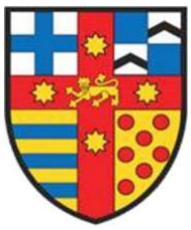
The utility of handheld and wearable devices in the diagnosis of cardiac arrhythmias



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A thesis submitted to fulfil requirements for the degree of

Master of Philosophy

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Statement of Originality

This is to certify that, to the best of my knowledge, the content of this thesis is of my own work. This thesis has not been submitted for any degree or other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

This thesis is presented as a record of the work conducted for the degree of Master of Philosophy at Westmead Clinical School, Sydney Medical School, Faculty of Medicine and Health, The University of Sydney.

Kartheek Garikapati

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Table of Contents

Statement of Originality ii

Acknowledgements iii

Table of Contents vi

List of Tables xiii

List of Supplemental Tables xiv

List of Figures xv

Abbreviations xvi

Abstract xix

Chapter 1. ***The role of contemporary wearable and handheld devices in the diagnosis and management of cardiac arrhythmias*** ***1***

1.1 Abstract **3**

1.2 Introduction **4**

1.3 Established non-invasive and invasive methods in the diagnosis and management of cardiac arrhythmias **5**

1.3.1 12-Lead ECG 5

1.3.2 Holter Monitor 5

1.3.3 External Loop Recorder 6

1.3.4 Implantable Loop Recorder 7

1.4 Contemporary wearable and handheld device technologies **8**

1.5 Mechanism of PPG in wearable devices **9**

1.5.1 Validation of PPG 11

1.5.2 Comparison of HR and HRV between ECG and PPG 11

1.5.3 Comparison of PPG derived PP interval to ECG derived RR interval 11

1.5.4 Limitations of PPG 12

1.6 AliveCor KardiaMobile Heart Monitor and Kardia Band 12

1.7 Smartwatches with ECG functionality 13

1.8 Wearable Patch Devices..... 14

1.9 Management of Specific Arrhythmias using Wearable or Handheld Devices 15

1.9.1 Atrial Fibrillation 15

1.9.1.1 AliveCor KardiaMobile Heart Monitor 15

1.9.1.2 Apple Watch (PPG and ECG) 15

1.9.1.3 Huawei Watch GT 16

1.9.1.4 Fitbit 17

1.9.2 Smartwatches with ECG functionality 17

1.9.2.1 Alternative Wearable Devices 18

1.9.3. FDA approved devices 18

1.10 Non-AF Arrhythmias 21

1.10.1 Wearable smartwatches 21

1.10.2 AliveCor KardiaMobile Heart Monitor 21

1.10.3 Wearable patches 22

1.11 Alternative Handheld Devices..... 22

1.12 Assessment of QT_c interval 23

1.13 Challenges and pitfalls of wearable and handheld devices..... 24

1.14 Conclusions 27

1.15 Figures 29

1.16 Tables 34

Chapter 2. Accuracy of a Handheld, Single Lead ECG Device in the Diagnosis of Cardiac Arrhythmias Against the Gold Standard of Cardiac Electrophysiology Study 46

2.1 ABSTRACT 46

2.1.1 Background 46

2.1.2 Objectives 46

2.1.3 Methods 46

2.1.4 Results 46

2.1.5 Conclusions 47

2.2 INTRODUCTION 48

2.3 METHODS 48

2.3.1 Study workflow 49

2.3.2 Electrophysiology study 49

2.3.3 AliveCor application 50

2.3.4 Patient demographics 51

2.3.5 Classification of arrhythmias 51

2.3.6 Statistical analysis 52

2.4 RESULTS 53

2.4.1 Baseline characteristics 53

2.4.2 Infallible diagnosis vs AliveCor rhythm interpretation 53

2.4.3 Inter-variability and intra-variability analysis 55

2.5 DISCUSSION 55

2.5.1 Previous studies 56

2.6 Limitations 58

2.7 CONCLUSION 58

2.8 TABLES 60

2.9 Figures 66

Chapter 3. Accuracy of commercially available handheld single lead ECG to cardiac telemetry and 12-lead ECG in identification of cardiac arrhythmias 68

3.1 ABSTRACT 68

3.1.1 Background 68

3.1.2 Objectives 68

3.1.3 Methods 68

3.1.4 Results 68

3.1.5 Conclusions 69

3.2 INTRODUCTION 70

3.3 METHODS 70

3.3.1 ECG Application 71

3.3.2 Classification of rhythms 71

3.3.3 Patient characteristics 72

3.3.4 Statistical analysis 72

3.4 RESULTS 73

3.4.1 Baseline characteristics 73

3.4.2 Telemetry and AliveCor vs. 12-lead ECG 73

3.5 DISCUSSION 75

3.6 LIMITATIONS 79

3.7 CONCLUSION 80

3.8 TABLES 81

Chapter 4. Smartphone-based single-lead ECGs versus traditional ambulatory Holter monitoring for definite diagnosis of cardiac arrhythmia in patients with palpitations: a randomised controlled trial (The AliveCor vs. Holter Trial) 89

4.1 ABSTRACT 89

4.1.1 Background 89

4.1.2 Objectives 89

4.1.3 Methods 89

4.1.4 Results 90

4.1.5 Conclusions 90

4.2 INTRODUCTION 91

4.3 METHODS 92

4.3.1 Study Design and randomisation 92

4.3.2 Study Setting and recruitment 92

4.3.3 Inclusion and exclusion Criteria 92

4.3.3.1 Sample size calculation 93

4.3.4 Study groups 93

4.3.4.1 Control Arm 93

4.3.4.2 Intervention Arm 94

4.3.5 Control of Bias 95

4.3.6 Study Outcomes 95

4.3.6.1 Primary outcome 95

4.3.6.2 Secondary outcomes 95

4.3.7 Adjudication of endpoints 96

4.3.8 Baseline visit 96

4.3.9 Participant timeline 96

4.3.10 Adverse events 96

4.3.11 Statistical analysis 97

4.4 RESULTS 97

4.4.1 Baseline characteristics 97

4.4.2 Primary outcomes 97

4.4.3 Secondary outcomes 98

4.5 DISCUSSION 98

4.6 Previous studies 99

4.7 Limitations 101

4.8 CONCLUSION 102

4.9 TABLES 103

4.10 Figures 108

4.11 Appendices (Supplemental material) 111

Chapter 5. Conclusions and future directions 114

Chapter 6. References 117

List of Tables

Table 1.1. Summary of wearable and handheld devices and clinical applications in arrhythmias 34

Table 1.2. Efficacy of wearable and handheld devices in the diagnosis of arrhythmias 36

Table 1.3. Registered active trials on wearable and handheld devices in arrhythmia detection 39

Table 1.4. Case studies on wearable and handheld devices in non-AF arrhythmias 44

Table 2.1. Baseline characteristics 60

Table 2.2. EPS vs AliveCor interpretation by the three reviewers' overall accuracy 61

Table 2.3. Proportional accuracy of EPS vs AliveCor interpretation 62

Table 3.1. Baseline characteristics 81

Table 3.2. 12-Lead ECG vs. combined reviewers' telemetry interpretation (proportional and overall accuracy) 82

Table 3.3. 12-Lead ECG vs. combined reviewers' AliveCor interpretation (proportional and overall accuracy) 83

Table 3.4. Telemetry vs. AliveCor interpretation by the reviewers' (overall accuracy and agreement) 84

Table 4.1. Baseline Characteristics for Holter Monitor (intervention) and AliveCor (control) 103

Table 4.2. Primary outcomes 105

Table 4.3. Secondary outcomes 106

List of Supplemental Tables

Supplemental Table 2.1. Inter-observer variability analysis. 64

Supplemental Table 2.2. Intra-variability analysis 65

Supplemental Table 3.1. 12-Lead ECG vs. combined reviewers' telemetry interpretation (overall accuracy) 85

Supplemental Table 3.2. 12-Lead ECG vs. combined reviewers' AliveCor interpretation (overall accuracy) 86

Supplemental Table 3.3. Inter-observer variability analysis 87

Supplemental Table 3.4. Intra-observer variability analysis..... 88

List of Figures

Figure 1.1. PPG waveform consisting of Direct Current (DC) and Alternative Current (AC) components 29

Figure 1.2. Beat-to-beat analysis from R-R intervals (RRI) and peak-to-peak intervals (PPI) 30

Figure 1.3. Limitations of PPG and sECG technologies are pictorially depicted 31

Figure 1.4. AliveCor (AliveCor Inc, Mountain View, CA, USA) recording of Sinus Rhythm (SR) and Atrial Fibrillation (AF) vs. conventional 12-lead ECG 32

Figure 1.5. Examples of Zio Patch and single-lead ECG (sECG) recording. 33

Figure 2.1. Workflow process for AliveCor vs EPS study 66

Figure 2.2. Examples of recorded arrhythmias from sECG 67

Figure 4.1. Study recruitment 108

Figure 4.2. Trial schema 109

Figure 4.3. Freedom from primary outcome at 6-months (AliveCor vs. Holter) 110

Abbreviations

AAD	anti-arrhythmic drug
AC	alternating current
AF	atrial fibrillation
AFL	atrial flutter
AI	artificial intelligence
AP	atrial pacing
AT	atrial tachycardia
AVB	atrioventricular block
AW	Apple Watch
BBB	bundle branch block
BMI	body mass index
bpm	beats per minute
cECG	continuous electrocardiogram
CHB	complete heart block
CI	confidence interval
CKD	chronic kidney disease
cMRI	cardiac magnetic resonance imaging
CNN	Convolutional Neural Network
CSANZ	Cardiac Society of Australia and New Zealand
DC	direct current
ECG	electrocardiogram
EGM	electrogram
ELR	external loop recorder
EPS	electrophysiology study
FB	Fitbit

GBD	Global Burden of Disease
GPS	global positioning system
HR	heart rate
HRS	Heart Rhythm Society
HRV	heart rate variability
ICD	implantable cardioverter defibrillator
ILR	implantable loop recorder
IQR	interquartile range
KB	Kardia Band
KMHM	KardiaMobile Heart Monitor
LVEF	left ventricular ejection fraction
MCT	Mobile Cardiac Telemetry
mECG	KardiaMobile electrocardiogram
ms	millisecond
NSVT	non-sustained ventricular tachycardia
NPV	negative predictive value
PAC	premature atrial complex
PFT	personal fitness tracker
PPG	photoplethysmography
PPI	peak-to-peak interval
PPM	permanent pacemaker
PPV	positive predictive value
PVC	premature ventricular complex
RCT	randomised controlled trial
RRI	R-R interval
SCD	sudden cardiac death
SD	standard deviation

sECG	single-lead electrocardiogram
SR	sinus rhythm
ST	sinus tachycardia
SVE	supraventricular ectopy
SVT	supraventricular tachycardia
VA	ventricular arrhythmia
VF	ventricular fibrillation
VP	ventricular pacing
VT	ventricular tachycardia
WCT	wide complex tachycardia
ZEUS	Zio ECG utilisation service

Abstract

Cardiac arrhythmias portend a significant morbidity and mortality in addition to a significant socioeconomic impact on our healthcare system. Thus, the ability to detect these arrhythmias in an accurate and timely manner remains critical in preventing resultant complications. Atrial fibrillation is associated with complications of stroke, heart failure, dementia and all-cause mortality, ventricular arrhythmias may lead to syncope and sudden cardiac death or cardiac arrest, and supraventricular arrhythmias may lead to recurrent hospitalisations. Furthermore, these arrhythmia result in a significant reduction in quality of life, loss of social and economic productivity for the patient and caregivers, and a major burden on the health care system. Diagnosis of these arrhythmias can be elusive and lead to multiple emergency department presentations, clinic visits and repeated investigations.

Novel wearable and handheld devices, which are capable of recording an electrocardiogram (ECG), provide an opportunity for patient empowerment and “on demand” detection of these arrhythmias. They may serve as an adjunct to or replacement of current existing methods for arrhythmia detection, and present an exciting opportunity for the detection, screening and surveillance of these arrhythmias. A number of such devices are available commercially. One such popular device, AliveCor Kardia (AliveCor Inc, Mountain View, California, USA) allows the patient to obtain a single lead ECG (sECG) “on demand”. This device has been demonstrated to be useful in the detection of atrial fibrillation in a number of clinical trials. Case reports have also highlighted its utility in the detection of other non-atrial fibrillation arrhythmias.

Atrial fibrillation remains the most common clinically sustained cardiac arrhythmia that we observe in clinical practice, both in an inpatient and outpatient setting. It has a number of therapeutic options, such as medications for rate and rhythm control, and interventional options such as catheter ablation which may be curative and provide a mortality benefit in those with concurrent systolic heart failure. The use of anticoagulants plays an important and

effective role in limiting thromboembolic complications. However, the diagnosis of atrial fibrillation may be difficult, if arrhythmic symptoms are episodic, and terminate before an ECG can be performed. Ambulatory monitoring may only assist with the diagnosis when symptoms are present and the patient is wearing the monitor. Access to these diagnostic tools may be limited to capitalise the symptom-rhythm correlation. Wearable and handheld devices may allow early detection of symptomatic and asymptomatic atrial fibrillation. Indeed, several large-scale clinical trials have shown enhanced detection of atrial fibrillation with these devices. Ventricular arrhythmias, comprising of ventricular tachycardia and ventricular fibrillation, compose the majority of sudden cardiac deaths. Therefore, early diagnosis of these disorders can be instrumental in preventing this devastating complication. However, these patients often present with syncope or sudden cardiac death, and hence utilisation of handheld and wearable devices can be challenging in these scenarios. In addition to ventricular arrhythmias and atrial fibrillation, a broader spectrum of supraventricular tachycardias have significant prevalence in the community, and their detection can similarly prevent devastating health complications.

The aim of this thesis is to highlight the existing body of literature on the utility of wearable and handheld devices in the diagnosis and management of cardiac arrhythmias. Furthermore, the thesis investigates the accuracy and utility of the AliveCor Kardia for the detection of cardiac arrhythmias in a systematic fashion.

Chapter 1 is an examination of the current literature, highlighting the evidence that exists for handheld and wearable devices in atrial and ventricular arrhythmias as well as the limitations that exist that prevent their widespread adoption. These limitations include a lack of empirical and large-scale data in certain arrhythmias but also the legal and regulatory barriers that still need to be addressed.

Chapter 2 compares the accuracy of the AliveCor for detection of a range of arrhythmias provoked during a cardiac electrophysiology study, which remains the gold

standard of cardiac arrhythmia diagnosis. Forty-nine patients underwent simultaneous recording of a 12-lead ECG, intracardiac electrogram recordings and a sECG recorded with an AliveCor. A total of 843 rhythms were captured and classified by three blinded reviewers and compared to the gold standard diagnosis based on intracardiac electrogram features. The AliveCor was found to be accurate in a broad range of captured rhythms including sinus rhythm, atrial fibrillation, atrial tachycardia, ventricular tachycardia, supraventricular and ventricular ectopy with possible future clinical implications beyond the detection of just atrial fibrillation and sinus rhythm.

Chapter 3 examines the accuracy of the AliveCor against the 12-lead ECG and telemetric monitoring in an inpatient setting. This was done through simultaneous rhythm acquisition from these three modalities with rhythms classified by blinded reviewers using the 12-lead ECG as the gold standard. Forty-three patients had 71 captured rhythms analysed. Though the sECG was able to identify a high proportion of cardiac arrhythmias with reasonable accuracy, it was found to not be as accurate as telemetric monitoring but may present a reasonable option where telemetric monitoring may not be available.

Chapter 4 is a randomised controlled trial of the AliveCor against multi-day Holter monitoring in the diagnosis of cardiac arrhythmias in patients with undiagnosed palpitations or syncope. Forty-one patients were randomised to intervention (AliveCor) or control (ambulatory 5-day Holter monitor on up to three occasions over a period of 6-months, with a minimum separation of 4-weeks). The follow-up period was over 6-months. The primary outcome was defined as; (symptom-rhythm correlation in severe sinus bradycardia, sinus tachycardia, supraventricular tachycardia, atrial flutter or fibrillation, premature atrial contractions, premature ventricular contractions, sustained or non-sustained ventricular tachycardia or high-grade atrioventricular block) or a predefined serious rhythm abnormality. At 6-months, there was no significant difference in the primary outcome between the two groups. However, there were a higher proportion of patients diagnosed with symptomatic or asymptomatic supraventricular

arrhythmias, atrial fibrillation, premature atrial and ventricular ectopy and non-sustained or sustained ventricular tachycardia in the control group. This was driven by a higher rate of asymptomatic arrhythmia detection in the control group, who had continuous monitoring. Scores for patient satisfaction and confidence/empowerment were higher in the intervention group. The trial shows that the AliveCor may be used as an equivalent technology for symptomatic arrhythmia diagnosis in an ambulatory setting.

Chapter 1. The role of contemporary wearable and handheld devices in the diagnosis and management of cardiac arrhythmias

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Signature of Supervisor (signed on behalf of co-authors)	As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct. [redacted]

1.1 ABSTRACT

Cardiac arrhythmias are associated with significant morbidity, mortality and economic burden on the health care system. Detection and surveillance of cardiac arrhythmias using medical grade non-invasive methods (electrocardiogram, Holter monitoring) is the accepted standard of care. Whilst their accuracy is excellent, significant limitations remain in terms of accessibility, ease of use, cost, and a suboptimal diagnostic yield (up to ~50%), which is critically dependent on the duration of monitoring. Contemporary wearable and handheld devices that utilise photoplethysmography and the electrocardiogram present a novel opportunity for remote screening and diagnosis of arrhythmias. They have significant advantages in terms of accessibility and availability with the potential of enhancing the diagnostic yield of episodic arrhythmias. However, there is limited data on the accuracy and diagnostic utility of these devices and their role in therapeutic decision making in clinical practice remains unclear. Evidence is mounting that they may be useful in screening for atrial fibrillation, and anecdotally, for the diagnosis of other brady and tachyarrhythmias. Recently, there has been an explosion of patient uptake of such devices for self-monitoring of arrhythmias. Frequently, the clinician is presented such information for review and comment, which may influence clinical decisions about treatment. Further studies are needed before incorporation of such technologies in routine clinical practice, given the lack of systematic data on their accuracy and utility. Moreover, challenges with regulation of quality standards and privacy remain. This state-of-the-art review summarises the role of novel ambulatory, commercially available, heart rhythm monitors in the diagnosis and management of cardiac arrhythmias and their expanding role in the diagnostic and therapeutic paradigm in cardiology.

1.2 INTRODUCTION

Cardiac arrhythmias, comprising of atrial arrhythmias such as atrial fibrillation (AF), supraventricular tachycardias (SVTs) and ventricular arrhythmias (VA), are a major cause of hospitalisations, and portend significant morbidity and mortality.[1] They are associated with increased cardiovascular complications such as syncope, fatigue, exertional dyspnoea, heart failure and death.[1] This can contribute to a decreased quality of life, disability, increased mortality and burden on the healthcare system.[1]

Each of the individual arrhythmias have a distinct risk profile of morbidity and mortality. AF is clinically the most common sustained cardiac arrhythmia observed in medical practice and is associated with a significant and independent risk of stroke and thromboembolism, cardiac failure and mortality.[2] It affects 1 in 4 adults aged ≥40 years during their lifetime.[3] The Global Burden of Disease (GBD) study in 2019 showed that 59.7 million individuals worldwide had AF or atrial flutter with the total number of attributable deaths close to 300,000 in 2019.[4] It also represents an underdiagnosed clinical condition, with previous studies indicating that approximately 10% of patients over the age of 65 who have pacemakers or implantable cardioverter defibrillators (ICDs) have subclinical and previously undetected AF.[5] In addition to this, AF also portends a significant economic burden as shown in the United States (US), with an estimated cost of $28.4 billion US dollars (USD) in 2016.[4]

Ventricular arrhythmias, in particular ventricular tachycardia (VT) and fibrillation (VF), are responsible for the majority of sudden cardiac deaths (SCD).[6] The majority of SCDs occur in patients who are considered at low risk and therefore early diagnosis is paramount. Additionally, SVT, with a prevalence of 225 per 100,000 people, causes significant debilitation, impaired quality of life and economic burden from repeated hospital or clinical visits.[4]

Accurate and timely diagnoses of arrhythmias is critical in preventing morbidity and mortality, allowing initiation of therapies for prevention of complications, such as anticoagulation in AF to prevent stroke, or insertion of ICDs in VA to prevent SCD, and medical

therapy or catheter ablation for all forms of arrhythmias. Ambulatory cardiac monitoring remains the most frequently used clinical tool to detect episodic arrhythmias.

There is an accumulating body of evidence that wearable and handheld devices may be a useful diagnostic tool for arrhythmia detection, increasing the potential for early diagnosis and initiation of therapy. Their widespread availability, accessibility and ease of use are major advantages in the diagnosis and surveillance of cardiac arrhythmias. The purpose of this state-of-the-art review is to summarise the advantages and disadvantages of existing methods of monitoring and contextualise the role of these novel devices in the diagnosis and management of cardiac arrhythmias.

1.3 ESTABLISHED NON-INVASIVE AND INVASIVE METHODS IN THE DIAGNOSIS AND MANAGEMENT OF CARDIAC ARRHYTHMIAS

The most commonly utilised methods for the diagnosis and surveillance of cardiac arrhythmias are the 12-lead electrocardiogram (ECG), continuous cardiac telemetry monitoring, single and multi-day Holter monitoring, external and implantable loop recorders (ELR and ILR) as well as pacemakers, and ICDs.[7]

1.3.1 12-Lead ECG

The 12-lead ECG allows non-invasive detection of cardiac arrhythmias.[8] However, it only provides a snapshot of the electrical activity in the heart at a particular moment, which reduces its utility in the diagnosis of paroxysmal arrhythmias. ECGs can capture arrhythmias whilst they are occurring but are not easily accessible to patients. Therefore, frequent hospital or clinical visits are often required before the diagnosis can be made.

1.3.2 Holter Monitor

The Holter monitor is the traditional ambulatory method for arrhythmia diagnosis. It serves as a battery-operated portable device with flashcard technology that records heart activity usually

over a period of 24–48-hours but with a duration of up to 1–2 weeks.[9] Its complexity can vary from a 2-lead or 3-lead Holter monitor to a 12-lead ECG Holter monitor, each attached with wires and small electrodes to a patient's skin.[10, 11] The device is able to display P-wave morphology, the QRS complex and the R-R interval, along with a more complex automated analysis of heart rate variability which can indicate autonomic tone.[10]

The main benefit of Holter monitoring is its ability to continuously record ECG data without patient participation, assisting detection of asymptomatic arrhythmias of prognostic significance such as AF or VAs, along with the capability of a patient-activated trigger for symptomatic episodes.[9, 10] However, the duration of recording may still be insufficient if symptoms are episodic.[9, 12] It is also frequently limited by patient non-compliance due to the cumbersome nature of carrying the device, managing the leads and electrodes (to be taken on and off before and after showering), skin sensitivity to prolonged electrode contact and logging of symptomatic events.[9]

Some of these disadvantages have limited the efficacy of Holter monitoring. It is estimated that traditional 24–48-hr Holter monitors have a diagnostic yield of only 10–15% for palpitations, and 1–5% for syncope and cryptogenic stroke.[13] This may result in repeat subsequent investigations including 12-lead ECGs, multiple Holter monitors, emergency departments visits and/or hospitalisations before a diagnosis is made, incurring an additional cost and burden on the healthcare system.

