COMPREHENSIVE EVALUATION OF CLINICAL CARE IN PATIENTS WITH CARDIAC IMPLANTED ELECTRONIC DEVICES AND ARRHYTHMIAS: ACTION TOWARDS IMPROVED WORKFLOW AND OUTCOMES

A thesis submitted to The University of Adelaide in fulfillment of the requirements of the degree of Doctor of Philosophy (Ph.D)

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ABSTRACT

Heart rhythm disorders contribute a great burden to modern healthcare, but new opportunities for optimal usage of resources and improved standards of care are available due to progress in technology. In particular, the diagnosis, treatment and follow-up of heart rhythm disorders is evolving with emergence of game-changing technologies. To maximise impact of these technological advances, appropriate identification of opportunities and integration into care delivery is needed. This thesis aims to address the following three specific areas in the field of heart rhythm disorders. First, to explore challenges for follow-up care of patients with a Cardiac Implantable Electronic Device (CIED). Second, to determine optimal CIED selection for patients requiring continuous heart rhythm monitoring. Last, to define the utility of modern digital technology for heart rhythm assessment with a focus on atrial fibrillation (AF) screening.

Chapter 1 provides a review of the current literature surrounding these topics. Chapter 2 and 3 each present research studies investigating in-hospital services for CIED checks in the Emergency Department and in the pre- and post-scan setting of Magnetic Resonance Imaging. These studies provide granular, patient-level details of current healthcare service utilisation that can be used to identify opportunities for improved care delivery. Acknowledging the growing burden of healthcare utilisation for follow-up and analysis of CIEDs, Chapter 4 pivots towards understanding the role of optimal implant technology to maximize efficiency of resources. Research presented in this chapter assesses current generation implant devices to demonstrate differences in the electrograms that are obtained by insertable cardiac monitors (ICM) with different sensing vector length. Chapter 5 then explores the utility of a longer sensing vector, by proxy of surface electrocardiogram (ECG) tracings simulating ICM rhythm strips, for obtaining optimal electrogram

sensing. This has implications for ICM selection in varying patients to optimise efficiency of continuous cardiac monitoring.

The recent growth in personal ownership of digital devices, such as smartphones and watches, that are capable of heart rhythm monitoring has provided a feasible alternate option for arrhythmia detection. However, in comparison to implantable devices, these technologies broadly vary in their mechanism of rhythm detection, complexity and fidelity of data acquisition. The increasing accessibility of such wearable or portable digital technology presents a clinical conundrum for its appropriate utility in healthcare settings. Chapter 6 investigates the utility of portable digital technology, specifically that which can obtain single-lead ECG tracings and apply automated algorithms for arrhythmia detection, to screen for the most common heart rhythm disorder of atrial fibrillation (AF). Chapter 7 assesses the ability of such personal digital devices to identify AF even in low-resource communities.

This body of work identifies opportunities where integration of emerging technologies in the management of heart rhythm disorders can guide strategic investment of expenditure and resource allocation to provide more efficient healthcare service that may improve patient outcomes.

DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint award of this degree. The author acknowledges that copyright of published works contained within this thesis resides with the copyright holder(s) of those works. I give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

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BRADLEY MATTHEW PITMAN

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Top: Professor Dennis H. Lau celebrating my CSANZ 2020 award with me.
Bottom Left: Dr Sok-Hui Chew with me in Soddo, Ethiopia.
Bottom Right (left to right): Dr Christopher X. Wong, Dr Dominik Linz, myself and Professor Prashanthan Sanders at a CHRD function.

