick screening daily. (…) I don't think 10 days of 1 minute screening is enough to say "You don't have AF," to really cause significant stroke reduction and life savings, but then the cost is really going to get high.

We've been using the patches here a little bit with reasonable success in the right patients. It sounds cold and callous, but there are patients who don't do well with the patches and generally they're already so high risk that they're already fully anticoagulated or they're at a point where we wouldn't anticoagulate them if we found AF. That'd be another interesting thing for a subset of patients, to say "Are there people that don't have diagnosed AF but you wouldn't do anything anyway, because they're hospice, because they can't take Coumadin?" All these impact measurements are extrapolated off these population statistics and they often grossly overestimate the scope of the disease and intervention that we do. (…) the actual number is always smaller and about a quarter to a third turns out to be the right number repeatedly in arrhythmias that we are actually going to treat or can treat for whatever reason. (…) if you look at the actual execution, a lot of people fall out of this. And that's something a lot of people don't want to talk about because they're downgrading their problem.

ZS: I saw a lot about undertreatment of anticoagulation in the literature. Have you seen that in your practice? Is it mostly people not knowing? Or not wanting it?

MP: Yes – both. (…) They're just too busy – the patient is up, and they're extremely hypertensive, they have chest pain, and they have a little AF on their pacemaker. So the clinician says "Well, I'll talk about their AF but that's a small priority because we have to talk about their chest pain now and their blood pressure now." The patients often wave it off, saying "Oh I'm not going to be on rat poison." The discussion has gotten very complex because there are [NOAC's] (…) and now there's the Watchmen. And this is why we're building an AF clinic specifically, so we can have an hour discussion just about stroke reduction in these patients. It is a hassle, physicians don't like giving Coumadin because they feel like the bad guy for giving it, and they know it's going to trigger more phone calls and chart checks and questions. (…) All that can be managed with good education but it takes time and the patients are often older and need it repeated, they don't get it, they often have prejudices. (…) And some of it is patients who just don't even want to engage in the discussion and are refusing unknowingly, and you almost need to say "I need you to hear this so you know what you're saying no to." And there's a lot of strong prejudices and biases especially in the rest homes, nursing homes, assisted living facilities, again to anticoagulants.

    It's gotten a lot better since the EMR's (…) But when we were in the paper chart days, I know that some of the partners wouldn't even bother looking at the pacer checks, because they didn't know how to read the checks, so unless you pointed it out to them they weren't going to go through that mess of data and find a 77% burden of AF. So if they don't look, they don't know and the patients don't complain.

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