1.3.3 External Loop Recorder

An ELR is a device that can be connected to a belt around the chest, without the need for traditional adhesive electrodes and can monitor the ECG continuously for up to a period of 30 days.[14] It is smaller than the Holter monitor in size and records data when activated by a patient or if triggered by an abnormal heart rhythm dependent on programming of the device.[15] The ECG signal is acquired from the chest electrodes, with data then transmitted to a central monitoring station remotely or physically loaded onto a computer, before being reviewed by a

physician.[16] In order for effective detection of abnormal conditions during routine activities, an accelerometer and/or gyroscope can also be used to improve the ECG signal, which itself can vary in complexity from a single-lead system to a complex array of electrodes covering the torso.[16]

The ELR is particularly useful in patients with infrequent palpitations (up to four weeks between symptoms).[17] This provides the advantage of longer-term monitoring as well as additional convenience. A drawback lies in that it is reliant on patients activating the recorder when symptoms occur and device detection of an abnormal heart rhythm and thus it has a limited role in syncope.[15, 17] Although it represents an increase in cost to the traditional Holter monitor, in a recent study by Francisco-Pascual et al., the authors randomised 149 patients with undifferentiated palpitations to a diagnostic protocol utilising ELR (91 patients) vs. standard of care (58 patients) and demonstrated a cost per diagnosis of €375.13 in the ELR group and €5184.75 in the control group, with a cost reduction of €11.30 for each % point of increase in diagnostic yield.[16, 18] It has a diagnostic yield of up to 87% in patients with unexplained palpitations, a significant improvement upon the traditional Holter monitor.[18]

1.3.4 Implantable Loop Recorder

An ILR is a small subcutaneous device which is capable of continuously monitoring and recording events for up to 4.5 years.[17,19,20] They are typically implanted subcutaneously in the left parasternal area of the chest.[14] There are two sensing electrodes built into the ILR external shell which are able to record a single-lead ECG that can be retrieved with a programmer.[21] Their recording functionality is inherently similar to the ELR; they retain information pertaining to relevant arrhythmias that are automatically detected based on predefined algorithms or when the ILR is activated by the patient.[14] ILRs especially provide value in patients with infrequent unexplained syncope. They are also valuable in detection of AF in cryptogenic stroke patients and facilitate potential arrhythmia-event correlation, if diagnosis of an underlying arrhythmia remains elusive.[17] They are however associated with higher costs compared to ELR. Their infection rates are low (1–2%) and provide a superior duration of long

term monitoring.[14, 22] Another advantage is they do not require removal during certain activities such as showering or swimming.[23]

ILRs are however limited by the registration of only one lead and limited storage capacity (generally less than one hour).[14] They also require a minor surgical procedure with possible local complications.[16] Mechanistically, the ILR provides a subcutaneous signal, as the electrodes are not in direct contact with the heart chambers, leading to the signal being affected by interference and electrical noise.[24] This can lead to an “undersensing” or “oversensing” phenomenon and incorrect detection of the R-waves.[24] However, despite their limitations, ILRs provide a superior diagnostic yield in unexplained, recurrent syncope when compared to ELR’s and Holter monitors of up to 88%.[9]

1.4 CONTEMPORARY WEARABLE AND HANDHELD DEVICE TECHNOLOGIES

Wearable devices are increasingly popular amongst consumers. They help facilitate timely medical attention, dramatically changing the diagnostic paradigm for cardiac arrhythmias.[12] Projected growth estimates predict a total of 929 million connected devices in 2021.[25] This technology is often reliant upon a Smartphone to maximise usability and functionality, with their tremendous potential highlighted by the fact that more than 70% of the world currently utilise mobile devices.[26] An estimated 20% of US residents currently own a wearable device and with a compound annual growth rate of 25%, the global market is expected to reach $70 billion USD by 2025. This novel technology also allows for the monitoring of vulnerable populations from the comfort of their own homes as well as patients
in more remote regions who may face disparities in access to care.[12, 27, 28]

The adoption of wearable devices has significantly accelerated after the coronavirus disease 2019 (COVID-19) pandemic, with the ever-increasing utilisation of telemedicine.[29]

These devices, which can capture multiple data streams of important physiological parameters such as heart rates and ECGs, also present simple and affordable options for cardiac monitoring.[12]

This review will focus on wearable devices that can aid in the diagnosis of cardiac arrhythmias through the mechanism of photoplethysmography (PPG) and single-lead electrocardiogram (sECG) as well as handheld sECG and multi-lead ECG devices such as the AliveCor (AliveCor Inc, Mountain View, CA, USA). Contemporary wearable device technologies are defined as consumer-grade, connected electronic devices that are an accessory, typically worn on the wrist or the body.[29] These devices are non-invasive as well as being easy to wear and operate, allowing the capture of a multitude of physiological parameters.[28] This allows significant autonomy for the consumer and facilitates a more informed shared decision-making process between the consumer and healthcare professional.

Contemporary wearable device technologies have an abundance of applications in cardiology through mechanisms such as the accelerometer, barometer, global positioning system (GPS), PPG, ECG, oscillometry as well as biomechanical and biochemical sensors.[29] They have tremendous scope in cardiovascular care including in cardiovascular risk assessment, lifestyle interventions, hypertension, heart failure, coronary artery disease and cardiac rehabilitation but their ever-growing utility lies in the field of cardiac arrhythmias.[29] Their efficacy and mechanism in cardiac arrhythmias are primarily through their capability of monitoring heart rate (HR), heart rate variability (HRV) and heart rhythm through PPG or ECG.[29,30]

1.5 MECHANISM OF PPG IN WEARABLE DEVICES

Wearable smartwatches include the Garmin (Garmin Ltd, Lenexa, Kansas, USA) Vivosmart 4, Fitbit (FB) (Fitbit Inc, San Francisco, CA, USA) Charge series, Huawei (Huawei Technologies Co., Ltd, Shenzhen, Guangdong, China) Watch GT, and Apple Watch (AW) (Apple Inc, Cupertino, CA, USA). These devices share a common mechanism in monitoring

the HR through PPG.[31-33] Whilst the AW4-6 series includes an ECG application, which was recently approved by the Food and Drug Administration in the USA and the Therapeutic Goods Administration in Australia, the large-scale validation of the AW has occurred with its PPG technology in the earlier series'.

The major advantage of smartwatches such as the AW and FB Charge 4 is that they are portable, water-resistant and allow continuous HR tracking (Table 1.1 and Table 1.2).[34-38] The AW has established utility in the diagnosis of AF but a common limitation of functionality with smartwatches that employ PPG, remains their underestimation of HR, especially when exceeding 100 beats per minute (bpm).[34-38]

PPG relies on an infrared, red or green light to measure volumetric variations in peripheral blood circulation.[39] The wrist typically can detect both optical and pressure sensors and produce a pulse signal.[40] The optical sensing method of PPG relies on capturing the intensity of light reflected from skin based on the light-emitting diodes and photodetectors.[40] A light source illuminates the underlying arteries while a photodetector collects the light reflected and transmitted through tissue.[41] The intensity of reflected light through skin is subject to blood volume.[40] The obtained voltage signal represents the pulsatile blood volume changes in the peripheral microvasculature induced by pressure pulse within each cycle and hence produce a HR.[39, 41] It is also imperative that the sensing unit remains in direct contact with the skin.

The PPG waveform consists of direct current (DC) and alternating current (AC) components (Figure 1.1).[39] The DC component of the waveform corresponds to the detected, transmitted or reflected optical signal from the tissue, and is dependent on tissue structure and the average volume of venous and arterial blood.[39] The AC component shows changes in the blood volume that occurs between the systolic and diastolic phases of the cardiac cycle; this frequency is dependent on the HR and is superimposed upon the DC (Figure 1.1).[39]

1.5.1 Validation of PPG

The two main methodologies for validation of PPG are through comparison of the HR between a PPG-derived signal and an ECG, and by comparing the PPG-derived peak-to-peak intervals (PPI) to an ECG derived R-R interval (RRI; Figure 1.2).[42]

1.5.2 Comparison of HR and HRV between ECG and PPG

Kroll et al. compared the personal fitness tracker (PFT) derived heart values to gold standard measurements of continuous ECG (cECG) monitoring in a group of 50 patients.[43] There was minimal discrepancy with PFT-derived heart values compared to cECG monitoring in sinus rhythm (SR), with an increased discrepancy with an alternate rhythm (average bias –0.99bpm [SR] vs. -5.02bpm [not in SR, P=0.02]).[43] Bolanos et al. demonstrated that HRV, an important marker of autonomic regulation of HR, illustrated the PPG signal had excellent agreement with ECG signals in healthy individuals.[44] These studies have been vital in establishing the validity of PPG in HRV signal derivation and analysis in ambulatory cardiac monitoring, particularly in healthy individuals.[43, 44]

1.5.3 Comparison of PPG derived PP interval to ECG derived RR interval

The concern lies in that the PPG wave lags behind the ECG signal by the time required for transmission of pulse wave.[45] Selvaraj et al. demonstrated that PPG-derived PPI and ECG-derived RRI showed a high correlation (median=0.97). The time domain, frequency domain and Poincaré plot (different measures of HRV) HRV parameters computed using RRI method and PPI method showed no significant differences ($P<0.05$).[45] Vandenberk et al. similarly measured 20,298 millisecond (ms) RRI and PPI in a total of 229 subjects who utilised the FibriCheck (an application that utilises PPG) compared to a synchronised ECG recording.[42] They demonstrated an excellent positive correlation ($rs=0.993$) between the PPI from FibriCheck and the RRI from the wearable ECG, providing further impetus behind the validity of PPG correlation with HR.[42]

1.5.4 Limitations of PPG

PPG technology limitations include its susceptibility to motion artifacts during routine activities and physical exercise.[46, 47] Environmental noise (e.g., powerline interference) may also affect the PPG signal, contributing to inaccuracies in HR estimation.[48] PPG HR measurements are up to 15% more inaccurate in people with dark skin compared to light skin, likely reflective of melanin absorbing more green light.[49]

Pressure disturbances that act on the probe, such as the force of contact between the PPG sensor and measurement site, can deform the arterial geometry through compression.[39] The subsequent reflected PPG signal will acquire a reduced AC amplitude. Paradoxically, insufficient pressure between the PPG sensor and measurement site can also cause a reduced AC amplitude.[39] The diversity of consumers for which wearable technologies are applicable (e.g., young and old, varying body habitus) underscores the potential challenges in extrapolating HR data from wearable devices (Figure 1.3).

1.6 ALIVECOR KARDIAMOBILE HEART MONITOR AND KARDIA BAND

The AliveCor represents a handheld device that can record electrical rhythms from the heart (Figure 1.4).[50] The AliveCor, which remains compatible with most mobile devices, rests on the individual's fingers and chest when recording an ECG.[50] There is transmission of electrical impulses from an individual's fingertip into ultrasound signals transmitted to their mobile device's microphone and can subsequently be reviewed on the KardiaMobile application.[50] This sECG is analogous to lead I on a 12-lead ECG and can be reviewed on the AliveCor KardiaMobile Application.[51]

Recently, the AliveCor 6-lead ECG has been introduced. This device provides the first personal solution for Einthoven's triangle, the concept of cardiac vectors central to

electrocardiography, enabling recording of all six limb leads.[52, 53] This allows measurement of the QRS complex (representative of ventricular depolarisation), T-wave axis and the QT interval (representation of the period of time of ventricular depolarisation and repolarisation).[52] The prolongation of this QT interval, most accurately measured in lead II, can lead to potentially fatal cardiac arrhythmias.[52] The major advantage of the AliveCor is that it is portable and provides symptom-rhythm correlation but requires the patient to actively record the ECG.
It may be helpful in the detection of paroxysmal, or intermittently symptomatic arrhythmias (Table 1.2).

The Kardia Band (KB) was an AW accessory utilised as a band which allowed patients to record a rhythm strip equivalent to lead I for 30-seconds. This was processed in tandem with an application that provided an instantaneous and automatic adjudication algorithm, classifying the rhythm as normal or abnormal.[54] Though it was highly efficacious in the diagnosis of AF, it has been discontinued, following the advent of the 6-lead AliveCor KardiaMobile ECG and the newer AW series which facilitate the use of the ECG.

1.7 SMARTWATCHES WITH ECG FUNCTIONALITY

In recent years, we have seen the adoption of smartwatches that utilise ECG functionality in addition to traditional PPG technology. These devices include the AW 4-6 series, Withings (Issy-les-Moulineaux, Paris, France), Move ECG, Fitbit Sense and Samsung (Samsung Group, Seocho District. Seoul, South Korea) Galaxy Smartwatch. Their mechanism of recording an ECG relies on an individual placing their finger on the crown of the device for at least 30 seconds after opening the related application on either the smartwatch or a smartphone, providing a sECG analogous to lead I.[55] The subsequent algorithm utilised for detection for AF is premised on the detection of irregularity of ventricular rhythm.

The major limitation of smartwatches with ECG functionality, similar to other portable technologies, lies in the requirement for patient activation of the device, minimising its utility in paroxysmal or asymptomatic arrhythmias. Given these devices are optimally suited for measuring lead I, it does limit its detection of P-waves, subsequently complicating physician

interpretation of the underlying atrial rhythm.[55] Another barrier to widespread adoption of these devices remains cost, with a range between $150 USD (Withings) to more than $1000 USD (AW with iPhone) and lack of reimbursement of some devices from health care providers, and no consistent reimbursement for health care professionals in interpreting these tracings.[55]

There remains a paucity of large-scale trials to evaluate smartwatch-based ECG applications and appraisal of false positives and false negatives rates of such devices. It is important that these issues are addressed before widespread adoption of these devices in screening, diagnosing, and managing arrhythmias can be implemented in the community.

1.8 WEARABLE PATCH DEVICES

Adhesive ECG patches represent another method of ambulatory monitoring for arrhythmias. They comprise a sensor system, a microelectronic circuit with recorder, and an internal battery embedded in a flexible synthetic matrix or resin.[56] They are utilised for medium-long term use, over a period of days to several weeks.[56] These devices will involve recording only devices or recording and transmitting devices, and usually provide a sECG.[57] These wearable patches include the recording only Zio (iRhythm Technologies, San Francisco, CA, USA) patch and the recording and wirelessly transmitting NUVANT (Corventis, Inc., San Jose, CA, USA) Mobile Cardiac Telemetry (MCT) system consisting of the PiiX patch.[12, 57]

Zio is a water-proof adhesive patch attached to the left pectoral region, which provides a sECG, and can be worn for up to 14-days without the need of battery replacement or recharging over this period (Figure 1.5).[12, 57-59] Patients can activate a button on the Zio Patch at any time, with the clinician later able to correlate the time of ECG tracings with symptoms.[57] The ECG data is transmitted locally to a gateway handheld device.[57] The Zio ECG utilisation service (ZEUS) receives this data and utilises beat-by-beat QRS detection and an advanced rhythm analysis algorithm to detect up to ten types of rhythms.[57]

NUVANT-MCT consists of a chest worn wearable patch and a portable data transmission device and provides real-time, wireless arrhythmia monitoring and analysis, with

a corresponding magnet that is used as a trigger when the patient is symptomatic.[12, 60, 61] The technology revolves primarily around the PiiX, a sECG wearable patch which transmits readings to a mobile phone-based device and subsequently to a monitoring centre for physician review.[57] These wearable patches similarly provide diagnostic yield with additional benefits of ambulatory convenience.

1.9 MANAGEMENT OF SPECIFIC ARRHYTHMIAS USING WEARABLE OR HANDHELD DEVICES

1.9.1 Atrial Fibrillation

The majority of data for handheld and wearable devices exists in the detection and management of AF. They have now been incorporated in multiple international guidelines for screening of AF[62, 63] but they have not been incorporated in a diagnostic work-up of AF. Future clinical practice may indicate initial PPG screening with handheld and/or wearable devices with confirmation of arrhythmia on sECG of handheld and/or wearable devices, potentially avoiding the use of other diagnostic tools, although this workflow remains to be validated in large scale studies.

1.9.1.1 AliveCor KardiaMobile Heart Monitor

Previous studies have demonstrated the efficacy of the AliveCor KardiaMobile Heart Monitor (KMHM) in a multitude of clinical settings with both diagnostic and management implications, including a high sensitivity (96.6%) and specificity (94.1%) in AF detection,[64] in the detection of silent AF and potential prevention of ischaemic strokes in the asymptomatic aging population,[65] and in the detection of recurrence of AF post-ablation or cardioversion.[66]

1.9.1.2 Apple Watch (PPG and ECG)

The Apple Watch is similarly efficacious in the diagnosis of AF. Perez et al. first demonstrated a positive predictive value of 0.84 (95% confidence interval [CI]=0.76–0.92) for patients who had an irregular pulse notification that correlated with an ECG patch.[67] Seshadri et al.

subsequently expanded upon the limitations in the treatment algorithm from Perez et al. (optical sensors in AW 1-3 series and a proprietary algorithm) by utilising an AW4 which used electrodes to generate an sECG providing rhythm notification and an sECG downloaded for physician interpretation, and highlighted a 41% sensitivity and 100% specificity for AF detection.[67,68]

These findings contrasted Apple's internal study of 290 subjects, where the algorithm that classified ECGs as AF had 98.3% sensitivity.[34] This discrepancy can partially be explained by Apple's internal study excluding 50 ECGs (17.2%) interpreted as unclassifiable, unreadable or device result not reported in their calculation of sensitivity in AF, whereas conversely Seshadri et al. included 29 ECGs (32%) interpreted as inconclusive in their calculation of sensitivity in AF. There remains a paucity of data into management outcomes associated with detection of AF using the AW. The ongoing HEARTLINE trial is the first randomised trial to investigate the detection of symptomatic and asymptomatic AF with the use of AW4 or a newer model to assess for improvement in clinical outcomes.[29] This trial aims to recruit 150,000 US residents aged ≥65 and evaluate the efficacy of the AW in the diagnosis of AF, evaluate improvement in cardiovascular outcomes and improve direct oral anti-coagulant adherence and persistence.[69] A summary of actively recruiting registered trials is provided in Table 1.3.

1.9.1.3 Huawei Watch GT

Guo et al. performed the second large screening study for AF after the Apple Heart Study in a total of 187,912 individuals ≥18 years of age across China.[70] Monitoring was performed for at least 14-days using a wristband (Honor Band 4) or wristwatch (Huawei Watch GT, Honor Watch). Among those with PPG monitoring, 0.23% or 424 patients received a "suspected AF" notification with the positive predictive value of PPG signals being 91.6% with 80% of high-risk patients with AF identified from this study successfully anticoagulated, highlighting the potential for large-scale screening and management implications.

1.9.1.4 Fitbit

There is limited data into the diagnostic yield of FB devices in AF. Koshy et al. demonstrated a significant HR underestimation in AF (Bias FB=-28 beats when compared to AW=-8 beats) with wide limits of agreement, raising concerns about the tachogram as an accurate modality for AF detection.[71] Al-Kaisey et al. similarly demonstrated in patients wearing an AW (PPG) or FB (PPG), the degree of underestimation of HR in AF was more pronounced with a HR>100bpm (bias of -28 beats for HR 100–120bpm, -48 for 120–140bpm, and -69 for >140bpm) compared to a slower HR (bias of -6 for HR 80–100bpm, <1 for 60–80bpm and -1 for <60bpm).[35]

The Fitbit Heart Study aims to address these issues through a novel PPG-based software algorithm for detecting AF and has currently recruited 455,699 patients in a large scale remote clinical trial.[36] Participants in whom an irregular heart rhythm is detected will be invited for a telehealth visit and subsequently mailed a one-week sECG patch monitor, with the primary objective to assess the positive predictive value (PPV) of an irregular heart rhythm detection for AF during the period of the ECG patch monitor.[36]

1.9.2 Smartwatches with ECG functionality

Avram et al. demonstrated the potential utility of the Samsung Galaxy Active Watch 2, a device with PPG and ECG capabilities for continuous detection of AF.[72] A total of 204 participants with a known prior diagnosis of AF or deemed at risk of AF were enrolled and results from a PPG and ECG algorithm were compared to those from a 28-day continuous ECG patch. The PPG algorithm was found to have 87.8% sensitivity and 97.4% specificity for AF whilst the ECG algorithm demonstrated similar results of 98.9% sensitivity and 99.3% specificity.[72]

Despite the promising results of this trial, there remains a paucity of other trials that explore ECG technology in smartwatches, with a need for further large-scale trials to validate use in a clinical setting.

1.9.2.1 Alternative Wearable Devices

Whilst there is a paucity of data on the utility of Garmin Smartwatches in AF diagnosis, there has been significant exploration of wearable patches. Steinhubl et al. randomised 2659 patients who wore a self-applied continuous ECG monitoring patch at home during routine activities for up to four weeks to either initiation of a patch at time of enrolment or with a delay of up to four months after enrolment.[73] New AF was identified by four months in 3.9% of the immediate group vs. 0.9% in the delayed group (absolute difference 3.0% [95% CI=1.8%–4.1%]), and active monitoring was associated with increased initiation of anticoagulants (5.7 vs. 3.7 per 100 person-years; difference, 2.0 [95% CI=1.9–2.2]), outpatient cardiology visits (33.5 vs. 26.0 per 100 person-years; difference, 7.5 [95% CI=7.2–7.9), and primary care visits (83.5 vs. 82.6 per 100 person-years; difference, 0.9 [95% CI=0.4–1.5]), highlighting diagnostic and management implications of wearable patches.[73]

Heo et al. similarly explored the diagnostic yield of patch monitoring for AF in high-risk asymptomatic patients with diabetes and/or chronic kidney disease (CKD).[74] A population of 608 individuals with diabetes without a prior diagnosis of AF, wore an ECG patch for 2-weeks, twice, over a 4-month period with a total follow-up period of 1-year.[74] AF was newly diagnosed in 7.3% of participants with CKD and 2.3% in those without CKD over the follow-up period ($P<0.05$).[74] This study highlights the utility of patch monitoring for AF in a high-risk asymptomatic patient demographic, with potential resulting improvement in clinical outcomes.

1.9.3 FDA approved devices[75]

Current handheld and wearable devices that have FDA Class II approval include handheld devices such as the Kardia Mobile sECG, Kardia Mobile 6-Lead ECG, Omron HCG 801, ECG check and wearable devices including the Apple ECG Application, Apple Photoplethysmography Analysis software, Fitbit ECG software, Fitbit Photoplethysmography Analysis software, Samsung ECG application, Garmin ECG Application, Withings Scan Monitor (ECG) and wearable patches including the Zio Patch and Nuvant-MCT as well as

implantable loop recorders such as the Reveal Insertable Loop Recorder System and external recorders such as the Biosensor Holter Monitor System.

The current indications for use for some of the available devices as per FDA approval include:

Kardia Mobile sECG:

- "The KardiaMobile Card System is intended to record, store and transfer single-channel electrocardiogram (ECG) rhythms".
- "The KardiaMobile Card System also displays ECG rhythms and output of ECG analysis from AliveCor's KardiaAI platform including detecting the presence of normal sinus rhythm, atrial fibrillation, bradycardia, tachycardia, and others".
- "The KardiaMobile Card System is intended for use by healthcare professionals, patients with known or suspected heart conditions and health-conscious individuals".
- "The device has not been tested and is not intended for paediatric use".

Apple ECG application:

- "The ECG app is a software-only mobile medical application intended for use with the Apple Watch to create, record, store, transfer, and display a single channel electrocardiogram (ECG) similar to a Lead I ECG".
- "The ECG app determines the presence of atrial fibrillation (AFib), sinus rhythm, and high heart rate (no detected AF with heart rate 100-150 bpm) on a classifiable waveform".
- "The ECG app is not recommended for users with other known arrhythmias".
- "The ECG app is intended for over-the-counter (OTC) use".
- "The ECG data displayed by the ECG app is intended for informational use only".
- "The user is not intended to interpret or take clinical action based on the device output without consultation of a qualified healthcare professional".

- “The ECG waveform is meant to supplement rhythm classification for the purposes of discriminating AFib from sinus rhythm and is not intended to replace traditional methods of diagnosis or treatment”.
- “The ECG app is not intended for use by people under 22 years old”.

Zio Patch:

- "The Zio® Patch is a prescription-only, single-patient-use, continuously recording EGG monitor that can be worn up to 14 days”.
- “It is indicated for use on patients who may be asymptomatic or who may suffer from transient symptoms such as palpitations, shortness of breath, dizziness, light-headedness, pre-syncope, syncope, fatigue, or anxiety”.