PUBLICATIONS AND COMMUNICATIONS TO LEARNED SOCIETIES

CHAPTER TWO

1. **Manuscript:**

   Pitman, B. M.; Schirripa, V.; Munawar, D. A.; Kadhim, K.; O'Shea, C. J.; Mishima, R. S.; Roberts-Thomson, K.; Young, G. D.; Wong, C. X.; Sanders, P.; Lau, D. H. (2022) *Should We Check It? Assessing Interrogation of Cardiac Implantable Electronic Devices in the Emergency Department–The CHECK-ED Study: Implications for Service Planning and Care Delivery.* **Heart Lung & Circulation.** Volume 31, Issue 8, Pages 1119-1125.
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2. **Presentation:**

   a. 41st Annual Heart Rhythm Society (HRS) scientific sessions, and published in abstract form **Heart Rhythm**, 17(5): S392, May 01, 2020. DOI: 10.1016/j.hrthm.2020.04.007
   b. Medical Staff Society research prize (MSSR), Royal Adelaide Hospital, Adelaide Australia, May 12th 2020, oral presentation.
   c. 40st Annual Heart Rhythm Society (HRS) scientific sessions, May 8-11, San Francisco, CA, USA and published in abstract form **Heart Rhythm**, 16(5): S143, May 01, 2019. DOI: 10.1016/j.hrthm.2019.04.015
   d. 12th Asia Pacific Heart Rhythm Society (APHRS) scientific sessions, 24-27 October, Bangkok, Thailand and published in abstract form **Journal of Arrhythmia**, 35: 598. DOI: 10.1002/joa3.12277

CHAPTER THREE

1. **Manuscript:**

   Pitman, B. M.; Ariyaratnam, J.; Williams, K.; Evans, M.; Reid-Smith, N.; Wilson, L.; Teo, K.; Young, G. D.; Roberts-Thomson, K. C.; Wong, C. X.; Sanders, P.; Lau, D. H. (2022) *The Burden of Cardiac Implantable Electronic Device Checks in the Peri-MRI Setting: The CHECK-MRI Study.* **Heart, Lung & Circulation.** Article In Press (accepted 7 Oct 2022).
   DOI: 10.1016/j.hlc.2022.10.005

2. **Presentation:**
    a. Central Adelaide Local Health Network (CALHN) Cardiology Safety and Quality meeting, Royal Adelaide Hospital, Adelaide Australia, Oct 27th 2020, oral presentation.
    b. 2021 – 69th Cardiac Society of Australia and New Zealand (CSANZ) Annual Scientific Meeting, and published in abstract form **Heart, Lung & Circulation** Volume 30, S150-S151. DOI: 10.1016/j.hlc.2021.06.130
    c. 2021 – 15th Annual Florey Postgraduate Research Conference, University of Adelaide, poster presentation.
    d. 2021 – 42nd Annual Heart Rhythm Society (HRS) scientific sessions, and published in abstract form **Heart Rhythm**, Volume 18, Issue 8, Supplement S467-476, S1-S540. DOI: 10.1016/j.hrthm.2021.06.258
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2. **Presentation:**
    a. 2021 – 43rd Annual Heart Rhythm Society (HRS) scientific sessions, poster session, and published in abstract form **Heart Rhythm**, Volume 19, Issue 5, Supplement S221. DOI: 10.1016/j.hrthm.2022.03.175
    b. 2021 – 42nd Annual Heart Rhythm Society (HRS) scientific sessions, and published in abstract form **Heart Rhythm**, Volume 18, Issue 8, Supplement S467-476, S1-S540. DOI: 10.1016/j.hrthm.2021.06.477

c. 2020 – European Society of Cardiology (ESC) Congress, 29 Aug – 1 Sept, 2020, and published in abstract form **European Heart Journal** Volume 41, Supplement 2, pg708. DOI: 10.1093/ehjci/ehaa946.0708
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CHAPTER FIVE

1. **Manuscript:**

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2. **Presentation:**

   a. 2022 – American Heart Association Scientific Sessions 2022, abstract 9552, presented as eposter “MO4137: Optimal Sensing Vector for Maximal Pwave Amplitude, Implications for Insertable Cardiac Monitor (ICM) Implantation”, and published in abstract form 30 Oct 2022. **Circulation**, Volume 146, Issue supplement 1.A9552. DOI: 10.1161/circ.146.suppl_1.9552
   b. 2022 – American Heart Association Scientific Sessions 2022, abstract 9763, presented as eposter “SU4090: Impact Of Device, Implant And Patient Factors On P-wave Amplitude From Insertable Cardiac Monitors: Insights From A Surface EKG Simulation Study”
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CHAPTER SIX