Reveal Insertable Loop Recorder System:

- “The Medtronic Model 9525 Reveal™ Insertable Loop Recorder is an implantable, patient activated monitoring system that records subcutaneous ECG and is indicated for patient who experiences transient symptoms that may suggest a cardiac arrhythmia”

Biosensor Holter Monitor System:

- “The Biosense Holter Monitor System is intended for patients requiring Ambulatory (Holter) monitoring from 1 to 24 hours. Such monitoring is used for the indications below”:

1. Evaluation of symptoms suggesting arrhythmia or myocardial ischaemia

2. Evaluation of ECG documenting therapeutic interventions in individual patients or groups of patients

3. Evaluation of patients for ST segment changes

4. Evaluation of patient’s response after resuming occupational or recreational activities (e.g., after M.I. or cardiac surgery)

5. Evaluation of clinical syndromes or situations where arrhythmia may increase the risk of sudden death

6. Clinical and epidemiological research studies.

1.10 NON-AF ARRHYTHMIAS

1.10.1 Wearable smartwatches

Hwang et al. demonstrated the accuracy of PPG-based wrist-worn wearable devices in the assessment of SVT or paroxysmal palpitations in 51 patients who were scheduled to undergo an electrophysiology study (EPS). The HR during induced SVT ranged from 108bpm to 228bpm and the accuracy (within ±10bpm of an ECG) was 100%, 90% and 87% for the Apple, Galaxy and Fitbit smartwatches, respectively.[76]

Whilst the data published on detection of VT is limited, there have been case series which have identified the possibility of diagnosing symptomatic VT and provided "symptom-rhythm correlation" through the utilisation of a Smartwatch and its functionality of PPG and sECG capture, as demonstrated by Burke et al.[77] In this case series, a 60-year-old police officer presented to hospital with a wide complex tachycardia consistent with VT that was identified by his AW sECG, correlating clinically with symptoms and ultimately led to cardiac magnetic resonance imaging (cMRI), a 12-lead ECG and an EPS which confirmed a diagnosis of arrhythmogenic right ventricular cardiomyopathy.[77] In the setting of limited case studies and a lack of large-scale trials, VT remains an underexplored entity in wearable and handheld devices, particularly when compared to atrial arrhythmias. A summary of published case reports and series on wearable devices in non-AF arrhythmias is provided in Table 1.4.

1.10.2 AliveCor KardiaMobile Heart Monitor

The AliveCor KMHM has been shown to be efficacious in the diagnosis of non-AF arrhythmias. It was shown to be diagnostically superior to or concordant with Holter monitoring in 82% of patients presenting to an urgent care centre with palpitations (detected arrhythmias included

premature atrial complexes (PACs), premature ventricular complexes (PVCs), SVT, VT, AF and inappropriate sinus tachycardia).[78] This was similarly validated in a cohort of 240 people presenting to an emergency department with palpitations and pre-syncope, who underwent standard care plus the use of the AliveCor (intervention, n=124) or standard care alone (control, n=116).[79] There was more than a five-fold increase in symptom-rhythm correlation with the AliveCor group (55.6% of participants, 69 patients) compared to the control group (9.5% of participants, 11 patients) with detected rhythms in the AliveCor group including ectopics (8 patients), SVT (3 patients) and AF/atrial flutter (9 patients).[79]

The accurate interpretation of the QRS and QTc is important in the classification and diagnosis of cardiac arrhythmias and prediction of SCD. In a total of 44 patients who underwent a simultaneous recording of a 12-lead ECG and the Kardia 6-Lead ECG, Stavrakis et al. demonstrated that the KardiaMobile 6-Lead ECG and 12-lead ECG had a median QRS amplitude and morphology waveform correlation of ≥0.92 (92%). The average QRS amplitude differences between the 2 methods ranged from 0.01 to 0.05 millivolts.[80] This highlights the accuracy of the KardiaMobile 6-lead ECG in producing clinically equivalent QRS complexes compared to a 12-lead ECG, allowing for potential future expansion of the diagnostic paradigm.

1.10.3 Wearable patches

There has. been exploration into the diagnostics of wearable patches in non-AF arrhythmias. The detection of paroxysmal arrhythmias (including AF, SVT and VA) has been shown to be significantly higher for a 14-day ECG patch than for a 24-hour Holter Monitor by Chua et al. (66% of patients vs. 9% of patients respectively, P<0.001) and Barrett et al. (96 vs. 61 arrhythmia events respectively, P<0.001).[58, 81]

1.11 ALTERNATIVE HANDHELD DEVICES

The AliveCor currently represents the handheld device that utilises sECG with the most robust set of data in multiple clinical settings. However, there are several other handheld devices that use sECG such as MyDiagnostick (Applied Biomedical Systems, BV, Maastricht, The

Netherlands), Omron HCG-801 (Omron Healthcare, Shimogyo-ku, Kyoto, Japan), Zenicor ECG (Zenicor Medical Systems, Gossamer Gardens, London, UK), Beurer ME 90 (Beurer GmbH, Ulm, Swabia, Germany) and the ECG check (Cardiac Designs Inc., Park City, Utah) which have been validated primarily in the setting of AF diagnosis (Table 1.1 and 1.2). There are several guidelines that now recommend the use of opportunistic screening for AF in persons aged 65-years or older with pulse palpation followed by an ECG and thus studies that evaluate the diagnostic utility and accuracy of handheld ECG devices are imperative.[62, 82, 83] A recent systematic review and meta-analysis by Wong et al. reviewed multiple sECG handheld devices (including the AliveCor) and their diagnostic accuracy for AF in the community and hospital setting.[84] They were able to identify six studies in the community setting and eight studies in the hospital setting. The pooled sensitivity was 89% (95% CI=81%–94%) in the community and 92% (95% CI=83%–97%) in the hospital. The pooled specificity was 99% (95% CI=98%–99%) in the community and 95% (95% CI=90%–98%) in the hospital. Notably, the accuracy of sECG devices varied with sensitivity ranging from 54.5% to 100% and specificity ranging from 61.9% to 100%.[84] These fluctuations in sensitivity and specificity in AF diagnosis highlight the need for ongoing validation of these devices in multiple clinical settings. The current lack of data into their utility beyond the scope of AF remains another area to be explored in the future. Table 1.1 to Table 1.4 provides a summary of handheld sECG devices, their clinical applications, efficacy, current exploration in clinical trials and case studies beyond atrial fibrillation.

1.12 ASSESSMENT OF QT_C INTERVAL

The QTc interval remains a vital measurement on an ECG with prolongation associated with VA and SCD. Novel wearable and handheld technologies with ECG capabilities provide additional diagnostic capabilities. Chung et al. and Koltowski have both illustrated the accuracy of the traditional AliveCor sECG for QTc interval measurement when compared to a 12-lead ECG.[85, 86] Puranik et al. investigated the AliveCor 6-lead ECG (which enables assessment of

lead II, the most accurate assessment of the QTc interval) in a group of 13 patients on QTc prolonging medications and compared this with an automated 12-lead ECG Bazett calculation of the QTc. The mean % difference between the two methods was only 3%, suggesting the clinical utility of the 6-lead ECG for QTc monitoring in a high-risk patient demographic.[87]

Spaccarotella et al. similarly evaluated the AW sECG against the 12-lead ECG in 119 patients in baseline SR. They obtained three sECG tracings from each patient with the AW placed in different locations (lead I recorded on the left wrist, lead II on the left lower abdomen and V2 in the fourth intercostal space at the left parasternal edge).[88] They demonstrated agreement among the QT intervals of I, II and V2 leads and the QT means using the standard ECG with Spearman's correlations of 0.866, 0.881, 0.793 and 0.914 ($P<0.001$) respectively. Maille et al. further assessed the efficacy of the Withings Move sECG against standard 12lead ECG for QTc evaluation in a group of 85 patients who had early stage COVID-19 and were treated with a hydroxychloroquine-azithromycin regimen (QT prolonging agent).[89] This study, which was conducted over ten-days with ECG recordings performed at baseline, day 6 and day 10, illustrated the difference in the two methods was <50ms in 98.2% of patients. Thus, the potential and accurate evaluation of QTc with wearable and handheld technologies is evident, particularly in the setting of the COVID-19 pandemic and increasing advent of telemedicine.

1.13 CHALLENGES AND PITFALLS OF WEARABLE AND HANDHELD DEVICES

Long-term data on management outcomes are limited at present. The impact of wearable and handheld devices can be profound in areas such as symptom-rhythm correlation in patients with infrequent arrhythmias as well as screening for asymptomatic arrhythmias in high-risk patients.[25] Their benefit lies in their 'on-demand' nature, accessibility, and usability; albeit at a cost directly to the patient.[90] They represent a useful adjunct for patients who have infrequent symptoms where conventional monitoring technologies such as Holter monitors have failed, or

are poorly tolerated, are inaccessible or when it is desirable to avoid direct patient contact with health care providers in a pandemic such as COVID-19. Indeed, the use of such devices has been recommended by recent societal position statements pertaining to the COVID-19 pandemic. The Cardiac Society of Australia and New Zealand (CSANZ) have recommended the use of smartphone or smartwatch acquired ECGs such as the AliveCor in select low risk patients during the lockdown (heightened restrictions) phase of the COVID-19 pandemic (e.g. those with undiagnosed, infrequent palpitations and a structurally normal heart), with the Heart Rhythm Society (HRS) guidelines also similarly acknowledging vital signs and ECG tracings could be obtained from digital wearables where possible in similarly low risk patients.[91, 92]

An area that will significantly influence the widespread implementation of wearable and handheld devices is related to cost. It remains imperative to assess cost of AF screening in relation to the effect on quality of life and stroke prevention. The REHEARSE-AF trial utilised the AliveCor for AF diagnosis in population screening with a cost of up to £8255 ($10,780 USD) per diagnosis but with no significant change in outcome of stroke/transient ischaemic event/systemic embolic events.[65] The SEARCH-AF trial demonstrated that the cost per stroke prevention in screening with the AliveCor in an asymptomatic population was up to $20,695 USD and $4,066 USD per quality-adjusted life-year gained, which was considered cost effective.[93] However, in order to minimise these costs further in the future, it is also imperative to minimise false positive screening which may lead to overutilisation of health resources. A recent study by Wyatt et al. emphasised this point. In this study of 264 patients who received clinical evaluation post abnormal pulse detection from an AW, a clinically actionable cardiovascular diagnosis was made in only 30 patients (11.4%). This led to a cascade of testing including 12-lead ECG, Holter monitoring and chest X-rays. These false positives in the setting of “abnormal pulse detection” can lead to provocation of patient anxiety. However, a significant limitation of the study remains its lack of access to claims data to assess the actual costs of patient evaluation, but these results are highly suggestive of inefficient resource utilisation.[94]

However, whilst some studies point towards increased financial and resource utilisation, there is also an opportunity to reduce healthcare costs through reduction of unnecessary hospitalisations and improvement of diagnostics and preventive care.[27, 95] Recently, the healthcare utilisation of a cohort of 188 patients using the KardiaMobile ECG (mECG) was compared 1-year prior to obtaining the device with 1-year after. mECG users were less likely to have Holter monitors ordered (30% vs. 6%, P<0.01), have fewer outpatient visits (562 vs. 382, P<0.01), have fewer cardiac specific emergency department visits (51 vs. 30, P<0.01), arrhythmia-related emergency department visits (45 vs. 20, P<0.01), and unplanned arrhythmia admissions (34 vs. 11, P<0.01) in the year after mECG use, compared to the year prior.[96] There is a growing trend towards remote and ambulatory monitoring enabled by technologies such as wearables and smartphones, with the market size expected to rise to around $70 billion by the year 2025 and the healthcare sector instrumental to this growth.[27,95]

Additionally, wearable devices allow for better self-management and intervention strategies which may aid in the diagnosis and development of treatments for conditions which were previously inadequately understood and explored.[12] However, before we can expect widespread acceptance of novel monitoring technologies, there is still an ongoing need for clinical trials that measure outcomes with AF screening that offset the potential flaws of low disease prevalence, misdiagnosis and high cost.[90, 97] It will also be important for clinical programs and electronic medical records providers to provide a mechanism for clinicians to convey feedback to measure the impact they have on care.[90] It is also important to note the vast amounts of data that can be generated from these devices and the information overload it may place on clinicians, another key point to be addressed prior to widespread adoption of this technology.

An additional barrier to adoption of wearable technology is the mismatch between the older generation who have the highest rate of arrhythmias and the younger generation who currently most utilise the technology. Seventeen percent of users in the United States are between 25–34 years of age, whilst only 3.3% of users are 65 years of age or older.[98] The

critical factors that need to be addressed to resolve this issue include reducing device complexity and cognitive load, catering devices to declining physical and mental faculties in the aging population and targeted marketing for the elderly population.[98] It is important that this marketing remains regulated however, and with the current expansion of wearable device technologies with an increasing range of biometrics beyond arrhythmia recognition, that devices do not automatically get recognised as medical grade technologies without appropriate clinical validation.

There exists controversy in the data provided from PPG signals, particularly when considering complex and diverse demographic and environmental factors.[12, 61] These factors include changes in temperature, body movements, hair, skin colour, and tattoos.[12, 99] A method which could be adopted more prominently in the future to address these potential limitations may be through the implementation of artificial intelligence (AI) for arrhythmia detection.[100] Kiranyaz et al. demonstrated that a Convolutional Neural Network (CNN) helped develop an automated algorithm for arrhythmia detection by assessing both real normal and synthesised abnormal beats.[100] They demonstrated that the probability of detecting abnormal ECG beats from the first three occurrences was higher than 99.4%.[100]

As we expect wearable sensors and handheld devices to become increasingly affordable and accessible in the future, it is imperative to consider patient's privacy and data protection, particularly in the setting of any internet-based application, with an aim to keep patient confidentiality and access to their information at the forefront.[101] This will remain a key factor in the advancement of these technologies, with careful resolution of legal regulation about privacy issues important for the adoption of these devices into the wider population.[10]

1.14 CONCLUSIONS

There is tremendous scope for the implementation of wearable and handheld devices into the general population for the screening, diagnosis, and subsequent earlier treatment of potentially life-limiting or life-threatening arrhythmias. These devices provide a unique opportunity to reduce the socioeconomic burden of arrhythmias on the healthcare system with potential

reduction in costs and hospital admissions, along with possible improvements in quality of life. In order to facilitate the appropriate widespread use of these devices, it is imperative to continue not only an evidence-based practice through the ongoing provision of large-scale trials to validate the accuracy of these devices as screening tools (particularly for non-AF arrhythmias), but also to protect patient privacy and maintain rigorous regulation of these novel technologies. There may be a shift from PPG only technologies with their inherent limitations to sECG devices that incorporate both PPG and ECG technology. If these measures are successful, we can expect a paradigm shift to a more personalised and patient-centric approach, improving both diagnostic and management outcomes whilst also empowering the patient in the provision of their own health.

1.15 FIGURES

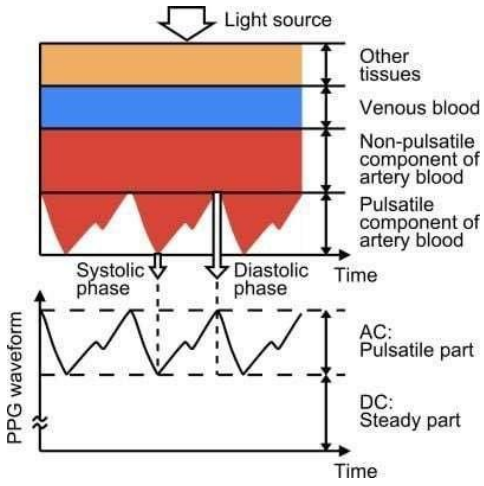

Figure 1.1. PPG waveform consisting of Direct Current (DC) and Alternative Current (AC) components[39]

(Adapted as per the Creative Commons Attribution License)

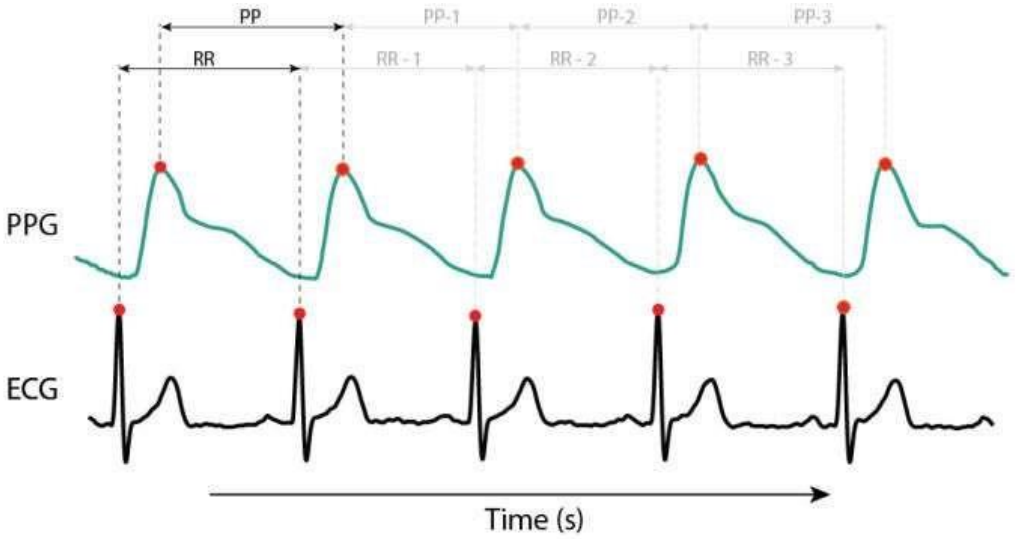

Figure 1.2. Beat-to-beat analysis from R-R intervals (RRI) and peak-to-peak intervals (PPI)[42]

(Adapted as per the Creative Commons Attribution License)

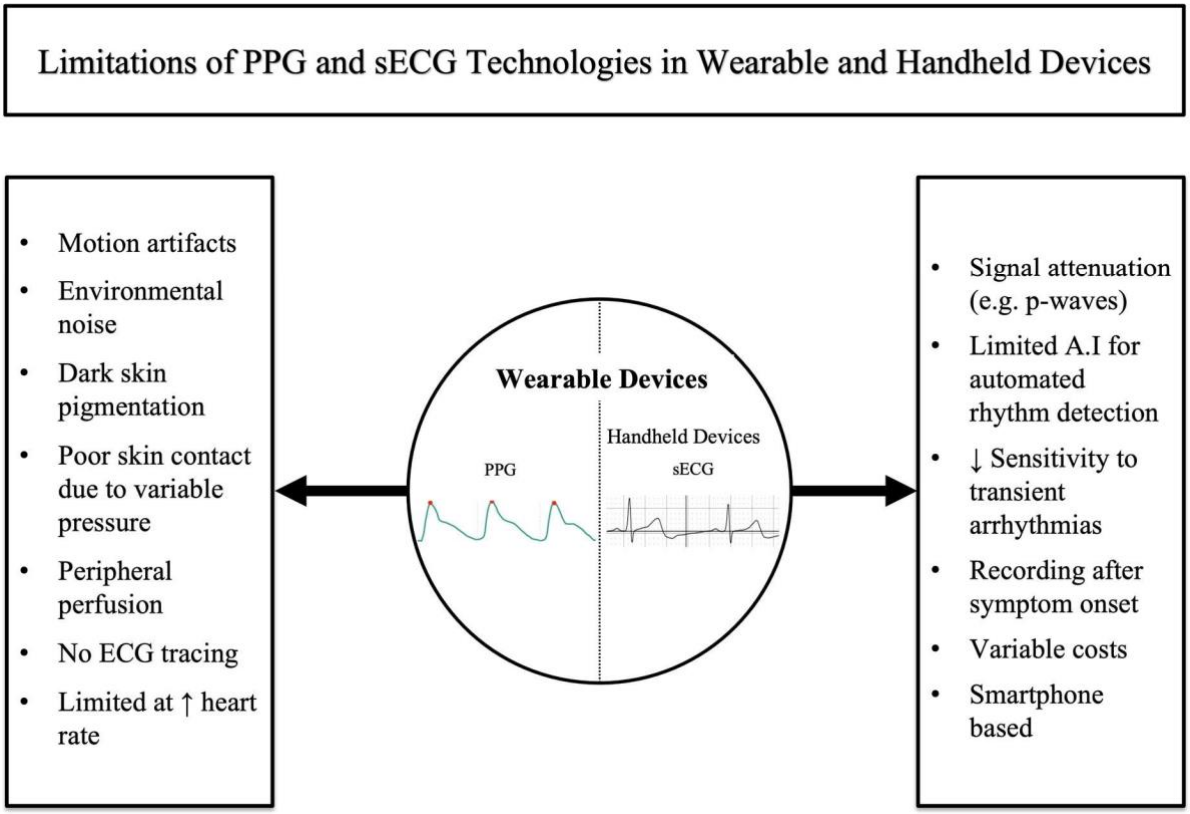

Figure 1.3. Limitations of PPG and sECG technologies are pictorially depicted

Abbreviations: AI, artificial intelligence; PPG, photoplethysmography; sECG, single lead ECG.

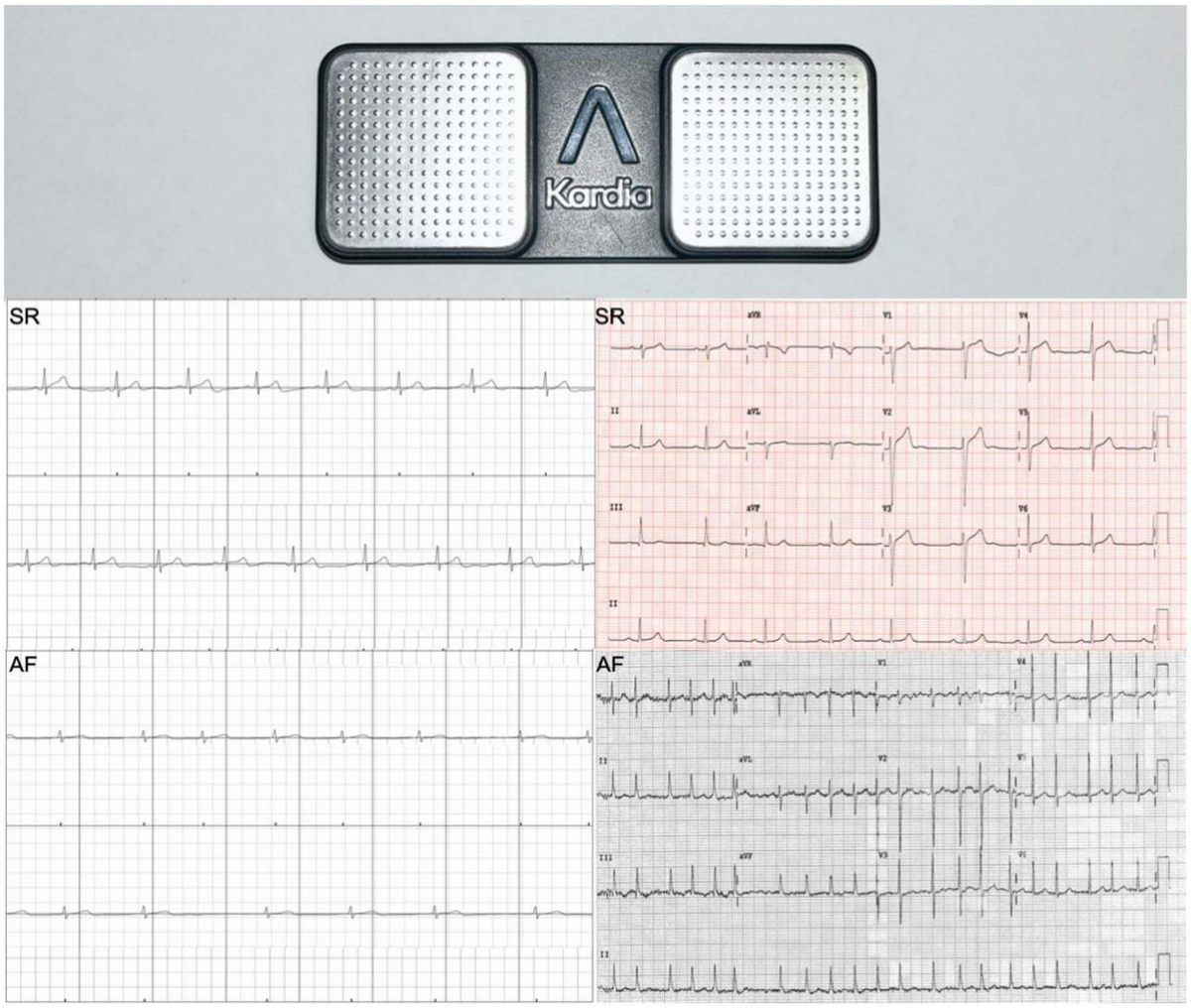

Figure 1.4. AliveCor (AliveCor Inc, Mountain View, CA, USA) recording of Sinus Rhythm (SR) and Atrial Fibrillation (AF) vs. conventional 12-lead ECG

From Top Left to Bottom Right, AliveCor SR, 12-lead ECG SR, AliveCor AF, 12-lead ECG AF.

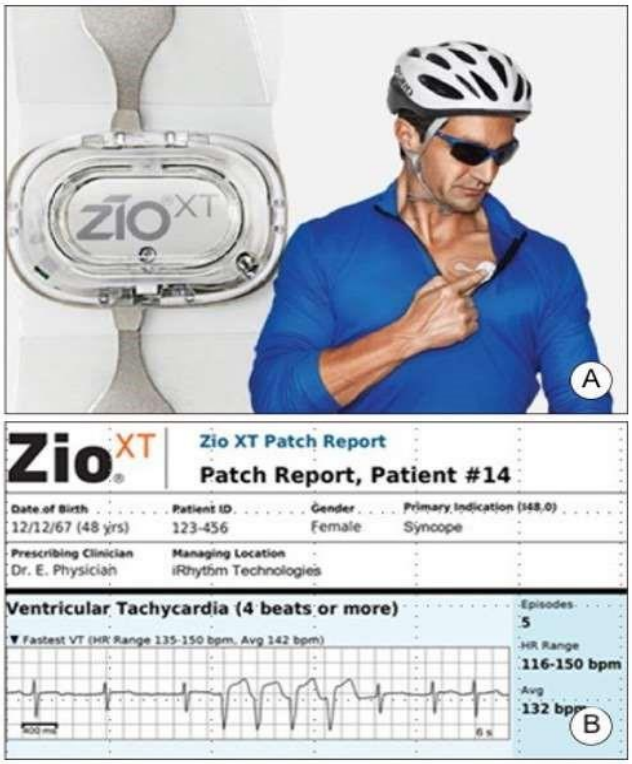

Figure 1.5. Examples of Zio Patch and single-lead ECG (sECG) recording

(A) Zio-Patch (iRhythm Technologies, San Francisco, CA, USA); and (B) sECG recording from Zio-Patch[102]

(Adapted as per the Creative Commons Attribution License)

1.16 TABLES

Table 1.1. Summary of wearable and handheld devices and clinical applications in arrhythmias

Device Name	Device Type	Clinical Applications
Apple Watch[37]	Wristwatch	Monitoring of HR, detection of irregular rhythm, ECG application with rhythm interpretation
Fitbit Charge 4[38]	Wristwatch	Monitoring of HR and HRV
AliveCor KardiaMobile[103]	Handheld device and smartphone application	Monitoring of HR, detection of irregular rhythm, ECG application with rhythm interpretation
MyDiagnostick[104]	Handheld device (rod with metallic electrodes on both ends)	Monitoring of HR, detection of irregular rhythm, ECG application with rhythm interpretation
Omron HeartScan (HCG 801)[105]	Handheld device with finger and chest electrodes	ECG recording only
Zenicor ECG[105]	Handheld device	ECG recording with cloud-based service
Beurer ME90[106]	Handheld device	Monitoring of HR, detection of irregular rhythm with ECG application

ECG Check[107]	Handheld device	Monitoring of HR, detection of irregular rhythm with ECG application
Garmin Vivosmart 4[108]	Wristwatch	Monitoring of HR and HRV
Huawei Watch GT[109]	Wristwatch	Monitoring of HR and HRV
Samsung Galaxy Smartwatch 2[110]	Wristwatch	Monitoring of HR, detection of irregular rhythm, ECG application with rhythm interpretation
Withings Move ECG[111]	Wristwatch	Monitoring of HR, detection of irregular rhythm, ECG application with rhythm interpretation
Fitbit Sense[111]	Wristwatch	Monitoring of HR, detection of irregular rhythm, ECG application with rhythm interpretation
Zio Patch[58]	Patch	14-day ECG monitoring, detection of arrhythmias
Nuvant-MCT[61]	Patch	Automatic and patient triggered 30-day rhythm monitoring, detection of arrhythmias

Table 1.2. Efficacy of wearable and handheld devices in the diagnosis of arrhythmias

Device Name	Strengths and Characteristics	Performance
Apple Watch[34, 113]	Portable, water-resistant, continuous HR tracking, extensive functionality	Underestimation of HR at HR >100 Up to >98% sensitivity and >99% specificity in diagnosis of AF
Fitbit Charge 4[35, 36, 38]	Portable, water-resistant, continuous HR tracking	Underestimation of HR at HR >100 Limited data into efficacy in AF, Fitbit Heart Study pending.
AliveCor KardiaMobile[64, 65, 103, 105]	Portable, provides symptom-rhythm correlation	Up to 98% sensitivity and 97% specificity for AF detection Proven benefit in asymptomatic screening for AF
MyDiagnostick[104]	Portable, provides symptom-rhythm correlation	Up to 100% sensitivity and 95.9% specificity for AF detection

Omron HeartScan (HCG 801)[105]	Portable, provides symptom-rhythm correlation	Up to 100% sensitivity and 92% specificity for AF defection
Zenicor ECG[105]	Portable, provides symptom-rhythm correlation, built-in rechargeable battery	Up to 96% sensitivity and 92% specificity for AF detection
Beurer ME90[106]	Portable, provides symptom-rhythm correlation	Up to 94% sensitivity and 77% specificity for AF detection
ECG Check[114]	Portable, provides symptom-rhythm correlation	Up to 100% sensitivity and 94% sensitivity for AF detection
Garmin Vivosmart 4[108]	Portable, water-resistant, continuous HR tracking	Limited data into efficacy in AF Lack of ECG functionality
Huawei Watch GT[70, 109]	Portable, continuous HR tracking, extensive functionality	Part of large trial which demonstrated PPV of 91.6% for detection of AF
Samsung Galaxy Smartwatch 2 [72,110]	Portable, continuous HR tracking, extensive functionality	ECG functionality, ECG algorithm for AF demonstrated up to 98.9% and 99.3% specificity

Withings Move ECG[111]	Portable, continuous HR tracking, extensive functionality	ECG functionality, limited data into efficacy in AF
Fitbit Sense[112]	Portable, continuous HR tracking, extensive functionality	ECG functionality, limited data into efficacy in AF
Zio Patch[58,83]	Portable, water-resistant Longer monitoring period than Holter monitor (14-days vs. 24-48 hours)	66% detection of paroxysmal arrhythmias, superior to Holter monitor
Nuvant-MCT[61]	Portable, symptom-rhythm correlation	Automatic and patient triggered cardiac rhythm monitoring Real-time analysis and transmission

Table 1.3. Registered active trials on wearable and handheld devices in arrhythmia detection

Registered Trials	Trial Type	Device	Primary Outcome	Estimated Enrolment
HEARTLINE-A Heart Health Study Using Digital Technology to Investigate if Early AF Diagnosis Reduces the Risk of Thromboembolic Events Like Stroke In the Real-world Environment[69]	Observational (Prospective Cohort Study)	Apple Watch Series 4 or later	Time from Randomisation to Clinically Confirmed Diagnosis of AF, Percent Days Covered by Direct Oral Anti - Coagulant Fills	150,000 participants
Accuracy of Cardiac Wearables Devices to Detect AF in a Real-World Cohort of Patients; Basel Wearable Study[115]	Observational (Prospective Cohort Study)	Apple Watch, KardiaMobile, Fitbit Sense, Samsung Galaxy Watch 3, Withings Move ECG Watch	Accuracy of wearable devices in detecting AF compared to nearly simultaneously acquired physician interpreted 12-lead ECG	334 participants

Accuracy of Rhythm Detection and Managing Data Deluge by a Wearable Smart Watch for Cardiac Arrhythmias (The WATCH-RHYTHM STUDY)[116]	Interventional (Clinical Trial)	Smartwatches	Assess AF detection by HR data from Smartwatch and confirm with ILR during the same period	200 participants
Diagnostic Validation of Wearable Continuous ECG monitoring patch, ATP-C120, in High-Risk Patients for New-onset AF[117]	Interventional (Clinical Trial)	Wearable patch (ATP-C120)	Rate of new-onset AF recognised by ATP-C120 patch device	320 participants
SAFER Wearables Study: A Study of the Acceptability and Performance of Wearables for AF screening in Older Adults[118]	Observational (Prospective Case-Control Study)	Wearable sECG chest device, Wearable wrist devices	The performance of each wrist-worn wearable approach for identifying AF participants	130 participants

Determine AF Burden with PPG Trial-Detection and Quantification of Episodes of AF using a Cloud Analytics Service Connected to a Wearable with PPG sensor[119]	Interventional (Clinical Trial)	PPG Bracelet or PPG Smartwatch utilising Preventicus Heartbeats Algorithm, Holter ECG	Number of detected AF episodes by the PPG sensors and Preventicus Heartbeats algorithm during the 48-hour trial period compared to the Holter ECG	2000 participants
AF Detection Using Garmin Wearable Technology[120]	Observational (Prospective Cohort Study)	Garmin Smartwatch and Garmin Chestband	Sensitivity and specificity of Garmin wearable device in detecting AF	120 participants
Effect of Wearable Devices on Patient-Reported Outcomes and Clinical Utilisation: A Randomised, Controlled Trial[121]	Interventional (Clinical Trial)	Apple Watch, Withings Move	Difference in the AF Effect on QualiTy-of-life (AFEQT) questionnaire global scoreline at 6 months compared to baseline between Apple Watch and	150 participants

			patients randomised to the Withings Move arm at 6 months compared to baseline.	
Post-Surgical Enhanced Monitoring for Cardiac Arrhythmias and AF (SEARCH-AF): A Randomised Controlled Trial[122]	Interventional (Clinical Trial)	Adhesive Patchbased Monitor SEEQ™ Mobile Cardiac Telemetry System or the CardioSTAT (Icentia Inc.) Cardiac Rhythm Monitoring Device	Number of participants with a cumulative AF/flutter duration of ≥6 minutes or documentation of AF/flutter by a 12-lead ECG	336 participants
Study Watch AF Detection at Home[123]	Observational (Prospective Cohort Study)	Wearable Watch, Zio XT Patch	Accuracy of AF detection based on sensitivity and specificity observed in a 14-day follow-up period	117 participants
Evaluation of Ambulatory	Interventional (Clinical Trial)	KardiaMobile and Biomonitor-2	Detection rates for AF/Flutter	150 participants

Monitoring of Patients after High-risk Acute Coronary Syndrome Using Two Different Systems: Biomonitor-2 and KardiaMobile[124]		(Implantable Cardiac Monitor)	during 1-year follow up Detection rates of ventricular arrhythmia in the ECG during follow-up Advanced conduction abnormalities and significant ST shifts (>1mm) in the ECG	
Early Diagnosis of Atrial Fibrillation in the Wait-Time Prior to Seeing a Cardiologist (CATCH-AF)[125]	Interventional (Clinical Trial)	KardiaMobile, Holter monitor	Time to atrial fibrillation compared between arms as analysed by Kaplan-Meier survival curves	220 participants

Table 1.4. Case studies on wearable and handheld devices in non-AF arrhythmias

Study Author	Device and mechanism	Diagnosis	Treatment
Waks et al. JAMA Intern Med 2015[126]	AliveCor and sECG	RVOT VT	Catheter ablation
Richly et al. Br J Cardiac Nurse, 2015[127]	AliveCor and sECG	SVT (AVNRT)	Beta-Blocker, declined electrophysiology study
Tabing et al. BMJ Case Rep, 2017[128]	AliveCor and sECG	SVT (AVNRT)	Catheter ablation
Goldstein et al. Oxf Med Case Reports. 2019[129]	Apple Watch and PPG	Atrial Flutter	Anticoagulation, electrical cardioversion and anti-arrhythmic
Siddeek et al. Ann Noninvasive Electrocardiol, 2020[130]	Apple Watch and sECG	SVT (AVNRT)	Catheter ablation
Burke et al. HeartRhythm Case Rep, 2020[77]	Apple Watch and sECG	VT in the setting of Arrhythmogenic RV Cardiomyopathy	ICD insertion and Beta-Blocker
Burke et al. HeartRhythm Case Rep, 2020[77]	Smartwatch and sECG	VT	Catheter ablation of an anterolateral papillary muscle focus

Ringwald et al. Am J Emerg Med, 2020[131]	Apple Watch and sECG	VT	Negative inotropes and ICD insertion
Phillips et al, Eur Heart J, 2021[132]	AliveCor and sECG	SVT (AVNRT)	Catheter ablation

Chapter 2. Accuracy of a Hand-held, Single Lead ECG Device in the Diagnosis of Cardiac Arrhythmias Against the Gold Standard of Cardiac Electrophysiology Study

2.1 ABSTRACT

2.1.1 Background

A commercially available single-lead ECG device may allow detection and diagnosis of cardiac arrhythmias. There is limited data on its accuracy in detecting arrhythmias other than atrial fibrillation.

2.1.2 Objectives

To compare the accuracy of a popular, commercially available handheld single-lead ECG device, the AliveCor KardiaMobile (AliveCor Inc, Mountain View, CA) for the diagnosis of various cardiac arrhythmias against a cardiac electrophysiology study (EPS), the gold standard for cardiac arrhythmia diagnosis.

2.1.3 Methods

Patients undergoing a clinically indicated EPS underwent simultaneous recording of their cardiac rhythms using standard practice 12-lead ECG and intracardiac electrograms, along with single-lead ECG via the AliveCor placed on the recumbent patient's chest. Three blinded reviewers interpreted the AliveCor tracings, and a fourth and final reviewer compared the diagnoses made between the AliveCor tracings and the findings on the EPS.

2.1.4 Results

From 49 patients, 843 cardiac rhythms were captured within 502 AliveCor recordings. Of the 502 recordings, 484 (96%) received at least one accurate rhythm diagnosis, and of 843 recorded rhythms, 756 (90%) were correctly identified. Accuracy was higher if the AliveCor recordings contained a single continuous rhythm (95%). The accuracy for identification of SR, AF, atrial tachycardia, ventricular tachycardia, supraventricular ectopics and premature

ventricular ectopics were 92%, 91%, 89%, 91%, 93% and 91%, respectively. Complete heart block and ventricular fibrillation was correctly identified in all recordings.

2.1.5 Conclusions

When compared against the gold standard of EPS electrogram interpretation, the single-lead ECG device, AliveCor KardiaMobile placed on the chest in a recumbent position has reasonable diagnostic accuracy in detecting sustained supraventricular and ventricular arrhythmias.

2.2 INTRODUCTION

Cardiac arrhythmias portend a significant burden of disease with decreased quality of life, increased morbidity and mortality, and resultant impact on the healthcare system.[1] Timely arrhythmia diagnosis is critical, with ambulatory cardiac monitoring remaining the most frequently used clinical tool to detect episodic arrhythmias.[13] However, the diagnostic yield of ambulatory monitoring in patients with unresolved palpitations is as low as 10–15%,[13] with limited patient accessibility to these investigations making symptom-rhythm correlation difficult to achieve in episodic arrhythmias.

A novel, commercially available, handheld single-lead (and more recently, 6-lead) electrocardiogram (ECG) device has emerged as a diagnostic tool for arrhythmia detection (AliveCor KardiaMobile; AliveCor Inc, Mountain View, California, USA). The AliveCor has been found to be accurate for the detection of sinus rhythm (SR) and atrial fibrillation (AF), with a paucity of data assessing its accuracy for non-AF arrhythmias.[51, 64, 85]

The diagnosis of various cardiac arrhythmias can be made accurately during a cardiac electrophysiology study (EPS) where a 12-lead ECG and intracardiac electrograms (EGMs) are available for review. In this study, we compared the accuracy of the single-lead ECG (sECG) derived from AliveCor for a myriad of spontaneous and inducible arrhythmias during an EPS where the arrhythmia diagnosis was infallible based on 12-lead ECGs and intracardiac EGMs.

2.3 METHODS

This was a prospective study whereby 50 patients undergoing routine, clinically indicated EPS±radiofrequency ablation for previously diagnosed or suspected cardiac arrhythmias at Westmead Hospital, Sydney, Australia, were recruited between August 2019 and November 2020. Written informed consent was obtained from all patients prior to the commencement of the study. The study was approved by the local Human Research Ethics Committee. Patients that had a poor baseline sECG performed at the time of recruitment were excluded.

2.3.1 Study workflow

A detailed study workflow is shown in Figure 2.1. An independent data collector (S.T.), blinded to the patients' history, recorded the AliveCor sECG tracings simultaneously to the intracardiac EGMs stored on the EPS continuous recording system (CardioLab EP Recording System, General Electric, Boston, Massachusetts, USA). The data collector provided three blinded reviewers (T.C., R.G.B., Y.K.) with deidentified sECGs for rhythm analysis. The data collector also provided a fourth reviewer with intracardiac EGMs for an infallible diagnosis and results of the three reviewers' analyses for final adjudication (S.K.). The presence of heart rhythm stability, or changes in rhythm or heart rate, either as a result of arrhythmia, pacing or medication, were used to determine the selection of EGMs for analysis. Where possible, as many examples of different rhythms in each patient were captured for analysis. This reviewer classified the diagnoses made by the three reviewers as correct or incorrect. Following this comparison, a percentage of accurate identification of the AliveCor rhythm recordings was obtained. This overall percentage agreement was an average of the percentage agreement of Reviewers 1, 2 and 3.

2.3.2 Electrophysiology study

The EPS was conducted as per the clinical indication, under either local sedation or general anaesthesia. Diagnostic catheters were positioned at the high right atrium, coronary sinus, His bundle, and the right ventricular apex. A standardised protocol for electrophysiologic evaluation was performed which included evaluation of anterograde and retrograde conduction, determination of atrial, ventricular and atrioventricular nodal refractory periods, Wenckebach cycle lengths and sinus node conduction recovery time. Depending on the arrhythmia being evaluated, one or more of the following induction protocols were followed: programmed ventricular stimulation with up to 4 extra-stimuli from the right ventricular apex; sensed single or double extra-stimuli from the atrium or ventricles; burst pacing down to the refractory cycle length from the atria or ventricles; arrhythmia entrainment. If it was deemed necessary for arrhythmia induction, pharmacological provocation using beta-adrenergic

agents such as isoprenaline and adrenaline were used as per the operator's clinical discretion. Additionally, if deemed necessary, diagnostic adenosine was administered.

Twelve-lead ECG data and intracardiac EGMs were simultaneously recorded on CardioLab EP Recording System (GE), with bandpass filtering performed between 30–500Hz, as is standard clinical practice. Each rhythm that occurred or was induced during the EPS was documented at the time on the EP recording system by a member of the clinical team, as per standard practice. A copy of the EGMs and ECGs were obtained for analysis.

2.3.3 AliveCor application

The AliveCor is a smart device-based, sECG recording device that displays ECG tracings in real time using proprietary smart device application software through the application of the AliveCor electrodes to the skin surface. The sECG tracing correlates with lead I of a 12-lead ECGs when held in the user's hands, and a pseudo-lead I when applied to the patient chest. The AliveCor samples at a frequency of 300Hz resulting in a temporal resolution of 3.3ms. In a supine patient, a finger from each (or one) hand can be placed on the AliveCor ECG electrode(s). In a recumbent patient undergoing an EPS under conscious sedation or general anaesthesia, this is not feasible. Therefore, in this study, the AliveCor was applied to the patient's chest inferiorly to the clavicle to replicate lead I on a 12-lead ECG. In patients where an R-wave was attenuated or not reliably detected, the AliveCor was rotated to replicate a lead II, III or aVL vector. A smartphone was placed within the detection field of the AliveCor to capture and store the sECG recordings.

The maximum duration of a single recording on the AliveCor was limited to 300 seconds. Throughout the duration of the EPS, a new AliveCor recording was commenced after every 5 minutes, to maximise interpretable rhythm recordings and to minimise selection bias. In order to ensure accurate and simultaneous comparisons, the time on each recording system was synchronised before the beginning of the procedure. Rhythms that occurred or were

induced during the EPS were stored within the smartphone in use, via the AliveCor smartphone application, for subsequent transmission and analysis.

2.3.4 Patient demographics

Baseline patient demographics were collected including patients' age, gender, body mass index (BMI), previous arrhythmia history, echocardiographic indices (left ventricular ejection fraction (LVEF), number of previously failed anti-arrhythmic drugs (AADs), baseline ECG rhythm and co-morbidities.

2.3.5 Classification of arrhythmias

An "infallible" diagnostic rhythm was based on evaluation of intracardiac EGMs and 12-lead surface ECG from the EPS. These included the following spontaneously occurring and inducible rhythms: SR, AF, atrial tachycardia (AT), premature ventricular complexes (PVC), ventricular tachycardia (VT), ventricular fibrillation (VF), supraventricular ectopy (SVE), and complete heart block (CHB). Pacing manoeuvres (e.g., atrial or ventricular pacing, atrial or ventricular extra-stimuli) that visibly resemble these rhythms on both 12-lead ECG and sECG, were included under the definitions of encompassing rhythms as classified below. Examples of these are shown in Supplemental material. For consistency of comparison between sECG and the infallible diagnoses from the EPS, the three reviewers were also asked to use the same classification for labelling their diagnosis.

The infallible diagnoses were classified as:

SR: encompassing sinus rhythm, sinus bradycardia and atrial pacing >600ms;

AF: encompassing atrial fibrillation, atrial flutter with variable conduction, atrial pacing with irregular conduction and supraventricular tachycardias with irregular conduction;

AT: encompassing (sustained and non-sustained) supraventricular tachycardias demonstrating typical His-Purkinje system conduction including sinus tachycardia (≥100bpm), focal atrial tachycardia, atrial pacing at cycle length ≤600ms, atrioventricular nodal re-entry tachycardia, atrioventricular re-entry tachycardia;

PVC: encompassing spontaneous or provocable premature ventricular complexes and ventricular paced extrastimuli (±bigeminy/trigeminy);

VT: encompassing spontaneous or provocable ventricular tachycardia (sustained and non-sustained), programmed ventricular stimulation and ventricular pacing ≤600ms;

VF: encompassing ventricular fibrillation and polymorphic VT;

SVE: encompassing spontaneous or provocable SVEs and atrial paced extra-stimuli (±bigeminy/trigeminy);

CHB: encompassing asystolic pauses ≥3 seconds.

Reviewers were given a 30 second snapshot of the rhythm recorded from the AliveCor tracings in electronic form in a portable document format (pdf), to allow magnification and blinded analysis. The snapshot contained either:

1. Unaccompanied rhythm: an isolated singular rhythm (e.g., AF, SR, VT); or
2. Accompanied rhythm: one or more rhythm including sinus rhythm (e.g., SR and atrial tachycardia).

Results were reported as overall accuracy (unaccompanied and unaccompanied rhythms) and accuracy of unaccompanied rhythms.

2.3.6 Statistical Analysis

SPSS version 27 (IBM Corp., Armonk, NY) was used for analysis. Continuous variables were expressed as mean±standard deviation (SD) if there was a normal distribution and as a median (25%–75%) interquartile range (IQR) if there was skewed data. For the intra- and inter-observer analysis, a random number generator was utilised to extract a near equivalent number of rhythms from each reviewer for repeat analyses, with this amounting to a total of 54 AliveCor recordings and a total of 103 infallible diagnoses. For the inter-observer analysis, each reviewer's first interpretation of an AliveCor recording was compared between individual reviewers and between the three reviewers as an entity. The Kappa statistic, which is a measure of inter-observer reliability was utilised with Cohen's Kappa (for two reviewers) and the Fleiss Kappa (adaptation of Cohen's kappa for three reviewers) with an additional %

agreement performed.[133] The Kappa result can be interpreted as such: values ≤0 indicate no agreement, 0.01–0.20 as none to slight, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1.00 as almost perfect agreement.[133] For the intra-observer analysis, a comparison was made between each reviewer's original interpretation of their own AliveCor recording compared to their own subsequent repeat interpretation of the same AliveCor recording. The Kappa statistic and % agreement was similarly performed to assess intra-observer variability.

2.4 RESULTS

From 49 patients, 502 AliveCor recordings containing 843 rhythms were interpreted. One patient was removed from the study due to an isoelectric AliveCor sECG, regardless of rhythm and despite normal intervals and amplitudes on 12-lead ECG and satisfactory screening.