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   a. 2021 – 42nd Annual Heart Rhythm Society (HRS) scientific sessions, Featured poster session, and published in abstract form **Heart Rhythm**, Volume 18, Issue 8, Supplement S467-476, S1-S540. DOI: 10.1016/j.hrthm.2021.06.147
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CHAPTER SEVEN

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PRIZES AND AWARDS DURING CANDIDATURE

2022 – Finalist: New Investigator Poster Prize at 70th annual scientific meeting of the Cardiac Society of Australia and New Zealand (CSANZ)

2022 – Adelaide Medical School/Biomedicine Research Travel Award.

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2020 – Winner: Allied Health, Science and Technology Prize at 68th annual scientific meeting of the Cardiac Society of Australia and New Zealand (CSANZ).

2020 – Finalist: Medical Staff Society Research (MSSR) Prize Presentation at Royal Adelaide Hospital.

2020 – Heart Rhythm Society Scientific Sessions Travel Scholarship.

2019 – The Hospital Research Foundation Higher Degree Research Scholarship.

CHAPTER ONE – LITERATURE REVIEW

1 LITERATURE REVIEW

1.1 INTRODUCTION

Heart rhythm disorders contribute a great burden to modern healthcare. Furthermore, provision of optimal healthcare service is challenging as there is great heterogeneity among patients with heart rhythm disorders and progress in healthcare technologies continue to transform the expected standard of care. Recent developments in technology have expanded the care options for patients who are being treated for heart rhythm disorders, or require diagnostics to identify possible arrhythmias. The main focus of this thesis is to identify opportunities for optimal integration of such new technology into the standard of care delivery. In particular, this thesis will aim to address the following three specific areas in the field of heart rhythm disorders. Firstly, to explore challenges for follow-up care of patients with a Cardiac Implantable Electronic Device (CIED). Secondly, to determine optimal CIED selection for patients requiring continuous heart rhythm monitoring. Thirdly, define the utility of modern digital technology for heart rhythm assessment with a focus on atrial fibrillation (AF) screening. The following literature review will highlight the importance of optimising service delivery for each of these three areas.

1.1.1 Healthcare utilisation and economic burden of heart rhythm disorders

The UK Biobank data indicate incident cardiac rhythm abnormalities occur at a rate of 0.5% per year which is similar to rates of stroke, myocardial infarction, and heart failure.(1) In particular, the frequency of heart rhythm abnormalities in middle-aged to older community-dwelling adults

is substantial, affecting >2% of individuals.(1) Bradyarrhythmias, AF and conduction system diseases account for most rhythm conditions with risk increasing in the setting of older age, traditional cardiac risk factors and heart failure.(1, 2) In the local setting of an aging population with increasing risk factor burden it is anticipated that the number of patients suffering heart rhythm disorders will increase, and that disease progression will further increase healthcare utilisation. The onset of new or recurrent paroxysmal arrhythmia often leads to hospital presentations, with hospitalisations being the main driver of healthcare resource utilisation. In some cases implantation of a CIED is indicated which requires ongoing follow-up services well beyond the index presentation. In Australia, public hospital expenditure is one of the largest and fastest growing areas of government expenditure(3), so it is imperative that maximal return on expenditure be achieved by healthcare resource allocation.