2.4.1 Baseline Characteristics

Baseline characteristics are described in Table 2.1. Overall mean age was 58±19 years, mean LVEF was 52±12%, mean BMI was 28±4 kg/m^2 and 71% of patients were male. Patients had previous history of arrhythmia including AF (n=21, 43%); VT (n=20, 41%), AT (n=18, 37%) and PVC (n=15, 31%). Bundle branch block (BBB) was observed at baseline rhythm in 12 (25%) as a result of conduction system disease or ventricular pacing from an underlying pacemaker/defibrillator.

2.4.2 Infallible Diagnosis vs AliveCor Rhythm Interpretation

The accuracy of AliveCor rhythm interpretation by the three reviewers compared to the gold standard EPS infallible diagnosis is shown in Table 2.2. and Table 2.3. Of the 502 recordings, 484 (96%) received at least one accurate rhythm diagnosis, and of 843 recorded rhythms, 756 (90%) were correctly identified. The total diagnostic accuracy of the 843 rhythms between the three reviewers was 756/843 (90%). Reviewers were able to accurately identify 212/224 (95%) unaccompanied continuous rhythms, whilst the number of recordings that contained an

accurate rhythm diagnosis was 484/502 (96%). Examples of these rhythms are shown in Figure 2.2.

Sinus Rhythm

Correct identification of SR was achieved in 253/273 recordings (93%; Table 2.2, 2.3). Overall accuracy of the identification of the presence of SR was 92%, with sensitivity and specificity values of 93% and 92%, respectively (Table 2.2).

Atrial Fibrillation

Unaccompanied AF was correctly identified in 30/34 recordings (88%), and in total, AF was correctly identified in 44/51 recordings (86%; Table 2.3). Overall accuracy for AF diagnoses was 91%, sensitivity 86% and specificity 92% (Table 2.2). In cases of misdiagnoses, interpretations of unaccompanied AF were SR (n=3) or AT with SVE (n=1) and interpretations of the rhythm when AF was accompanied by other rhythms were SR with AT (n=3).

Atrial Tachycardia

Unaccompanied AT were identified correctly in 72/73 recordings (99%) and in 176/181 (93%) of total recordings (Table 2.3), with overall accuracy of 89%, sensitivity 92% and specificity 88% (Table 2.2). AT was identified correctly in a smaller proportion of recordings when it was accompanied by other rhythms (104/118; 88%; Table 2.3). The single instance of misdiagnosed unaccompanied AT was interpreted as VT (Table 2.4). Misdiagnosed accompanied AT was interpreted as AF (n=3), VT (n=7), VF (n=1), SVE (n=1), PVC (n=2).

Ventricular Tachycardia

Unaccompanied VT was accurately identified in 45/51 recordings (88%), and when VT was accompanied by other rhythms, VT was correctly identified in 183/198 recordings (92%; Table 2.3). Overall diagnostic accuracy for VT was 91%, sensitivity 92% and specificity 91% (Table 2.2). In the 6 recordings in which unaccompanied VT was misdiagnosed, the most common interpretation provided was AT (n=5) or AF (n=1, Table 2.4). Incorrect interpretations

for VT when accompanied by other rhythms (n=9) were that of AT (n=5), with the remainder identified as AT/AF with a bundle branch block (n=4).

Complete Heart Block and Ventricular Fibrillation

Both CHB (n=5) and VF (n=11) were correctly identified on all occasions. In 21/28 recordings (75%), SVE's were correctly identified. When incorrectly identified, the most common misinterpretation was AF (n=5), whilst 2 were not reported upon during interpretation. Overall accuracy for the identification of SVEs was 93%, with a sensitivity and specificity of 75% and 94% respectively.

Premature Ventricular Contractions

Correct identification of PVCs occurred in 63/86 recordings (73%). The provided misdiagnoses were AF (n=5), VT (n=1), but most commonly not differentiated, and identified as SR (n=17). Overall accuracy of PVC identification was 91%, and sensitivity and specificity were 73% and 95%, respectively.

2.4.3 Inter-variability and intra-variability analysis

Inter-observer variability analysis for AliveCor tracings showed a Kappa between 0.38–0.54 for the reviewers and an agreement percentage between 85–94% (Supplemental Table 2.1). Intra-observer variability analysis for AliveCor tracings showed a Kappa between 0.35–0.79 and agreement percentage between 85–97% (Supplemental Table 2.2).

2.5 DISCUSSION

This study is the first of its kind to evaluate the accuracy of the handheld sECG device (AliveCor KardiaMobile), for the diagnosis of various cardiac arrhythmias against the gold standard cardiac EPS, where the arrhythmia diagnosis was considered "infallible" based on evaluation of intracardiac EGMs and 12-lead surface ECG. We found that AliveCor sECG tracings can reliably be used to detect a range of arrhythmias with >85% accuracy which includes AF (86%), AT (93%) and VT (93%). Detection of non-sustained arrhythmias and premature complexes may be limited through the use of the AliveCor, with only 75% of SVEs

and 73% of PVCs being diagnosed correctly, and subsequently an over-diagnosis of AF made. Finally, we elucidated that it was possible to identify life-threatening arrhythmias such as VT, VF and CHB with a moderate to high degree of accuracy. These findings suggests that the AliveCor may prove a useful tool in the diagnosis of cardiac arrhythmias in the ambulatory setting. Whilst the present results hold true for sECG recordings from the anterior chest when recumbent, it is plausible that diagnostic accuracy may improve with acquisition of sECG through the fingertips. However, acquisition of the sECG through fingertip application could not safely be performed during EPS in order to preserve sterile environments and given the patients were under sedation or general anaesthesia. Further research will need to be conducted to clarify if the arrhythmia diagnosis made via fingertip-acquired sECG rhythm is accurate for non-AF arrhythmias. Furthermore, the accuracy of the recognised rhythm may improve with the use of a 6-lead ECG released by the same vendor and may need further investigation.

2.5.1 Previous Studies

Several studies have validated the use of the AliveCor in both the screening and diagnosis of patients with asymptomatic or symptomatic AF.[64-66] Whilst this study has been able to further reinforce and validate the diagnostic yield of the AliveCor in AF, the large-scale validation of the AliveCor in non-AF arrhythmias remains limited.

The utility of the AliveCor in the diagnosis of arrhythmias additional to AF was investigated by Rischard et al., by comparing AliveCor sECGs to concomitant 12-lead ECGs presented to blinded cardiologist reviewers. The sensitivity and specificity of the AliveCor sECGs diagnosed by reviewers were 82% and 92% for AF (n=275), 26% and 98% for other supraventricular tachycardia (n=94), and 60% and 100% for wide-QRS tachycardia (n=5).[134] Our study extends on the work by Rischard et al. by incorporating intracardiac EGMs and an increased quantity of non-AF arrhythmia ECGs.

Goel et al. compared the ability of the AliveCor (for a duration of 1-month) against the 24-hour Holter Monitor for detection of non-AF arrhythmias in a population of 50 patients who presented to an urgent care with palpitations.[78] The AliveCor was shown to be at least concordant with simultaneous Holter monitoring in 82% of patients with detected arrhythmias that included atrial and ventricular ectopy, SVT, VT, AF, and inappropriate sinus tachycardia. Our study differed in terms of the range and volume of arrhythmia assessment and comparison against the gold standard of arrhythmia diagnosis.

Reed et al. similarly validated the AliveCor in a cohort of 240 people presenting to an emergency department with palpitations and pre-syncope, who underwent standard care plus the use of the AliveCor (intervention, n=124) or standard care alone (control, n=116). There was more than a five-fold increase in the symptomatic rhythm detection of the AliveCor group with detected rhythms including (48 SR, 12 sinus tachycardia, 8 ectopics, 8 AF, 3 SVT and 1 atrial flutter). Our study extrapolated these results through the large-scale diagnostic validation of VT and AT against the gold-standard comparator of an EPS, in addition to as the volume of PVCs that were assessed in our study, furthering the existing diagnostic paradigm.

There remain several other isolated reports of AliveCor in the diagnosis of VT and SVT. Waks et al. demonstrated the symptom-rhythm correlation diagnosis of a wide-complex tachycardia in an active 62-year-old gentleman with an episode of near-syncope.[126] An EPS was eventually performed which revealed a right ventricular outflow tract tachycardia, resulting in treatment with catheter ablation. There have also been several case reports of the AliveCor in the diagnosis of SVT (specifically atrioventricular nodal re-entry tachycardia) with treatment implications including commencement of beta-blocker therapy and catheter ablation.[126, 128, 132] Despite these studies, there remains a lack of large-scale evidence for VT and SVT diagnosis, with our trial establishing the validity of the AliveCor in both these settings.

Our study supports the existing literature which demonstrates the ability to diagnose both narrow and broad-complex arrhythmias. The study also expands upon the existing

diagnostic paradigm through the multitude and volume of arrhythmias explored and through comparison to the diagnostic gold standard.

2.6 LIMITATIONS

The AliveCor sECG was acquired whilst applying the AliveCor to the supine patient's chest, as opposed to the standard approach of application of fingers to the AliveCor electrodes, resulting in attenuation of P-wave and R-wave amplitudes in selected patients. It is plausible our results may have improved with a typical application of the AliveCor; however, the preservation of sterile fields and patient sedation/analgesia rendered this approach unachievable. The analysis of sECG tracings were performed by investigators blinded to patients' clinical history; additional clinical data may assist an interpreter in making an accurate diagnosis. The AliveCor sECG tracings were recorded during a cardiac EPS; whilst the interpreters were blinded to the patients' clinical history, this may have led to an interpreter bias towards a positive arrhythmia diagnosis, despite the presence of non-arrhythmia sECGs. Additionally, interpreter bias may have formed towards what were deemed clinically insignificant findings, such as premature complexes in the context of sustained AF. Despite these limitations, there was observable diagnostic efficacy for a large volume of arrhythmias, albeit indicating the need for further large-scale studies to expand upon our findings. Further studies are also needed to validate the accuracy of the 6-lead ECG iteration of AliveCor, and other ECG-capable wearables (e.g. Apple watch, Apple Inc, Cupertino, California, USA). If the 6-lead AliveCor is validated, it may potentially address the limitation of the single-lead AliveCor in that it would also provide more information about the QRS morphology and QTc interval, important in stratifying ventricular arrhythmias and conditions associated with sudden cardiac death.

2.7 CONCLUSION

This study demonstrates an sECG acquired from a recumbent patient's chest using the AliveCor KardiaMobile application may be used to diagnose a broad range of sustained

arrhythmias with reasonable accuracy when compared against the gold standard of rhythm diagnosis in the cardiac EPS. The findings suggest that the AliveCor KardiaMobile may be a reasonably useful tool for the investigation of cardiac arrhythmias in an ambulatory setting.

2.8 TABLES

Table 2.1. Baseline characteristics

Patient characteristics	n=49
Female gender, n (%)	14 (29%)
Age, mean±SD, years	58.3±18.9
Body mass index, mean±SD	28.3±4.2
LVEF %, mean±SD (%)	51.6±12.2
Previous history of arrhythmia, n (%)	47 (96%)
Atrial Fibrillation, n (%)	21 (43)
Atrial Tachycardia, n (%)	18 (37)
Ventricular Tachycardia, n (%)	20 (41)
Premature Ventricular Complexes, n (%)	15 (31)
Baseline Bundle Branch Block, n (%)	12 (25)
Left Bundle Branch Block n (%)	6 (12)
Right Bundle Branch Block n (%)	6 (12)
Number of failed AADs, median (IQR)	1 (1–2)
Hypertension, n (%)	25 (51)
Hyperlipidaemia, n (%)	22 (45)
Diabetes, n (%)	5 (10)
Structural Heart Disease, n (%)	22 (45)
Ischaemic Heart Disease, n (%)	11 (22)
Congenital Heart Disease, n (%)	2 (4)

Abbreviations: AAD, anti-arrhythmic drug; LVEF, left ventricular ejection fraction; SD, standard deviation.

Table 2.2. EPS vs AliveCor interpretation by the three reviewers' overall accuracy

This table represents the infallible diagnosis identified from the intracardiac EGMs during the EPS and the comparative interpretation by the three electrophysiologist reviewers for the AliveCor.

Diagnosis from EPS	*n*	Overall accuracy (%) (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	*P*-value
Sinus Rhythm	273	92.4 (89.8–94.6)	92.7 (88.9–95.5)	92.1 (87.9–95.3)	0.871
Atrial Fibrillation	51	91.0 (88.2–93.4)	86.3 (73.7–94.3)	91.6 (88.6–94.0)	<0.001
Atrial Tachycardia	191	89.4 (86.4–92.0)	92.2 (87.4–95.5)	87.8 (83.6–91.2)	0.002
Ventricular Tachycardia	198	91.2 (88.4–93.6)	92.4 (87.8–95.7)	90.5 (86.6–93.5)	0.049
Ventricular Fibrillation	11	98.4 (96.9–99.3)	100.0 (71.5–100.0)	98.4 (96.8–99.3)	0.008
Supraventricular Ectopy	28	93.0 (90.4–95.1)	75.0 (55.1–89.3)	94.1 (91.6–96.0)	<0.001
Premature Ventricular Complexes	86	90.8 (88.0–93.2)	73.3 (62.6–82.2)	94.5 (91.8–96.5)	1.000
Complete Heart Block	5	99.8 (98.9–100.0)	100.0 (47.8–100.0)	99.8 (98.9–100.0)	1.000
Total	843	93.3 (92.5–94.0)	89.7 (87.4–91.7)	94.2 (93.4–95.0)	<0.001

Table 2.3. Proportional accuracy of EPS vs AliveCor interpretation

This table represents the Infallible Diagnosis generated from the intracardiac EGMs during the EPS and the comparative interpretation by the three electrophysiologist reviewers for the AliveCor recordings contained a single continuous rhythm.

Diagnosis from EPS	Correct Interpretation	Proportion Correct (%)	95% Confidence Interval
All Recordings	484/502	96.4	94.4–97.7
All Rhythms	756/843	89.7	87.4–91.6
Sinus Rhythm	253/273	92.7	89.0–95.2
Atrial Fibrillation	44/51	86.3	74.3–93.2
Atrial Tachycardia	176/191	92.1	87.5–95.2
Ventricular Tachycardia	183/198	92.4	87.9–95.4
Ventricular Fibrillation	11/11	100.0	74.1–100.0
Supraventricular Ectopy	21/28	75.0	56.6–87.3
Premature Ventricular Contractions	63/86	73.3	63.1–81.5
Complete Heart Block	5/5	100.0	56.6–100.0
Unaccompanied Rhythms	212/224	94.6	90.9–96.9
Sinus Rhythm only	64/65	98.5	91.8–99.7
Atrial Fibrillation only	30/34	88.2	73.4–95.3

Atrial Tachycardia only	72/73	98.6	92.6–99.8
Ventricular Tachycardia only	45/51	88.2	76.6–94.5
Ventricular Fibrillation only	1/1	100.0	20.7–100.0
Accompanied Rhythms	544/619	87.9	84.9–90.1
Sinus Rhythm	189/208	90.9	86.2–94.1
Atrial Fibrillation	14/17	82.4	54.8–91.0
Atrial Tachycardia	104/118	88.1	81.1–92.8
Ventricular Tachycardia	138/147	93.9	88.8–96.8
Ventricular Fibrillation	10/10	100.0	72.3–100.0
Supraventricular Ectopy	21/28	75.0	68.6–97.1
Premature Ventricular Contractions	63/86	73.3	63.1–81.5
Complete Heart Block	5/5	100.0	56.55–100.0

Supplemental Table 2.1. Inter-observer variability analysis

This represents the inter-reviewer agreement between the reviewers for their first interpretation of an AliveCor tracing.

Reviewer Comparison	Kappa	95% CI	Agreement (%)
Reviewer 1 and Reviewer 2	0.38	0.12–0.64	91/103 (88)
Reviewer 1 and Reviewer 3	0.54	0.21–0.87	97/103 (94)
Reviewer 2 and Reviewer 3	0.47	0.22–0.73	92/103 (89)
Reviewer 1, 2 and 3	0.45	0.33–0.56	88/103 (85)

Supplemental Table 2.2. Intra-variability analysis

This represents the intra-reviewer agreement between the reviewer's original interpretation of an AliveCor tracing versus their repeat interpretation of the same AliveCor tracing.

Individual Reviewer	Kappa	95% CI	Agreement (%)
Reviewer 1	0.79	0.37–1.00	35/36 (97)
Reviewer 2	0.35	-0.35–1.00	30/33 (91)
Reviewer 3	0.36	-0.15–0.88	29/34 (85)

2.9 FIGURES

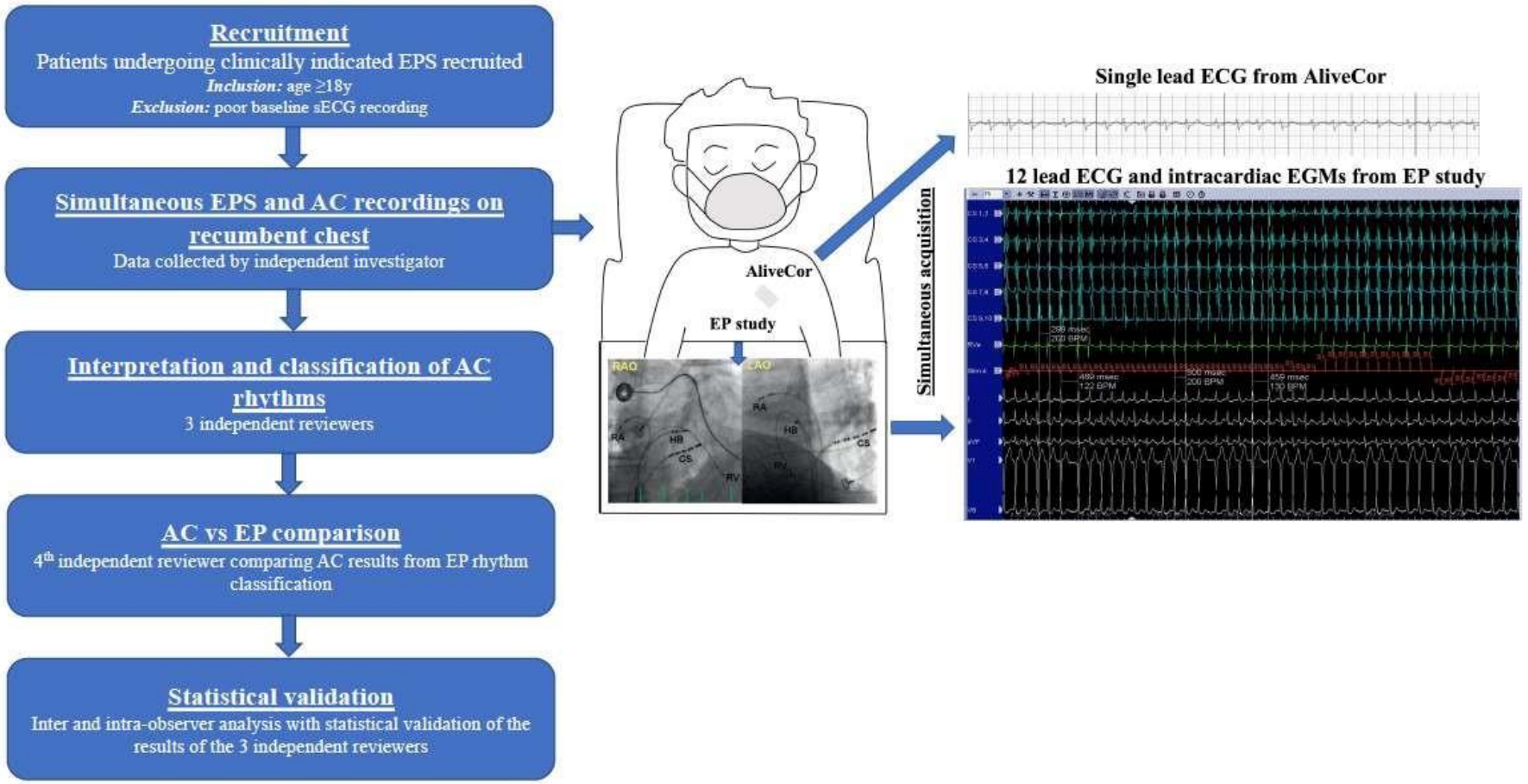

Figure 2.1. Workflow process for AliveCor vs EPS study

Abbreviations: EPS, electrophysiology study.

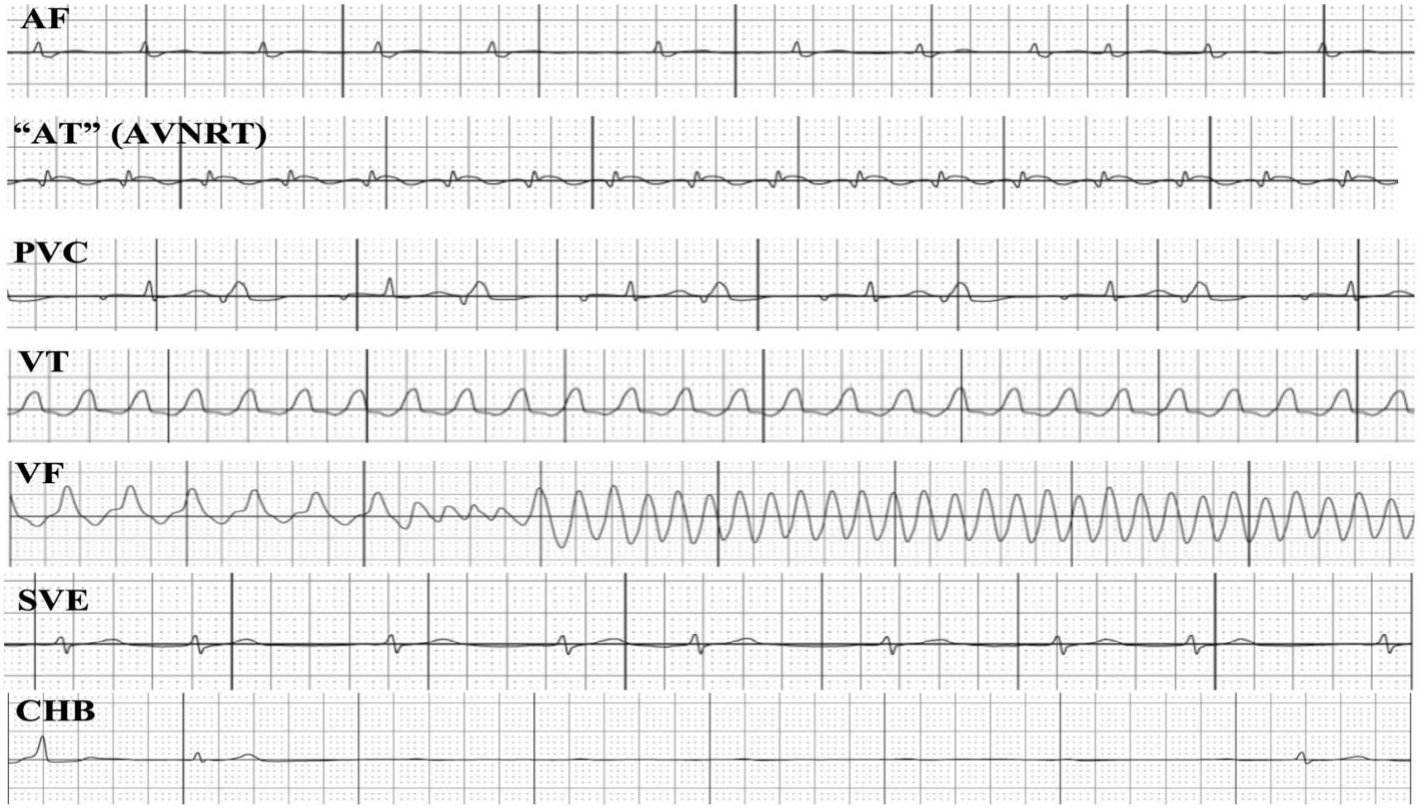

Figure 2.2. Examples of recorded arrhythmias from sECG

The corresponding intracardiac electrograms are shown in Supplemental Material.

Abbreviations: AF, atrial fibrillation; AT, atrial tachycardia; AVNRT, atrioventricular nodal re-entrant tachycardia; CHB, complete heart block; PVC, premature ventricular complex; SVE, supraventricular ectopy; VF, ventricular fibrillation; VT, ventricular tachycardia.