Healthcare is a finite commodity due to limited resources and associated cost considerations for provision of care. Globally, the demand for services relating to care of heart rhythm disorders is increasing with greater usage of CIEDs and more electrophysiological procedures,(4) but with a greater emphasis on value-based arrhythmia care.(5) In Australia, our aging population has seen significant annual increases in the number of pacemaker (PPM) (6) and implantable cardioverter defibrillator (ICD) (7) implants performed over recent 10-year analysis periods. Similarly, AF hospitalisations have also increased by 200% over a 15-year period equating to a 6% annual increase.(8) It is now been reported that hospitalisations in Australia for AF have surpassed both myocardial infarction and heart failure with associated growing cost burden.(9) An estimated $881 million was spent on the diagnosis and treatment of AF in 2015–16 according to the Australian Institute of Health and Welfare, equivalent to 8.4% of recurrent expenditure on

cardiovascular disease and 0.8% of recurrent expenditure on all health conditions.(10) Poor prognosis also adds to the healthcare burden as it has been reported that within 1-year of presentation to an emergency department with AF from a cohort of over eight global geographical regions, more than 10% of patients died, 4% had a stroke, and 12% were admitted to hospital for heart failure.(11) In particular, hospital readmissions for AF patients are a major source of preventable healthcare expenditure(12), but digital technology that can identify arrhythmia may be able to assist patient and clinician management of recurrent bouts of arrhythmia to minimise hospitalisation.(13)

1.1.2 Healthcare utilisation and economic burden of CIEDs

Regarding the service burden imposed by CIED care, the trend is increasing with recent 2017 Australian survey reporting an increase in the number of PPM, ICD and biventricular device implants.(14) The annual cost of just pacemaker procedures between 2008 to 2017 in Australia has increased from $178 to $329 million.(6) All implants carry additional impact on the healthcare service beyond the index implantation procedure, with ongoing servicing, monitoring and hardware revision required throughout their lifetime. This issue of ongoing service burden has been identified by the Medical Technology Association of Australia (MTAA) in their 2021 evaluation report of options for reforms and improvements to the Prostheses List, which includes CIEDs.(15) This report by MTAA details cardiac technical services in the Australian private sector and was produced in partnership with local CIED manufacturers, independent accounting firm KPMG, and an Industry Working Group which included clinicians, private health fund representatives, private hospitals and government officials. This group estimated 423,000 occasions of service for both scheduled and unscheduled technical services are provided per year

by industry employed allied professionals for CIEDs in the private sector after implant, which among many others includes; in-clinic follow ups, inpatient device checks, remote transmission reviews, ad-hoc emergency department checks and peri-MRI scan/radiotherapy device checks.(16) Through KPMG modelling it was estimated that the cost for providing these technical services in the 2019-20 financial year (FY) was in the range of $66 to $96 million, with a median cost of $79 million.(15) This was forecast to increase annually, with a projected estimate for FY22-23 in the range of $86 to $125 million, with median cost of $103 million.

These services are essential requirements of CIED follow-up and patients expect this as standard of care, for streamlined and safe access to surgical interventions, diagnostic imaging as well as palliative care that require CIED reprogramming. Ongoing CIED service provision has additional benefits including optimisation of device settings performed at follow-up occasions of service to ensure appropriate CIED therapy provision, reduce battery drain and diagnosis of new arrhythmias. These may in part be responsible for a slight decline in the number of PPM battery replacements locally.(14) The MTAA and KPMG estimates provided for follow up CIED services are exclusive of the public sector provision, but indeed highlight the enormous and growing burden of providing care for patients with heart rhythm disorders.

Heart rhythm disorders are best managed by a collaborative approach between patients, physicians, nurses and allied health professionals, with incorporation of state-of-the-art medical technology. In recent times, the major driver for real growth of local public hospital expenditure has been the average salaries of hospital staff accounting for 37% of growth, compared to only 14% from changing hospital utilisation rates.(3) Indeed, clinical expertise is invaluable to patient

outcomes as highlighted by the MTAA report for estimated CIED services by industry employed allied professionals,(15) but the cost burden ensures that personnel resources are finite. Optimal allocation of clinician resource can be achieved through utilisation of technology that improves both patient outcomes and clinical workflow.(13) Examples of such technology that will be discussed in the following sections include new implantable device hardware, advanced programmable device software, or new digital technologies for hand-held devices commonly owned by patients and clinician.