Chapter 3. Accuracy of commercially available handheld single lead ECG to cardiac telemetry and 12-lead ECG in identification of cardiac arrhythmias

3.1 ABSTRACT

3.1.1 Background

A novel, commercially available single-lead ECG device (sECG, AliveCor) may be useful in identifying cardiac arrhythmias.

3.1.2 Objectives

We sought to compare the accuracy of AliveCor, to telemetric monitoring and a 12-lead electrocardiogram (ECG).

3.1.3 Methods

Inpatients on cardiac telemetry for clinical indications underwent simultaneous acquisition of a 12-lead ECG, telemetry and AliveCor tracings whilst experiencing a range of clinically significant cardiac rhythms. Blinded reviewers independently analysed and interpreted the AliveCor, telemetry 12-lead ECG tracings. Interpretation of the heart rhythm from the 12-lead ECG was taken as the gold standard. The proportion of correctly identified rhythms, accuracy, positive and negative predictive value of telemetry and AliveCor tracings was compared.

3.1.4 Results

Forty-three patients had 71 captured rhythms analysed. Compared to the 12-lead ECG, reviewer analysis showed an overall accuracy of 89% for AliveCor tracings, and 96% for telemetry tracings (P<0.001, for AliveCor vs. telemetry). Telemetry tracings had a higher accuracy for correct rhythm identification, compared to AliveCor tracings for sinus rhythm (91% vs. 74%, P=0.004), atrial fibrillation/flutter (93% vs. 81%, P=0.016), premature ventricular complexes (93% vs. 86.1%, P=0.03), supraventricular ectopy (93% vs. 74%,

P=0.006), and ventricular pacing/bundle branch block (95% vs. 89%, P<0.001). Both methods were similar for correctly identifying atrial pacing, high degree atrioventricular block, supraventricular tachycardia and wide complex tachycardias.

3.1.5 Conclusions

In an inpatient population undergoing simultaneous acquisition of 12-lead ECG, telemetry and sECG, tracings from a sECG can correctly identify a high proportion of cardiac arrhythmias with reasonable accuracy. Telemetry tracings, however, were more accurate than sECG in identifying most cardiac arrhythmias. A sECG may be a reasonable surrogate for cardiac rhythm identification for intermittent rhythm monitoring when telemetry or ambulatory monitoring is unavailable.

3.2 INTRODUCTION

The use of the AliveCor KardiaMobile (AliveCor Inc, Mountain View, CA) single-lead electrocardiogram (sECG) application has been previously established for the identification of sinus rhythm (SR) and atrial fibrillation (AF).[65, 79, 135, 136] It may be useful in identifying cardiac rhythm abnormalities as a substitute for Holter, event or loop recorders, and in patients experiencing transient symptoms including palpitations.[79, 136]

Inpatient cardiac telemetry monitoring provides real-time information about a patient's heart rhythm to the treating clinical team, enabling expeditated identification of rhythm abnormalities which may guide treatment.[137] However, availability of monitored beds within hospitals, primarily exists within departments such as cardiology and intensive care units. As it may be a limited resource elsewhere, it is primarily reserved for patients identified at higher risk of experiencing a cardiac arrhythmia or electrocardiogram (ECG) abnormality. Inpatients admitted to departments lacking telemetry monitoring rely heavily on the performance of traditional 12-lead ECGs for patient heart rhythm monitoring, which may be a time and resource consuming process.[138]

In this study, we investigated the accuracy of an AliveCor sECG compared to inpatient cardiac telemetry monitoring and 12-lead ECG, through blinded reviewer interpretation of simultaneously recorded heart rhythm tracings performed on the AliveCor, telemetry, and 12lead ECG.

3.3 METHODS

This was a prospective, blinded study in which 43 patients aged ≥18 years admitted for cardiac telemetry monitoring to Westmead Hospital, Sydney, Australia, between May and November 2021 were recruited. Patients who had a poor baseline AliveCor single-lead ECG (sECG) performed at the time of recruitment were excluded. Written informed consent was obtained from all patients prior to the commencement of the study. The study was approved by the local Human Research Ethics Committee.

3.3.1 ECG Application

Study investigators simultaneously performed a 12-lead ECG, AliveCor sECG and telemetry ECG recording on recruited patients. Patients were required to remain supine during ECG recording, with standard electrode placement for the 12-lead ECG being preserved during this study. Patients held the AliveCor as per manufacturer guidelines, with arms relaxed in their lap and placing fingers from each hand on the AliveCor electrodes to replicate ECG lead I. Telemetry monitoring electrode placement comprised of five leads placed on the torso (four limb leads and one chest lead replicating V1). However, in keeping with standard visualisation configuration of telemetry ECG monitoring, telemetry tracings were saved as a paired lead II and chest lead combination.

3.3.2 Classification of Rhythms

Two blinded reviewers (R.G.B., T.C.) each independently analysed and interpreted the AliveCor tracings, telemetry tracings and 12-lead ECG tracings. The 12-lead ECG rhythm was taken as the gold standard for comparison. Interpretation of the rhythm from the 12-lead ECG, was classified by one investigator (S.K.), privy to all of the patients' clinical information. If the two reviewers lacked consensus for the interpretation of the 12-lead ECG, a third blinded reviewer acted as an adjudicator (Y.K.). For consistent comparison, the rhythms defined by reviewer interpretation of the gold standard 12-lead ECG were grouped as follows:

SR: encompassing sinus rhythm and sinus bradycardia;

AF: encompassing atrial fibrillation and atrial flutter;

Atrial pacing (AP): encompassing atrial pacing;

Atrioventricular block (AVB): encompassing high degree (Type II and complete) atrioventricular block;

Bundle branch block (BBB): encompassing either left or right bundle branch block morphology;

Premature ventricular complex (PVC): encompassing premature ventricular complexes;

Supraventricular ectopic beats (SVE): encompassing supraventricular ectopic beats;

Supraventricular tachycardia (SVT): encompassing regular, narrow complex tachycardias;

Ventricular pacing (VP): encompassing ventricular or biventricular pacing from an implanted device; or

Wide complex tachycardia (WCT): encompassing wide QRS complex tachycardias of either sustained or non-sustained duration.

Reviewers were asked to interpret each of the telemetry and AliveCor tracings. Where the diagnosis was uncertain, reviewers listed three differential diagnoses, consistent with clinical practice. Reviewer interpretations of telemetry tracings and AliveCor tracings were combined and reported as a proportion of correct interpretations against the gold standard 12-lead ECG defined rhythm. Interpretations were also reported for overall accuracy, to incorporate rhythm identification prevalence and the rates of positive and negative predictive values.

3.3.3 Patient characteristics

Baseline patient characteristics were collected including the patient's age, gender, body mass index (BMI), left ventricular ejection fraction (LVEF), presence of ischaemic heart disease and presence of an implantable cardioverter defibrillator or pacemaker.

3.3.4 Statistical Analysis

SPSS version 28 (IBM Corp., Armonk, NY) was used for analysis. Continuous variables were expressed as mean±standard deviation (SD) if there was a normal distribution and as a median (25%–75%) interquartile range (IQR) if there was skewed data. Proportion and accuracy were reported using descriptive statistics. For accuracy, the 95% confidence intervals are "exact" Clopper-Pearson confidence intervals. Chi-squared or Fisher's exact test

were used when comparing categorical variables. A 2-tailed P-value of <0.05 was considered statistically significant.

For the inter-observer analysis, each reviewer's interpretation of an AliveCor tracing was compared to the other reviewer's interpretation of the same AliveCor tracing. This was repeated for each reviewer's interpretation of each telemetry tracings. The Kappa statistic, which is a measure of inter-observer reliability was utilised with Cohen's Kappa (for two reviewers) with an additional % agreement performed.[133] The Kappa result can be interpreted as such: values ≤0 indicate no agreement, 0.01–0.20 as none to slight, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1.00 as almost perfect agreement.[133]

For the intra-observer analysis, each reviewer's interpretation of each AliveCor tracing was compared to the reviewer's own AliveCor tracing re-interpretation. The Kappa statistic and percentage agreement was similarly performed to assess intra-observer variability.

3.4 RESULTS

3.4.1 Baseline characteristics

Baseline patient characteristics are summarised in Table 3.1. Patients were predominantly male (64%), with mean age 67±18 years, mean LVEF 51±12%, mean BMI 30±7kg/m^2. Ischaemic heart disease was present in 19 (44%) of patients, and 16 (37%) had an implanted pacemaker or implantable cardioverter defibrillator.

3.4.2 Telemetry and AliveCor vs. 12-lead ECG

Telemetry, AliveCor and 12-lead ECG tracings were simultaneously acquired in 43 patients, demonstrating a total of 71 identifiable rhythms. Identified rhythms included: SR (n=22); AF (n=16); AP (n=2); AVB (n=2); PVC (n=8); SVE (n=1); SVT (n=1); VP and BBB (n=18); and WCT (n=1). The proportion of correct rhythm identification and overall accuracy for telemetry and AliveCor sECG tracings, as compared to gold standard 12-lead ECG diagnoses, are described in Table 3.2 and Table 3.3. Comparison of accurate rhythm identification for

telemetry and AliveCor, percentage agreement between telemetry and AliveCor, and the overall accuracy is shown in Table 3.4. Sensitivity, specificity, positive and negative predictive values for correct rhythm identification for telemetry and AliveCor tracings is shown in Supplemental Table 3.1 and 3.2, respectively. The overall accuracy for identification of various cardiac rhythms was 96% for telemetry and 89%, with statistical significance favouring telemetry tracings (P<0.001, Table 3.2–3.4).

Sinus Rhythm

In comparison to the 12-lead ECG, reviewers identified SR on telemetry tracings correctly in 21/22 tracings (95.5%), with an overall accuracy of 90.7% (Table 3.2), positive predictive value (PPV) and negative predictive value (NPV) of 87.5% and 94.7%, respectively (Supplemental Table 3.1). Compared to the 12-lead ECG, reviewers identified SR correctly from the AliveCor in 22/22 tracings (100%; Table 3.3) with a PPV and NPV of 67% and 100%, respectively (Supplemental Table 3.2). With the 12-lead ECG as a comparator, accuracy for identifying SR was greater with telemetry compared to AliveCor (90.7% vs. 74.4%, P=0.004, Table 3.4).

Atrial Fibrillation

In comparison to the 12-lead ECG, reviewers identified AF on telemetry correctly in 15/16 tracings (93.8%; Table 3.2), with an overall accuracy of 93% (PPV: 88.2%, NPV: 96.2%; Supplemental Table 3.1). Compared to the 12-lead ECG, reviewers identified AF correctly in 16/16 AliveCor tracings (100%; Table 3.3; PPV 67%, NPV 100%, Supplemental Table 3.2). With the 12-lead ECG as a comparator, accuracy for identifying AF was greater with telemetry, compared to the AliveCor (93 vs. 81.4%, P=0.016; Table 3.4).

Non-AF and SR Rhythms

Compared to the 12-lead ECG, reviewers were able to correctly identify all tracings of AVB (n=2), WCT (n=1), SVT (n=1) and AP (n=2) with both telemetry and AliveCor tracings (Table 3.2, 3.3). Compared to the 12-lead ECG, reviewers identified PVCs correctly in 7/8 (87.5%) telemetry tracings and 8/8 (100%) AliveCor tracings (Table 3.2, 3). However, the

accuracy was higher for telemetry than for AliveCor tracings (93% vs. 86.1%, P=0.03; Table 3.4). There was only one tracing of SVE available for analysis. Compared to 12-lead ECG, reviewers were not able to identify SVE accurately on telemetry (0%, Table 3.2; PPV: 0%, NPV: 97.6%, Supplemental Table 3.1), but were able to identify it accurately on the AliveCor tracing (Table 3.2, 3.3; PPV: 8.3%, NPV: 100%, Supplemental Table 3.2).

Compared to the 12-lead ECG, reviewers were able to identify VP/BBB correctly in 17/18 (94.4%) telemetry tracings with an overall accuracy of 95.4% (Table 3.2, PPV: 94.4%, NPV: 96.0%; Supplemental Table 3.1). Reviewers were able to identify VP/BBB correctly in 14/18 (78%) AliveCor tracings with an overall accuracy of 88.7% (Table 3.3, PPV: 93.3%, NPV: 95.7%, Supplemental Table 3.3). Compared to the 12-lead ECG, the accuracy was higher for telemetry, compared to the AliveCor for identifying VP/BBB correctly (95.9% vs. 88.9%, P<0.001, Table 3.4).

Overall interpretation

Reviewer interpretation for the correct rhythm was higher for telemetry, compared to AliveCor tracings across all individual rhythm, except for atrial pacing, high grade AVB, SVT and WCT (Table 3.4).

Inter-observer comparison

Inter-observer comparison of reviewers' interpretations showed a Kappa coefficient of 0.34 and proportional agreement of 87.3% for telemetry tracings and a Kappa coefficient of 0.31 and proportional agreement of 71.8% for AliveCor tracings (Supplemental Table 3.3). Intra-observer comparison of reviewer telemetry and AliveCor interpretation returned a Kappa coefficient of 0.15 and 0.37 and proportional agreement of 64.7% and 88.7% for the first and second reviewer, respectively (Supplemental Table 3.4).

3.5 DISCUSSION

This study is the first of its kind to directly compare rhythm interpretation of tracings derived from telemetry and AliveCor sECGs, with the gold standard of simultaneously acquired 12-lead ECG in an inpatient cohort. It shows that overall accuracy of reviewer interpretation was

significantly higher with telemetry compared to the sECG AliveCor tracings. However, analysis of correctly identified rhythms (defined by gold standard 12-lead ECG), across the combined rhythm groups, returned a comparable proportion of correct diagnoses from both telemetry and AliveCor analysis (93.0% vs. 94.4%). This is likely a result of an increased quantity of differential diagnoses provided during reviewer interpretations of AliveCor tracings. The higher accuracy with telemetry is likely explained by the presence of the additional ECG leads on telemetry, compared to the single lead available on AliveCor for diagnostic confirmation of the rhythm.

Poor reviewer agreement between telemetry and AliveCor interpretations was observed during analysis of both SR and AF tracings, at 79.1% and 83.7% respectively. Analysis of AliveCor tracing interpretations returned significantly reduced overall accuracy for SR compared to telemetry (P=0.004) and also compared to 12-lead ECG (P<0.001). Similarly, analysis of AliveCor tracings containing AF also returned significantly reduced overall accuracy compared to telemetry (P=0.016) and compared to 12-lead ECG (P=0.004). For both rhythms, accuracy was largely affected by reduced PPV (66.7% vs. 66.7%) from which overall accuracy is partially derived, attributable to a greater number of differential diagnoses provided within a small cohort. This also resulted in a specificity for 47.6% for SR and 70.4% for AF, in the context of a sensitivity of 100% for both rhythms.

This presents a paradox, considering the frequency at which SR and AF are encountered in the patient population.[137] It should be recognised that these results demonstrate a conservative approach to rhythm diagnosis. Similar outcomes were observed by Desteghe et al. in a study investigating the accuracy and cost effectiveness of utilising an AliveCor for AF screening in hospitalised patients. Desteghe classified AliveCor tracings as SR, AF or atrial flutter (AFL), and later grouped AF and AFL for analysis, as with the present study. Comparison of automated AliveCor rhythm interpretations to electrophysiologist diagnoses returned an improved sensitivity and reduced specificity.[136] As above, this was likely attributable to a conservative diagnosis of arrhythmias where there was reviewer uncertainty.

A study by Koshy et al. in a cohort of 51 consecutive patients with AF or AFL presenting for a cardioversion, demonstrated greater overall accuracy when AliveCor tracings were reviewed by a cardiologist.[138]

In contrast to the AliveCor, telemetry tracing interpretation of SR demonstrated reasonable sensitivity (95.5%) and specificity (85.7%). In AF, sensitivity (93.8%) and specificity (92.6%) were also reasonable. Whilst overall accuracy from telemetry interpretation for SR (90.7%) and AF (93.0%) were not significantly reduced, these values make it apparent that conservative reviewer diagnosis is preserved in the telemetry interpretations, as well as the AliveCor interpretations. The cause of conservative reviewer diagnosis is not definitive; however, it is possibly resultant of an absence of clearly defined P-waves in SR tracings, and minimal R-R variability in AF tracings. Whilst these characteristics on an AliveCor tracing may potentially dispute the definition of interpretability, they present real-world clinical variables that should be accounted for.

The inclusion of paced rhythms from implanted cardioverter defibrillators (ICD) or permanent pacemakers (PPM) in the present study provides a semblance of what may be observed in a typical cohort of telemetry-monitored patients. Narrow complex (QRS duration <120ms) paced rhythms were not represented in this study. The majority of ventricular paced and BBB rhythms were correctly identified on both telemetry (95.4%) and AliveCor (88.7%) tracings during reviewer analysis. A similar result was observed in a study by Abudan et al. investigating the safety of using an AliveCor for heart rhythm assessment in patients with ICDs or PPMs, in which it was demonstrated that 90% of paced rhythms recorded on the AliveCor were interpretable.[141]

There were key differences in protocol for analysis between the present study and the work by Abudan and colleagues. Primarily, heart rhythm reviewers in that study were unblinded to patients' implanted device history and status, that may have led to a reviewer bias towards diagnosing paced rhythms. Conversely, reviewers in the present study remained blinded to patient history, multiple differential diagnoses were permitted, and reviewers were

not required to specify the presence of VP spikes. It is plausible that knowledge of the patients implanted device status, or more definitive reviewer diagnoses may have affected analysis results in our study.

It is notable that the sensitivity of AliveCor interpretation was markedly reduced compared to telemetry (77.8% vs. 94.4%) whilst specificity remained equal (96.0% vs. 96.0%). Whilst this was likely partially affected by a small sample size, the reduced sensitivity is likely resulting from the lack of appreciation or acknowledgement of broad complex QRS complexes. It is reasonable to argue that BBB morphologies have distinctive ECG characteristics that should be recognisable on the AliveCor lead I vector. However, it is worth considering that ECG classic definitions are frequently supported by the presence of additional available ECG leads.[142] Based on this, it is possible that reviewers declined to give a diagnosis of BBB or pacing in lieu of additional ECG leads or visualisation of clear pacing spikes.

It is also plausible that some of the distinctive ECG characteristics observed in lead I during these rhythms may be attenuated by moderate levels of signal artefacts. This may be demonstrated in a study performed by Rischard et al. utilising the KardiaBand (AliveCor, Inc., Mountain View, California) technology, that included 166 patients with VP, returned a sensitivity of 34% and specificity of 99%. The same study included 307 patients with BBB and demonstrated sensitivity of 59–62% and specificity of 96.%.[134] In the case of other ECG waveforms, such as atrial fibrillation or flutter waves, another study performed by Rajakariar et al. demonstrated how the interpretability of AFL in standard (lead I) AliveCor configuration may be unclear.[143] These findings may explain some of our results, but also underscore that a potentially higher level of scrutiny and attention is required by clinicians reviewing sECGs.

Reviewer analysis returned perfect interpretation for both telemetry and AliveCor for both AVB and WCT rhythms, though only a small sample size existed in this study. Similar findings have been reported previously.[126, 134] However, accurate identification of potentially malignant arrhythmias remains an important clinical finding, though, demonstrated in the work

by Rischard et al., it is possible that results may vary in a larger cohort with a higher incidence of potentially malignant rhythms.

3.6 LIMITATIONS

This study was performed across a small sample size at a single tertiary centre and larger studies may yield varied results. It is possible that the novel 6-lead ECG may have yielded similar accuracy to telemetry tracings and requires further prospective investigation. Overall accuracy is derived from NPVs and PPVs and should therefore be interpreted along with proportional accuracy. It is possible that in a larger cohort, statistical values may change. The analysis of ECG tracings was performed by investigators blinded to patients' clinical history; additional clinical data may assist an interpreter in making an accurate diagnosis.

Electrode positioning of 12-lead ECG, AliveCor and telemetry limb leads were standardised, however there may be subtle variation in the placement of the telemetry chest lead which may have affected interpretability of some telemetry tracings. The quantity and scope of recordable rhythms was largely limited to clinically stable patients, subsequently leading to an underrepresentation of severe arrhythmias, such as AVB, WCT and SVT. A more substantial number of patients in these cohorts may have led to differing results.

For telemetry and AliveCor analysis, AFL and AF diagnosed by 12-lead ECG were grouped together, as were VP and BBB. Distinction between these rhythms during analysis may have led to differing results, however this is unlikely to have major effect on immediate clinical management. With a greater scope of differential diagnoses available to experts, interpretation by multiple reviewers inherently affects outcomes of sensitivity and specificity. It is possible that a binary approach to ECG interpretation may lead to differing results, however this does not accurately represent clinical practice. Similarly, the binary identification of P-waves was not required for a diagnosis of SR, which may have led to diagnoses of SR being made based on R-R regularity, which may have also affected the results.

3.7 CONCLUSION

When compared to the gold standard of 12-lead ECG, sECG is able to identify a range of cardiac rhythms with reasonable accuracy but remains less accurate than telemetry in an inpatient population undergoing simultaneous 12-lead ECG, Holter and sECG analysis. Whilst larger studies are required, it is possible that AliveCor may be a reasonable alternative to intermittent heart rhythm monitoring in patients, when telemetry or ambulatory monitoring is not available.

3.8 TABLES

Table 3.1. Baseline characteristics

Patient characteristics	n=43
Female gender, n (%)	16 (36%)
Age, mean ± SD, years	66.7 ± 18.2
Body mass index, mean ± SD	29.9 ± 6.9
LVEF %, mean ± SD (%)	51.3 ± 12.3
Ischaemic Heart Disease, n (%)	19 (44)
CIED Implanted, n (%)	16 (37)

Abbreviations: CIED, cardiac implantable electronic device; LVEF, left ventricular ejection fraction; SD, standard deviation.

Table 3.2. 12-Lead ECG vs. combined reviewers' telemetry interpretation (proportional and overall accuracy)

This table represents the rhythm diagnosis identified from the 12-lead ECG, number of examples and the comparative proportional and overall accuracy of combined reviewer interpretation of the telemetry tracings.

Diagnosis from 12-Lead ECG	n	Telemetry Proportion Correct (%)	Telemetry Overall Accuracy (%) (95% CI)
Sinus Rhythm	22	21 (95.5)	90.7 (77.9–97.4)
Atrial Fibrillation/Flutter	16	15 (93.8)	93.0 (80.9–98.5)
Atrial Pacing	2	2 (100)	100 (91.8–100)
High Degree Atrioventricular Block	2	2 (100)	100 (91.8–100)
Premature Ventricular Complexes	8	7 (87.5)	93.0 (80.9–98.5)
Supraventricular Ectopy	1	0 (0)	93.0 (80.9–98.5)
Supraventricular Tachycardia	1	1 (100)	93.0 (80.9–98.5)
Ventricular Pacing & Bundle Branch Block	18	17 (94.4)	95.4 (84.2–99.4)
Wide Complex Tachycardia	1	1 (100)	100 (91.8–100)
Total	71	66 (93.0)	95.9 (93.4–97.6)

Table 3.3. 12-Lead ECG vs. combined reviewers' AliveCor interpretation (proportional and overall accuracy)

This table represents the rhythm diagnosis identified from the 12-lead ECG, number of examples and the comparative proportional and overall accuracy of combined reviewer interpretation of the AliveCor tracings.

Diagnosis from 12-Lead ECG	n	AliveCor Proportion Correct (%)	AliveCor Overall Accuracy (%) (95% CI)
Sinus Rhythm	22	22 (100)	74.4 (58.8–86.5)
Atrial Fibrillation/Flutter	16	16 (100)	81.4 (66.6–91.6)
Atrial Pacing	2	2 (100)	95.4 (84.2–99.4)
High Degree Atrioventricular Block	2	2 (100)	100 (91.8–100)
Premature Ventricular Complexes	8	8 (100)	86.1 (72.1–94.7)
Supraventricular Ectopy	1	1 (100)	74.4 (58-8–86.5)
Supraventricular Tachycardia	1	1 (100)	95.4 (84.2–99.4)
Ventricular Pacing & Bundle Branch Block	18	14 (77.8)	88.7 (74.9–96.1)
Wide Complex Tachycardia	1	1 (100)	100 (91.8–100)
Total	71	67 (94.4)	88.9 (85.3–91.8)

Table 3.4. Telemetry vs. AliveCor interpretation by the reviewer's (overall accuracy and agreement)

This table represents the rhythm diagnosis identified from the 12-lead ECG and comparative proportional and overall accuracy of combined reviewer interpretation of telemetry and AliveCor tracings and the extent to which interpretations agreed between modalities

Diagnosis from 12-Lead ECG	n	Proportion Correct (%)		Agreement	Overall Accuracy (%)		*P* value
		Telemetry	AliveCor	(%)	Telemetry	AliveCor	
Sinus Rhythm	22	21 (95.5)	22 (100)	79.1%	90.7	74.4	0.004
Atrial Fibrillation/Futter	16	15 (93.8)	16 (100)	83.7%	93.0	81.4	0.016
Atrial Pacing	2	2 (100)	2 (100)	95.3%	100	95.4	NS
High Degree Atrioventricular Block	2	2 (100)	2 (100)	100.0%	100	100	NS
Premature Ventricular Complexes	8	7 (87.5)	8 (100)	88.4%	93.0	86.1	0.03
Supraventricular Ectopy	1	0 (0)	1 (100)	72.1%	93.0	74.4	0.006
Supraventricular Tachycardia	1	1 (100)	1 (100)	93.0%	93.0	95.4	NS
Ventricular Pacing & Bundle Branch Block	18	17 (94.4)	14 (77.8)	88.4%	95.4	88.7	<0.001
Wide Complex Tachycardia	1	1 (100)	1 (100)	100.0%	100	100	NS
Total	71	66 (93.0)	67 (94.4)	88.9%	95.9	88.9	<0.001

Supplemental Table 3.1. 12-Lead ECG vs. combined reviewers' telemetry interpretation (overall accuracy)

This table represents the rhythm diagnosis identified from the 12-lead ECG and the sensitivity, specificity, positive and negative predictive values and overall accuracy of combined reviewer interpretation of the telemetry tracings.

Diagnosis from 12-Lead ECG	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
Sinus Rhythm	95.5%	85.7%	87.5%	94.7%	90.7%
Atrial Fibrillation/Flutter	93.8%	92.6%	88.2%	96.2%	93.0%
Atrial Pacing	100.0%	100.0%	100.0%	100.0%	100.0%
High Degree Atrioventricular Block	100.0%	100.0%	100.0%	100.0%	100.0%
Premature Ventricular Complexes	87.5%	94.3%	77.8%	97.1%	93.0%
Supraventricular Ectopy	0.0%	95.2%	0.0%	97.6%	93.0%
Supraventricular Tachycardia	100.0%	92.9%	25.0%	100.0%	93.0%
Ventricular Pacing & Bundle Branch Block	94.4%	96.0%	94.4%	96.0%	95.4%
Wide Complex Tachycardia	100.0%	100.0%	100.0%	100.0%	100.0%
All Rhythms	94.4%	96.2%	84.8%	98.7%	95.9%

Supplemental Table 3.2. 12-Lead ECG vs. combined reviewers' AliveCor interpretation (overall accuracy)

This table represents the rhythm diagnosis identified from the 12-lead ECG and the sensitivity, specificity, positive and negative predicative values and overall accuracy of combined reviewer interpretation of the AliveCor tracings.

Diagnosis from 12-Lead ECG	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
Sinus Rhythm	100.0%	47.6%	66.7%	100.0%	74.4%
Atrial Fibrillation/Flutter	100.0%	70.4%	66.7%	100.0%	81.4%
Atrial Pacing	0.0%	100.0%	-	95.4%	95.4%
High Degree Atrioventricular Block	100.0%	100.0%	100.0%	100.0%	100.0%
Premature Ventricular Complexes	100.0%	82.9%	57.1%	100.0%	86.1%
Supraventricular Ectopy	100.0%	73.8%	8.3%	100.0%	74.4%
Supraventricular Tachycardia	100.0%	95.2%	33.3%	100.0%	95.4%
Ventricular Pacing & Bundle Branch Block	77.8%	96.0%	93.3%	85.7%	88.4%
Wide Complex Tachycardia	100.0%	100.0%	100.0%	100.0%	100.0%
All Rhythms	94.2%	87.7%	62.5%	98.6%	88.9%

Supplemental Table 3.3. Inter-observer variability analysis

This represents the inter-reviewer agreement between the reviewers for their interpretation of a telemetry ECG tracing and an AliveCor ECG tracing.

Reviewer Comparison	Kappa	95% CI	Agreement (%)
Reviewers 1 and 2: Telemetry	0.34	-0.09–0.77	62/71 (87.3)
Reviewers 1 and 2: AliveCor	0.31	0.04–0.59	51/71 (71.8)

Supplemental Table 3.4. Intra-observer variability analysis.

This represents the intra-reviewer agreement between the reviewer's interpretation of a telemetry ECG tracing versus their interpretation of the simultaneously recorded AliveCor ECG tracing.

Individual Reviewer	Kappa	95% CI	Agreement (%)
Reviewer 1: Telemetry and AliveCor	0.15	-0.14–0.44	46/71 (64.7)
Reviewer 2: Telemetry and AliveCor	0.37	-0.07–0.81	63/71 (88.7)

Chapter 4. Smartphone-based single-lead ECGs versus traditional ambulatory Holter monitoring for definite diagnosis of cardiac arrhythmia in patients with palpitations: a randomised controlled trial (The AliveCor vs. Holter Trial)

4.1 ABSTRACT

4.1.1 Background

Handheld devices such as the AliveCor represent a novel diagnostic tool for the detection of cardiac arrhythmias.

4.1.2 Objectives

To examine, in a pilot randomised trial over a 6-month period, if the AliveCor is superior to Holter monitoring in arrhythmia diagnosis amongst patients with undiagnosed palpitations and/or presyncope.

4.1.3 Methods

Forty-one patients were randomised to receive a single-lead electrocardiogram (intervention, sECG) or standard of care (control; ambulatory 5-day Holter monitor on up to three occasions over a period of 6-months, with a minimum separation of 4-weeks). Primary outcome was defined as a symptom-rhythm correlation (severe sinus bradycardia, sinus tachycardia, supraventricular tachycardia [SVT], atrial flutter or fibrillation [AF], premature atrial contractions [PAC], premature ventricular contractions [PVC], sustained or non-sustained ventricular tachycardia [NSVT, VT] or high-grade atrioventricular block) or a predefined serious rhythm abnormality. Secondary outcomes were defined as each of the individual rhythm abnormalities, either symptomatic or asymptomatic, and patient satisfaction, confidence/empowerment scores.

4.1.4 Results

At 6-months, the primary outcome was met in 62% of the control and 70% of the intervention groups (P=0.48). Symptomatic paroxysmal SVT was diagnosed in 15% of the intervention versus 0% of the control group (P=0.07). There were a higher proportion of patients diagnosed with symptomatic or asymptomatic SVT, AF, PACs, PVCs, and NSVT/VT in the control, compared to the intervention groups. Scores for patient satisfaction and confidence/empowerment were higher in the intervention group (P<0.05).

4.1.5 Conclusions

This pilot randomised trial found no overall difference in symptomatic arrhythmia detection rates with the novel handheld single-lead ECG device, compared to standard care of multiday Holter monitoring in patients with undiagnosed palpitations and/or pre-syncope.

4.2 INTRODUCTION

Cardiac arrhythmias represent a major contributor to hospitalisations and outpatient clinic visits resulting in significant healthcare utilisation. Prevalent arrhythmias such as atrial fibrillation (AF) are associated with increasing morbidity from stroke, dementia and heart failure whereas more malignant arrhythmias such as ventricular tachycardia (VT) are associated with sudden cardiac death.[144] The accurate and timely diagnoses of these arrhythmias is critical in the management paradigm such as the initiation of anticoagulation therapy for AF and defibrillator therapy to prevent sudden cardiac death in VT.

A novel, commercially available handheld device, AliveCor KardiaMobile (Mountain View, California, USA) is able to record a single-lead (and more recently, a 6-lead) electrocardiogram (sECG). This device provides the opportunity to diagnose a range of cardiac arrhythmias in the ambulatory setting.[126, 145] Whilst the AliveCor is well established in confirming sinus rhythm (SR) and AF, there is emerging data it may be useful in the diagnosis of non-AF arrhythmias.[146] There is only limited randomised trial data comparing the accuracy and utility of the AliveCor, compared to multi-day Holter monitoring for the diagnosis of cardiac arrhythmias.[65]

We hypothesised that a patient-led wearable sECG system (the AliveCor KardiaMobile) would be equivalent to routine care of repeated ambulatory 5-day Holter monitoring for the diagnosis of arrhythmias in patients with undiagnosed, symptomatic palpitations or pre-syncope. We evaluated this in a single-centre pilot randomised trial of sECG vs. sequential 5-day Holter monitoring with follow-up over a 6-month period.

4.3 METHODS

4.3.1 Study Design and Randomisation

This was a single-centre, parallel group, two arm, unblinded randomised clinical trial, run over a period of two-years. We included patients with a history of palpations and/or pre-syncope and randomised them to receive either a sECG device (AliveCor) or standard care (defined as 5-day ambulatory Holter monitoring at three separate time points) for a period of 6-months to determine which approach provides a superior diagnostic yield of cardiac arrhythmias. Patients were randomised in a 1:1 ratio into intervention (AliveCor) or control groups in variable blocks of 2, 4 and 6 using a password-protected web portal (REDCap, Vanderbilt University, Nashville, TN, USA).

4.3.2 Study Setting and Recruitment

Between November 2019 and April 2021, 41 patients were recruited from outpatient cardiology clinics at Westmead Hospital, Sydney, Australia. All participating patients were provided written informed consent prior to the commencement of the study procedures. The recruitment process and exclusion of patients is illustrated in Figure 4.1.

4.3.3 Inclusion and Exclusion Criteria

Patients aged ≥18 years were included if they had (i) ≥2 episodes of palpitations or presyncope in the preceding 6-months; (ii) the initial 12-lead electrocardiogram (ECG) had failed to detect arrhythmia; and (iii) had a smartphone and/or a smartwatch capable of running the AliveCor application. Patients were excluded if they had one or more of the following: (i) were pregnant or breast feeding, or have a concomitant illness, physical impairment, or mental condition which in the opinion of the study team/primary physician could interfere with the conduct of the study including outcome assessments; (ii) showed inability or unwillingness to provide written informed consent; (iii) were deemed unable to complete study procedures; (iv) had a medical illness with anticipated life expectancy of <3-months; (v) had a poor baseline sECG recording on preliminary screening; (vi) showed lack of understanding of how to record sECG

after initial consultation; and/or (vii) did not possess a smartphone compatible with running the AliveCor application.

4.3.3.1 Sample size calculation

Based on the published yield of multi-day Holter of 60% (averaged to 60%),[13] we anticipated a 30% absolute increase in yield with sECG to a yield of 90% for a symptom-rhythm correlation. Given a power of 80% and P=0.05, and a 10% dropout, we estimated 68 patients would be required for this study. Due to recruitment difficulties and restrictions in the context of the COVID-19 pandemic, a total of 41 patients were recruited.

4.3.4 Study groups

4.3.4.1 Control Arm

Patients randomised to the control arm were managed to a prespecified protocol as standard of care. This comprised of an initial 5-day Holter monitor, along with additional 5-day Holter monitors on up to three occasions over a period of 6-months, with a minimum separation of 4-weeks. Patients were instructed on use of the Holter monitor by a member of the study team, which included instructions to maintain a symptom diary in free text format, allowing patients to enter time, duration and nature of symptoms that were recorded during the Holter period. Patients were instructed to seek medical attention in the event that they had prolonged symptoms or symptoms that concerned them for a 12-lead ECG and medical review. All results of the Holter monitor were reviewed on the day of their return. The patient was deemed to have reached the primary endpoint if they had:

1. A rhythm documentation in the context of symptom recurrence whilst wearing the Holter monitor (symptom-rhythm correlation),
2. An asymptomatic severe arrhythmia (defined in primary outcomes).

4.3.4.2 Intervention Arm

Patients randomised to the intervention arm were provided with the AliveCor KardiaMobile (Mountain View, California). Patients were instructed in the recording and transmission of sECG via the instructional videos within the AliveCor smartphone application and with training from a study team member. Initial setup included the input of patient's study identification numbers into the AliveCor application. All patients were able to record and transmit their deidentified sECG independently upon completion of training to the secure email server at Westmead Hospital. The AliveCor allows a sECG recording for up to 300 seconds.[147] The AliveCor is utilised by placing fingers from each hand on the device electrodes, from which the AliveCor detects ECG signals which are subsequently transmitted to the patient's smartphone via ultrasound into a sharable portable document format.

Patients allocated to the sECG group were instructed to:

1. Record and transmit sECG on a minimum of a once daily basis but ideally to send an sECG twice daily (morning and night) for general rhythm monitoring and screening of asymptomatic arrhythmia;
2. Record and transmit an indefinite number of sECGs during the times that they experience symptomatic palpitations;
3. Seek medical attention in the event that they had prolonged symptoms or symptoms that concerned them for a 12-lead ECG and medical review.

Patients were not restricted on the duration of the sECG recording. Transmitted sECGs were reviewed during business hours, within 24-hours of sECG receipt. The patient was deemed to have reached the primary endpoint if they had:

1. A rhythm documentation in the context of symptom recurrence during the recording of an sECG (symptom-rhythm correlation);
2. An asymptomatic severe arrhythmia (defined in primary outcomes).

4.3.5 Control of Bias

Blinding of patients was not possible as both interventions require the patient to be aware and adherent to a diagnostic test. Reporting of endpoints was unable to be done in a blinded fashion given the distinct characteristics of an AliveCor vs. Holter rhythm tracing.

4.3.6 Study Outcomes

4.3.6.1 Primary outcome

The primary outcome of the study was defined as the proportion of patients that achieved a symptom-rhythm correlation or had a serious rhythm abnormality (defined below) over the 6-month follow-up period. Rhythms that were defined as a valid endpoint for symptom-rhythm correlation included the following: severe sinus bradycardia (≤40 beats per minute [bpm], not occurring when the patient is asleep), sinus tachycardia ([ST] ≥100bpm, occurring when the patient is inactive), supraventricular tachycardia (SVT), atrial flutter, AF, premature atrial complexes (PAC), premature ventricular complexes (PVC), VT, Mobitz type II atrioventricular block or complete heart block. Rhythms valid as a serious rhythm abnormality (symptomatic or asymptomatic) included severe sinus bradycardia (≤40bpm, not occurring when the patient is asleep), SVT (≥30 seconds duration), atrial flutter (≥30 seconds duration), AF (≥30 seconds duration), VT (≥30 seconds duration), Mobitz type II atrioventricular block or complete heart block.

4.3.6.2 Secondary outcomes

Secondary outcomes were rhythm abnormalities that were either symptomatic or asymptomatic and defined as:

1. Proportion of patients with each of the individual rhythm outcomes of sinus bradycardia, ST, SVT, atrial flutter, AF, PAC, PVC, VT, Mobitz type II atrioventricular block or complete heart block;
2. Proportion of patients with ≥10 seconds of AF, atrial flutter, SVT or VT;

3. Patient satisfaction on a scale of 1–10 (1 being poor, 10 being excellent) with the sECG device or the Holter monitor for usability of either device and whether the device made them feel empowered or gave them a sense of confidence on arrhythmia diagnosis (Appendix 4.2);
4. Adverse events (Appendix 4.3).

4.3.7 Adjudication of endpoints

Two independent investigators (K.G., S.T.) reviewed the sECG and Holter tracings for classification of the rhythm abnormalities. Automated rhythm classifications on either platform were not used for analysis. Disagreements were resolved adjudication by a third investigator (S.K.).

4.3.8 Baseline visit

For baseline assessment, the following information was collected including details of medical history, concomitant medications, results of baseline imaging, including but not limited to an echocardiogram. In the event there was no echocardiogram performed, this was booked during the timeframe of the study period. All baseline and subsequent follow-up were recorded in pre-formed REDCap database and in the hospital Electronic Medical Record.

4.3.9 Participant Timeline

All eligible participants will be randomised and followed up for a period of 6-months. The trial schema is described in Figure 4.2 and Appendix 4.1.

4.3.10 Adverse Events

Any adverse events occurring as a result of sECG or Holter monitoring were recorded. This list of adverse events is shown in Appendix 4.3.

4.3.11 Statistical Analysis

SPSS version 27 (IBM Corp., Armonk, NY) was used for analysis. Continuous variables were expressed as mean±standard deviation (SD) if normally distributed and interquartile range (IQR) was used if the data was clearly skewed. Continuous variables were compared using a Student's t-test if normally distributed, or a Mann-Whitney U test if they were not normally distributed. Chi-squared or Fisher's exact test were used when comparing categorical variables. Free from arrhythmia diagnosis was estimated using the Kaplan-Meier method and the log rank chi-squared method. A 2-tailed P-value of <0.05 was considered statistically significant.

4.4 RESULTS

In total, 41 patients were recruited, of which 21 were randomised to the Holter monitor (control) arm and 20 to the AliveCor (intervention) arm. Median follow-up of the 41 patients was for 182 (IQR: 178–188) days. Mean compliance with the 5-day Holter monitor (maximum monitoring duration of 120 hours) in the control arm was 108.6±17.19 hours (91%). In the intervention arm, the proportion of interpretable sECG tracings were 7502/7540 (99.5%).

4.4.1 Baseline Characteristics

Baseline characteristics were similar between the two groups (Table 4.1). Mean age of the population was 46±18 years, and 66% were female. All patients had preserved left ventricular function (mean left ventricular ejection fraction 63±5%) and all patients were in SR at baseline. There were no significant statistical differences in the aforementioned baseline characteristics between the control and intervention group.

4.4.2 Primary Outcomes

The proportion of patients in the control and intervention group reached a primary outcome which is described in Table 4.2. At the end of the study period, the primary outcomes were reached in 67% of the control and 75% of the intervention arm. By Kaplan-Meir analysis, 62%

of patients were diagnosed with the primary outcome in the control arm compared to 70% of patients in the intervention arm at 6-months (P=0.48; Figure 4.3).

There was no significant difference between the control and intervention groups in subtypes of the symptom-rhythm correlation for sinus tachycardia, PVCs and PACs, however more patients with SVT were diagnosed in the intervention (15%) vs. the control group (0%; P=0.07; Table 4.2). There were no significant differences between the control and intervention groups of a serious rhythm abnormality (Table 4.2).

4.4.3 Secondary Outcomes

Amongst each of the individual secondary outcomes tested (symptomatic and asymptomatic arrhythmias), there were a higher proportion of patients diagnosed with the following arrhythmias in the control vs. intervention groups: SVT (62% vs. 20%, P=0.007), PACs (100% vs. 35%,

P<0.001), PVCs (100% vs. 40%, P<0.001; Table 4.3). The proportion of patients with AF and VT/non-sustained ventricular tachycardia (NSVT) were numerically higher in the control, compared to the intervention groups (AF 10% vs. 0%, P=0.15, and VT/NSVT: 14% vs. 0%, P=0.09; Table 4.3).

A greater proportion of patients reported a satisfaction score of ≥8/10 for usability of the sECG compared to the Holter monitor (77% vs. 38%, P=0.03; Table 4.3). A greater proportion of patients felt empowered (score ≥8/10) with the sECG compared to the Holter (69% vs. 19%, P=0.006; Table 4.3). There was 1 adverse event in the control (rash) and none in the intervention arm (Table 4.3).

4.5 DISCUSSION

This pilot randomised controlled trial (RCT) compares the efficacy and tolerability of a commercially available sECG device (AliveCor Kardia) to the standard of care, the multi-day Holter monitor for the diagnosis of arrhythmias in a selected population presenting with palpitations and/or pre-syncope. The main findings were:

1. The sECG was similar to the Holter in the diagnosis of symptomatic cardiac arrhythmias (70% vs. 62% at 6-months), with the notable exception of symptomatic paroxysmal SVT, where the yield of the sECG was higher;
2. The Holter monitor was superior to the sECG in the overall detection of some arrhythmias such as SVTs, PACs, PVCs and VT/NSVT which was driven by a higher detection rate of asymptomatic arrhythmias, given the continuous nature of monitoring with the Holter;
3. Patient satisfaction in terms of usability, sense of empowerment and confidence for arrhythmia diagnosis was higher with the sECG, compared to the Holter monitor.

This data suggests that the sECG can play an important role in the diagnosis of paroxysmal arrhythmias, showing at least equivalence, or in some cases, superiority for the diagnosis of highly symptomatic intermittent and episodic arrhythmias, with greater patient satisfaction and empowerment in reaching an arrhythmia diagnosis. The Holter monitor, however remains superior in detection of asymptomatic arrhythmias, given the continuous nature of monitoring. Further larger randomised trials are needed to confirm our findings.

4.6 PREVIOUS STUDIES

There has been limited RCT data in the field of AliveCor vs. Holter monitoring in the diagnosis of patients with palpitations and pre-syncope with the exception of the IPED (Investigation of Palpitations in ED) study.[77] This study was in a cohort of 240 patients who presented to the emergency department with palpitations or pre-syncope, who underwent standard care plus the use of the AliveCor or standard care over a period of 3-months. There was notably a greater than five-fold increase in symptom-rhythm correlation in the AliveCor group (55.6% of patients) compared to the standard of care group (9.5% of patients), with detected rhythms including SVT, AF/atrial flutter and ectopy. Our study differed from this in that we extended our time frame over a period of 6-months and defined our standard of care with an initial 5-day Holter monitor with the opportunity for up to two additional 5-day Holter monitors over the 6-month follow-up period. We also additionally defined an asymptomatic serious rhythm

abnormality as a primary outcome in addition to a symptom-rhythm correlation. Moreover, the IPED study did not mandate a protocol for investigations in the control group, and this was left to the discretion of the treating physician. Indeed, it seems that the Holter monitor was used infrequently with results showing that of the 9.5% of patients diagnosed with arrhythmia in the control group, 8/116 patients (7%) were diagnosed using a Holter, and 3/116 (2.6%) on a 12-lead ECG. This study may therefore have overestimated the benefit of the sECG.

The Holter monitor, due to continuous recording, may be able to record incidental arrhythmias which may be symptomatic or asymptomatic. However, the yield of the Holter monitor, particularly the 24–48-hour monitor, can be limited with a diagnostic yield as low as 15% in patients with intermittent palpitations, as reported by Steinberg et al. in the 2017 ISHNE-HRS expert consensus statement on ambulatory ECG and external cardiac monitoring/telemetry.[13, 148, 149] In our study, 62% of patients reached a primary outcome of a symptomatic arrhythmia diagnosis at 6-months with the use of the Holter. This increase in diagnostic yield may be attributed to an extended period of Holter monitoring (5-days, instead of 24–48-hours) and broader definition of symptomatic arrhythmias including sinus tachycardia, which reflects real-world clinical practice and highlights the potential to diagnose sustained, asymptomatic arrhythmias with prolonged Holter monitoring. It is feasible that our results would have been more favourable toward the sECG group if we used a shorter period of monitoring e.g., 24–48-hours, or if we used less stringent criteria for symptom-rhythm correlation such as exclusion of sinus tachycardia. Further studies are needed to confirm these findings.

Whilst the AliveCor has had extensive validation in SR and AF, a limited number of studies have explored its' use as a first-line investigative tool in patients with unexplained palpitations. Newham et al. demonstrated in a cohort of 20 patients, who underwent evaluation for palpitations with the AliveCor over a period of 12-weeks, that 85% had symptom-rhythm correlation and 45% had the detection of an arrhythmia.[150] Cullen et al. also demonstrated in a population of 290 patients that presented to an emergency department with palpitations or

pre-syncope, of whom 237 (81.7%) were fitted with the AliveCor, that 7.2% had a cardiac diagnosis (12 AF/atrial flutter, 5 SVT and 1 atrial tachycardia) with resultant change in anti-arrhythmic or anticoagulant therapy, similar to the 8.8% cardiac diagnosis in the IPED study.[79, 136] The AliveCor has also similarly been explored in children with palpitations, with Macinnes et al. demonstrating the AliveCor had a superior diagnostic yield for tachyarrhythmias and a higher patient satisfaction when compared with the conventional cardiac event monitor.[151] Our study expanded upon these studies in an adult population through direct comparison of the AliveCor with a Holter monitor and demonstrated an overall 75% diagnostic yield for patients with undiagnosed palpitations/pre-syncope over a period of 6-months and demonstrated that it may be non-inferior to the Holter over a period of 6-months. We were also able to provide 15% of patients with a diagnosis of SVT highlighting the potential to diagnose paroxysmal, symptomatic arrhythmias.