1.1.3 Opportunities for technology application in CIED and arrhythmia care

The growing service burden of heart rhythm disorders has identified a need for improvements in care provision. It is evident that CIED follow-up is an area of significant projected expense and resource demand. The MTAA evaluation of the current Prothesis List for government reimbursement of medical devices identified that CIEDs, unlike many medical prothesis such as a joint replacements or ocular lenses, have a very high lifetime service requirement due to ongoing follow up.(15) One of the major challenges is that about 5% of these service occasions are unscheduled.(16) Along with *Ad Hoc* inpatient CIED checks on hospital wards, the greatest sources of unscheduled services include ED presentations for approximately 19% of unscheduled CIED services and MRI scans for approximately 17%, which are more problematic for service planning and scheduling.(15) The MTAA document reported that CIEDs on average require two scheduled services per year (i.e.; doctor consultation rooms or hospital device follow-up clinic), and that for every scheduled service, a CIED will require on average 0.087 unscheduled services and 0.77 remote monitoring services.(15) The unscheduled services are particularly a challenge for efficiency of service delivery.

The introduction of remote monitoring for CIEDs has allowed device interrogations to occur without needing in-office or hospital presentation. The Heart Rhythm Society expert consensus statement provides a class 1A recommendation for combining remote CIED monitoring and interrogation into standard follow-up management strategy.(17) Occasions of remote monitoring service do not impose the same logistical challenge of in-person CIED interrogation, so the impact of providing the service can be considered separately, however such a service has additional issues which need consideration. It has been well established that there is a significant workload burden attributable to analysis of transmissions from remote monitoring, with an over representation of transmissions coming from implantable loop recorders (ILR) compared to other CIEDs.(18) In particular, ILR alert transmissions require greater manual processing workload as false-positives occur for up to 60% of alert transmissions.(19) It was reported that all false-positive asystole and bradycardia alerts were due to undersensing, highlighting the importance of adequate electrogram (EGM) amplitude for rhythm strips obtained by these devices. Miniaturisation of ILR has been achieved for newer generation insertable cardiac monitors (ICM) but differences in the EGM amplitude obtained from different models has been reported for both R-wave (20), and P-wave (21) that may have impact on corresponding transmission workload burden.

Another opportunity for technology integration into arrhythmia care may be the utilisation of digital handheld and wearable technology, which has evolved markedly with many patients and clinicians now having access to personal devices capable of arrhythmia screening.(22) This increasingly affordable and accessible technology has created a conundrum for healthcare

professionals regarding their appropriate integration into diagnostic pathways.(23) Although many of these technologies are being targeted to AF detection, it is not known what utility they may have for AF screening and what inherent limitations there are with such technology. Integration into standard clinical practice is dependent on both physician and patient acceptance(24), which is best achieved by an evidence-based approach and avoiding implementation design error.(25) Type 1 Design Error (User-Reality Error) occurs when designers do not accommodate user characteristics, tasks, context of use, needs, or preferences. Type 2 Design Error (Clinical-Reality Error) occurs when designers do not accommodate the clinical reality, including biomedical knowledge, clinical workflows, and organizational requirements. Therefore, it is vital that the present state of health services is recognised, and that appropriate opportunities for technology intervention is identified before attempting deployment of new technology into clinical workflow.

1.2 THE CURRENT LANDSCAPE OF CLINICAL FOLLOW-UP SERVICES FOR CIED

There is a current need for improved in-hospital CIED follow-up services as this is an area of growing concern regarding healthcare resource utilisation. The increasing number of patients with a CIED coupled with increased patient life expectancy is drastically increasing demand for healthcare services such as for radiology imaging and emergency department assessments. Such presentations invariably require device interrogations and this can be problematic as has been noted in the literature.