A number of studies have explored the sECG in terms of patient's usability and patient empowerment. The REHEARSE-AF study demonstrated in a population of 500 patients utilising the AliveCor, that the majority of patients were satisfied with the device and found it easy to use without restriction of activities or causing anxiety.[65] Hermans et al. similarly demonstrated in a cohort of patients who were monitored post-catheter ablation for AF, simultaneously with the AliveCor and the Holter, that the AliveCor was found to be more convenient in daily usage than the Holter ($P<0.001$).[152] Our study both aligned and expanded upon these results and illustrated that patients felt the AliveCor was more usable than the Holter and felt a greater sense of empowerment.

4.7 LIMITATIONS

Our study utilised a small sample size of 41 patients, and thus may have been underpowered to definitively establish superiority of either the AliveCor or Holter in the diagnosis of undiagnosed palpitations/pre-syncope. It was also not possible to blind the treating clinician and in the reporting of endpoints, due to the distinct characteristics of an AliveCor and Holter tracing. The compliance with the AliveCor and Holter monitor is also patient dependent, but

we believe this represents real-world clinical practice. Despite this, we were able to demonstrate similar diagnostic efficacy between the control and interventional arms over a six-month period, with diagnostic superiority for highly symptomatic paroxysmal SVT with the sECG. We recognise the importance of further large-scale studies to expand upon our findings.

4.8 CONCLUSION

This pilot single-centre RCT shows that the sECG, when employed over 6-months, has similar yield for the diagnosis of symptomatic cardiac arrhythmias as compared to 5-day Holter monitoring. The sECG may be superior for the diagnosis of highly symptomatic paroxysmal SVT. The Holter, owing to the continuous nature of the monitor was superior to the sECG in the diagnosis of asymptomatic arrhythmias. Patient usability and confidence was higher with the sECG. A larger randomised trial is needed to confirm our findings.

4.9 TABLES

Table 4.1. Baseline characteristics for Holter Monitor (intervention) and AliveCor (control)

Patient Characteristics	Holter Monitor, n=21 (%)	AC, n=20 (%)	P-value
Age, years, mean±SD (%)	47±18.5	45±18.6	0.73
Female gender	13 (62)	14 (70)	0.59
BMI, kg/m^2 mean±SD (%)	27.3±5.8	27.1±5.8	0.91
LVEF, mean±SD (%)	63±5	62±5	0.53
Anti-arrhythmic at baseline, n (%)	2 (10)	0 (0)	0.15
ECG rhythm at baseline, n (%)			
Sinus Rhythm	14 (67)	15 (75)	0.58
Sinus Tachycardia	5 (24)	5 (25)	0.94
Sinus Rhythm + PVC	1 (5)		0.32
Sinus Rhythm + PAC	1 (5)		0.32
Hypertension, n (%)	6 (29)	4 (20)	0.51

Hypercholesterolaemia, n (%)	7 (33)	6 (30)	0.84
Diabetes, n (%)	4 (19)	2 (10)	0.42
Ischaemic Heart Disease, n (%)	1 (5)	0(0)	0.32
Renal Failure, n (%)	0 (0)	0 (0)	-
Prior History of Thyroid Dysfunction, n (%)	2 (10)	3 (15)	0.63
Prior History of Mental Health Illness, n (%)	5 (24)	4 (20)	0.76
Smoker (current or previous), n (%)	4 (19)	5 (25)	0.65

Table 4.2. Primary outcomes

Primary Outcome	Holter Monitor (n=21)	AliveCor (n=20)	P-value
Primary outcome	14/21 (67)	15/20 (75)	0.58
Symptom-rhythm correlation (n/number of patients) (%)	11/21 (52)	14/20 (70)	0.24
Sinus tachycardia	7 (33)	6 (30)	0.84
Premature ventricular complex	2 (10)	4 (20)	0.37
Supraventricular tachycardia	0 (0)	3 (15)	0.07
Premature atrial complexes	2 (10)	1 (5)	0.55
Serious rhythm abnormality (asymptomatic) (n/number of patients) (%)	3/21 (14)	1/20 (5)	0.33
Atrial fibrillation	2 (10)	0 (0)	0.15
Supraventricular tachycardia	1 (5)	0 (0)	0.32
Sinus bradycardia (≤40bpm)	3 (14)	1 (5)	0.33

Table 4.3. Secondary outcomes

Secondary Outcomes	Holter Monitor (n=21) (%)	AliveCor (n=20) (%)	*P*-value
Proportion of patients with individual rhythm outcomes			
Sinus bradycardia (≤40bpm)	3 (14)	1 (5)	0.33
Sinus tachycardia (≥100bpm)	21 (100)	18 (90)	0.14
Supraventricular tachycardia	13 (62)	4 (20)	0.007
Atrial flutter	0 (0)	0 (0)	-
Atrial fibrillation	2 (10)	0 (0)	0.15
Premature atrial complex	21 (100)	7 (35)	<0.001
Premature ventricular complex	21 (100)	8 (40)	<0.001
VT/NSVT	3 (14)	0 (0)	0.09
Mobitz Type II AV block	0 (0)	0 (0)	-
Complete heart block	0 (0)	0 (0)	-
Proportion of sustained arrhythmia documentation (≥10 seconds)			

Atrial fibrillation	2 (10)	0 (0)	0.15
Supraventricular tachycardia	2 (10)	4 (20)	0.37
Ventricular tachycardia	0 (0)	0 (0)	-
Atrial flutter	0 (0)	0 (0)	-
Adverse events	1 (5) (Rash)	0	0.32
Completed Patient Satisfaction Surveys for Allocated Device	16 (81)	13 (65)	
How would you rate the usability of the single-lead or the Holter device? (Scale of 1–10, 1 being poor, 10 being excellent)	6 (38) patients rated 8+/10	10 (77) patients rated 8+/10	0.034
Did the sECG or the Holter make you feel empowered or give you a sense of confidence? (Scale of 1–10, 1 being poor, 10 being excellent)	19% of patients rated 8+/10	69% of patients rated 8+/10	0.006

4.10 FIGURES

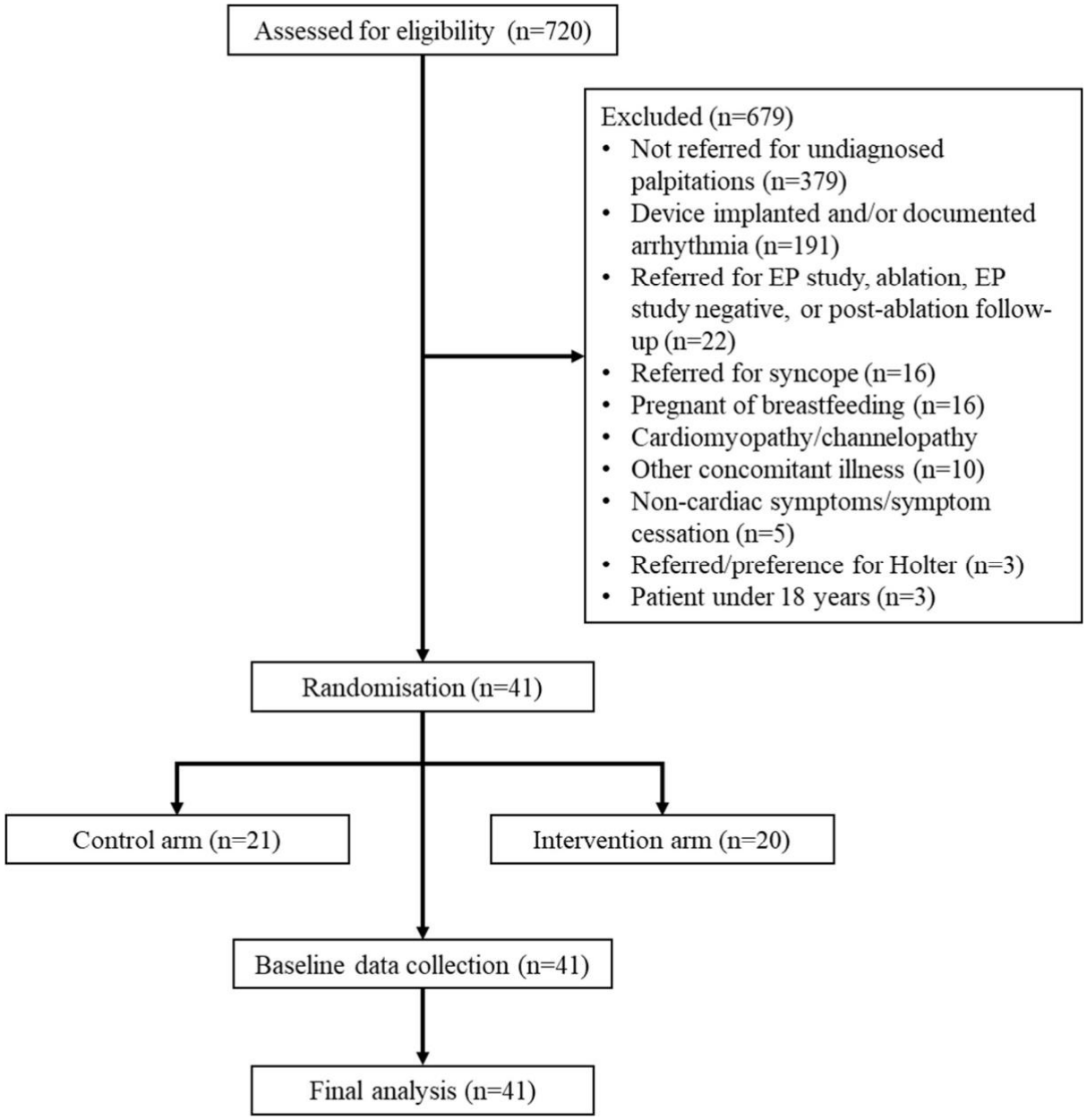

Figure 4.1. Study Recruitment

Of 720 patients assessed for eligibility, 41 were included and randomised.

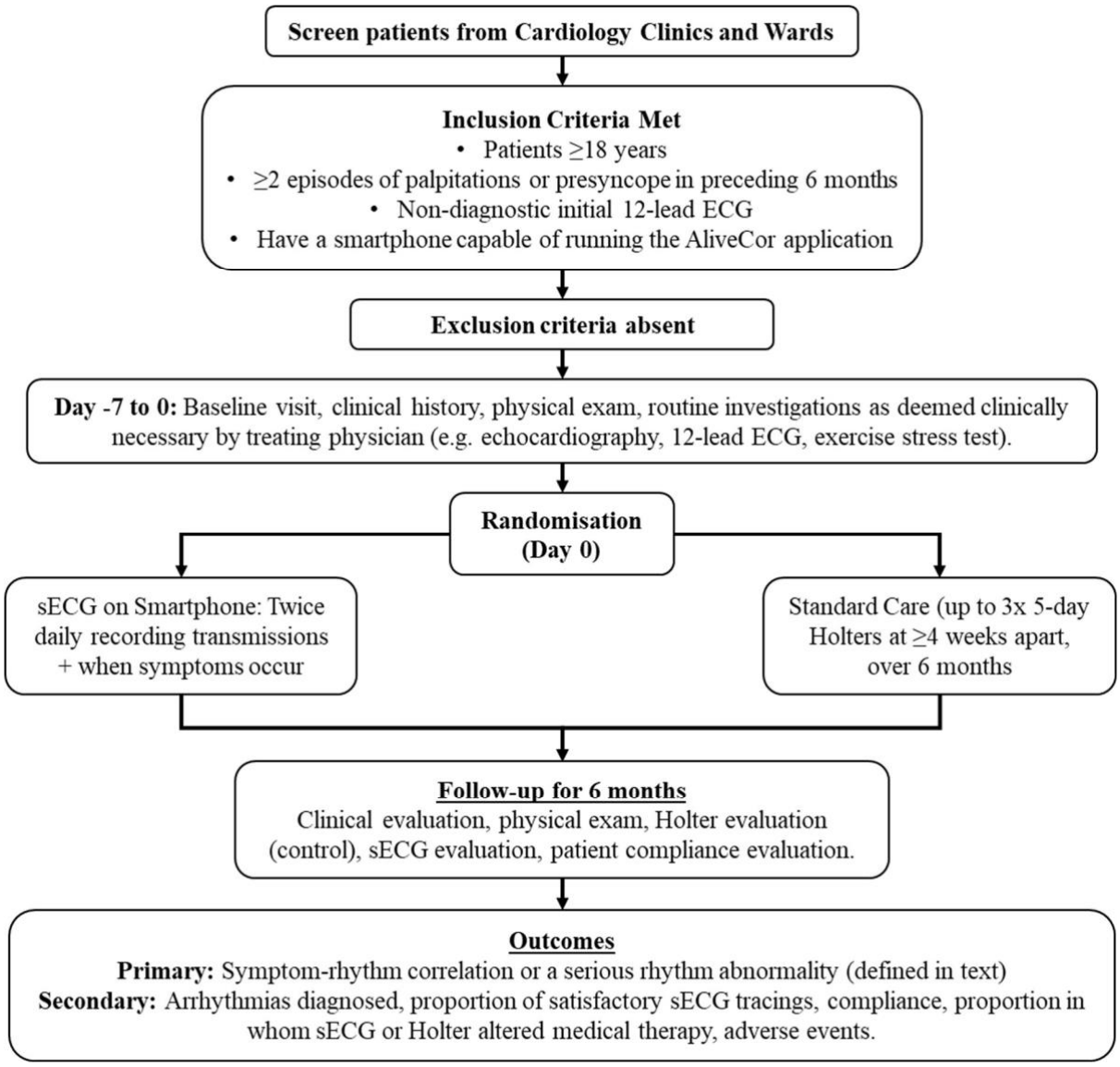

Figure 4.2. Trial Schema

The trial protocol compromising of inclusion criteria, study visits and requirements, follow-up and outcomes are summarised.

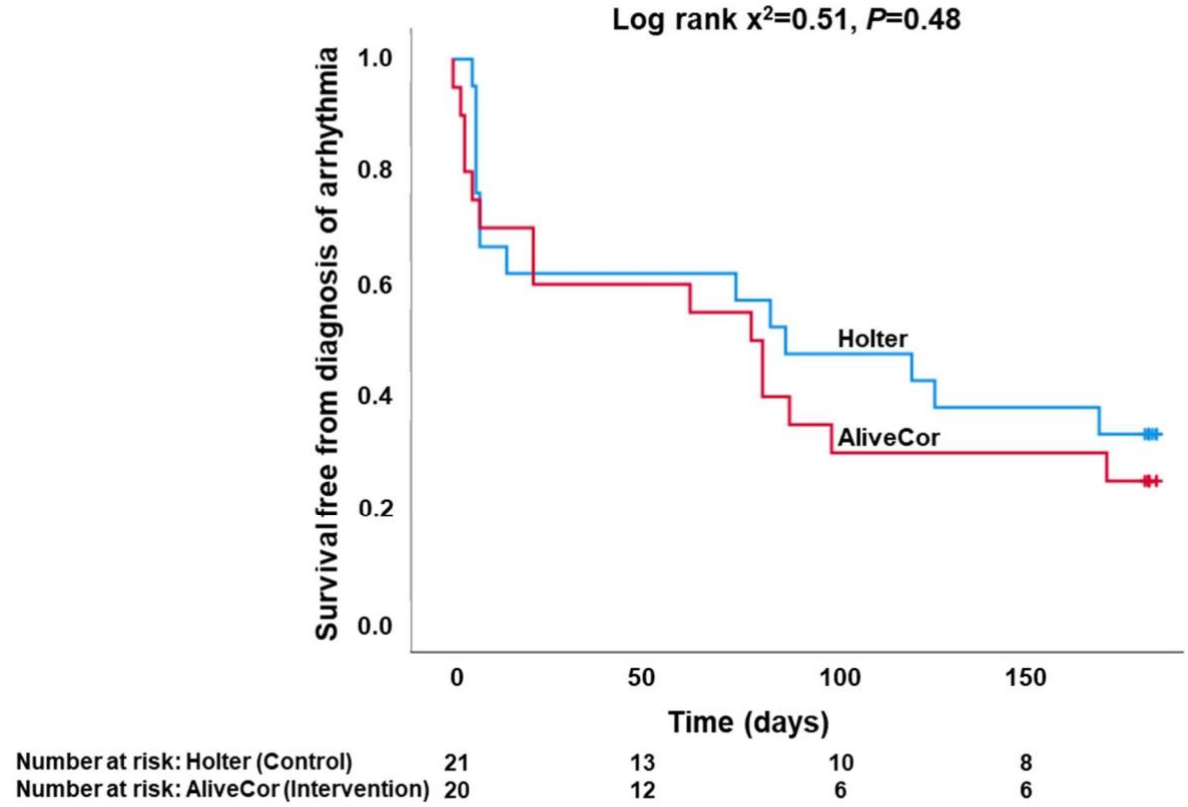

Figure 4.3. Freedom from Primary Outcome at 6-months (AliveCor vs. Holter)

There was no significant difference in the primary outcomes between the control (Holter) or intervention groups (AliveCor).

4.11 APPENDICES (SUPPLEMENTAL MATERIAL)

Appendix 4.1. Timetable of data collection

Study Periods	**Baseline**	**Randomisation**	**Follow-Up**		
Study Time	-7 to 0 days	Day 0	1-month	3-months	6-months
Study visit window from randomisation	±7-days	±2-days administration	±5-days	±5-days	±5-days
Evaluation					
Inclusion Criteria	X				
Exclusion Criteria	X				
Informed Consent	X				
Randomisation		X			
Clinical History	X		X		
Physical examination	X		X		
Smartphone compatibility check	X				
sECG/Holter Education	X		X	X	X
Baseline laboratory tests	X				
Echocardiogram		X	X	X	X
Follow-up of outcomes	X		X (Ongoing for sECG)	X (Ongoing for sECG)	X (Ongoing for sECG)
Adverse events			X	X	X

Appendix 4.2. Patient satisfaction survey

1. On a scale of 1–10, how would you rate the usability of the single-lead or the Holter device (1, being poor; 10, being excellent)?
2. On a scale of 1–10, did the single-lead ECG or the Holter make you feel empowered or give you sense of confidence (1, not at all; 10, greatly boosted your confidence)?

Appendix 4.3. Adverse events

Adverse events are expected to be rare, but will be adjudicated by the Events Committee within the following categories:

- Death (cardiac) (Arrhythmic, Non-arrhythmic, e.g., heart failure)
- Death (non-cardiac)
- Complications related to sECG or Holter (rash, failure to record or detect severe arrhythmia, as per previous definition).

Chapter 5. Conclusions and Future Directions

Wearable and handheld devices are a rapidly expanding technology that provide an exciting and unique opportunity in the diagnosis and management of cardiac arrhythmias. They may limit and possibly prevent the devastating complications of atrial and ventricular arrhythmias, by way of early diagnosis and treatment. They may also reduce health care expenditure by limiting emergency department and clinic visits. The main barrier to the adoption of these technologies to date has been a lack of large-scale validity in detecting a variety of arrhythmias in the outpatient and inpatient setting, as well as the legal and regulatory concerns that must be addressed before these devices can be widely adopted.

The aim of this thesis was to explore and address some of these limitations, namely that of a lack of exploration and data beyond arrhythmias such as sinus rhythm and atrial fibrillation, but into more complex bradyarrhythmias and tachyarrhythmias of both atrial and ventricular aetiology. The thesis chose to use one such popular commercially available handheld device, the AliveCor Kardia (AliveCor Inc, Mountain View, California, USA) for systematic evaluation. Our methodology sought to do this through comparison of the AliveCor against the gold standards of a cardiac electrophysiology study, ambulatory multi-day Holter monitoring and inpatient cardiac monitoring.

In Chapter 2, we compared the AliveCor against the gold standard of cardiac arrhythmia diagnosis, the electrophysiology study. We demonstrated a high level of accuracy in the detection of a broad spectrum of atrial and ventricular arrhythmias. This was validated with expert reviewers including cardiologists, electrophysiologists and cardiac physiologists lending further impetus behind the potential to extrapolate the use of handheld devices in a broader clinical setting and spectrum of arrhythmias. Although our study reviewed a total of 843 cardiac rhythm recordings, there is still the requirement of further large-scale validation before we can expect these devices to be utilised in a broader spectrum of arrhythmias. Furthermore, we tested the AliveCor single-lead ECG placed on the recumbent patient's chest,

which may not replicate clinical practice as often patients are ambulatory when using this system. Further study is needed to validate the AliveCor against other continuous monitoring techniques such as implantable loop recorders.

Chapter 3 evaluates AliveCor against the 12-lead ECG and telemetric monitoring in an inpatient clinical setting, with the primary focus being to examine if arrhythmia diagnosis can be made with similar accuracy with the sECG. The handheld sECG device demonstrated at least comparable, albeit slightly reduced (89% compared to 96%) accuracy to telemetric monitoring when compared against the gold standard of 12-lead ECG diagnosis in a total of 71 rhythms. This data suggested that the AliveCor may be useful as a substitute for inpatient cardiac telemetry in a subset of highly symptomatic patients in whom inpatient cardiac telemetric monitoring may not be available. However, this pilot study requires validation with a larger study across diverse patient age groups.

Chapter 4 was an important randomised trial which compared the AliveCor against multiple ambulatory multi-day Holter monitor in 41 patients with undiagnosed palpitations or syncope. It demonstrated that overall, AliveCor was equivalent in arrhythmia diagnosis to multi-day Holter monitoring for undiagnosed palpitations or syncope. However, symptomatic paroxysmal supraventricular tachycardia, had a higher detection rate (15%) with the AliveCor compared to multi-day Holter monitor (0%). There was a higher proportion of patients diagnosed with symptomatic or asymptomatic supraventricular tachycardia, atrial fibrillation, premature atrial and ventricular ectopy and non-sustained or sustained ventricular tachycardia in the multi-day Holter, compared to the AliveCor group, attributed to the higher rate of asymptomatic arrhythmias detected in the multi-day Holter monitoring group. The latter was attributed to the continuous nature of monitoring with the Holter. Scores for patient satisfaction and confidence/empowerment were higher with the AliveCor, compared to the Holter group. The trial showed that the AliveCor may be used as an alternative to Holter monitoring in ambulatory patients with undiagnosed palpitations or syncope. As the trial recruited a small population, further larger populations are needed to confirm these findings.

The thesis demonstrated that the commercially available handheld device recording a single-lead ECG was useful in a range of clinical settings for arrhythmia diagnosis, with reasonable accuracy. Importantly, this was the first such systematic evaluation in the literature for non-atrial fibrillation arrhythmias. A broad range of clinical questions remain unanswered and should be evaluated in future work. First, the utility of these devices should be evaluated in larger randomised trials compared to ambulatory monitoring, to validate our findings. The novel 6-lead ECG system also developed by AliveCor, should be validated in a similar fashion with cardiac electrophysiology study, telemetry and ambulatory Holter monitoring. The utility of this devices in the diagnosis of underlying rhythm abnormalities in cryptogenic stroke should be the subject of future investigation. The device could also be evaluated for screening for atrial fibrillation in the broader community at risk of developing the arrhythmias, particularly in the elderly. Similarly, high risk populations such as diabetics, those with renal disease, hypertension, prior myocardial infarction or non-ischemic cardiomyopathies could be screened for atrial and ventricular arrhythmias with this device. Ambulatory evaluation of athletes could be studied, particularly in the community setting. Objective assessment of the financial impact of such devices would provide valuable information about cost effectiveness compared to standard care and may be useful in planning the incorporation of such device use in the healthcare sector, in policy and practice. The impact of a large amount of data captured with the device on the health care provider needs further investigation. Deep learning algorithms could be adapted for automated detection and notification of detected rhythms, to assist with relieving the health care burden associated with interpretation of recordings transmitted. Finally, the role of these devices in detecting arrhythmias post-catheter ablation needs future investigation.

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