1.2.1 Challenges of CIED checks in the Emergency Department

Requests from the ED for interrogation of CIEDs are a major source of unplanned clinical workload due to the nature of patient presentations. Suggested approaches for initial ED management of these patients has been described (26-28), with consensus that CIED interrogation should be performed when clinically appropriate and particularly when malfunction is suspected. However there are a range of CIED types, with different functions to treat various arrhythmias, that are produced by a number of different manufacturers with brand-specific features and functionality.(29) As such, it can be difficult for clinicians and ED staff to readily interpret normal CIED function without device interrogation.(30) Due to this complexity, the task of CIED interrogation is routinely performed by trained and experienced allied health professionals, industry representatives, or specialist clinicians by bedside interrogation of the CIED using specific programmers that allow data extraction and CIED reprogramming. The scope of services that can be provided by these professional groups are detailed in the Heart Rhythm Society 2022 Policy Statement Update: Recommendations on the role of industry-employed allied professionals.(31) The service of in-person CIED interrogation specifically allows for immediate rectification of certain malfunctions(32), identification of device logged clinically relevant arrhythmias(33), and assessment of diagnostics obtained by CIED sensors(34) that can assist management of patients in the ED. Furthermore, CIED interrogation in the ED can also help to avoid administering unnecessary treatment by providing timely clinical information to corroborate other routine diagnostic testing.(35) The unscheduled nature of such checks remains a challenge, with Mittal, *et al.* (2016) reporting in their analysis that 57% of CIED checks in the ED occurred outside of traditional business hours, with 76% of the checks to evaluate an ICD shock occurring outside of traditional business hours.(36) Consequently, as the resource of specialists to perform these CIED interrogations is limited, and the unscheduled nature of these interrogation requests can be

challenging to accommodate in a timely manner, it is important to ensure there is clinical value from the majority of these occasions.

1.2.2 Variance in yield of CIED checks in the Emergency Department

There are reports in the literature of cohorts who specifically received CIED interrogation in the ED, but these have varying definitions of the resulting clinical yield. One small prospective convenience-sample study of 44 patients who had a Medtronic CIED interrogation in ED found that ED physicians reported 60% of checks assisted patient care by providing confirmatory or new diagnostic CIED information.(37) The same group later reported in a separate study of 60 patients who had Boston Scientific devices, that only 18% of CIED checks in the ED required device reprogramming during the index encounter.(38) They later reported in a retrospective analysis of 182 CIED interrogations in the ED for Boston Scientific devices that a total of 52 (29%) interrogations had cardiac episodes (including dysrhythmia, shock events, overdrive pacing), but that only 27 CIED checks required further review or programming optimization with 7 (4%) required immediate reprogramming.(39) As this was from a rural, community ED where electrophysiology consultation was not available on nights or weekends, any checks requiring further review present a particular challenge. In another study that also assessed Boston Scientific CIEDs, but which analysed 509 checks including 294 (58%) ED checks, it was reported that only 34% had no arrhythmia or CIED system concerns which implies a high yield of checks with issues.(36) In comparison, a large study of Medtronic CIED checks in a multi-center design which included 6,135 (87% of total) checks from the ED, found that actionable events that were defined as arrhythmia or device/lead abnormalities were noted to occur infrequently with an overall total yield of 9.1%.(40) Importantly, only 64% of the ED checks in the study were

performed due to clinical or suspected CIED malfunction indications highlighting the importance of appropriate triage. Indeed, actionable events were more common for those check performed for suspected device problems (30.4%) or audible alerts (52.6%).(40) A recent study assessing 129 consecutive checks of only Medtronic defibrillators reported that 31% required modifications were defined by CIED reprogramming for 27 and medication changes for 13, suggesting defibrillator devices may have more benefit from in-person interrogation.(41) The yield from CIED checks in the ED for different device types, different presenting symptoms and for after-hours occasions of service is not known. The unknown yield and challenge of limited resourcing for CIED checks in the ED has led to exploration of alternative methods for CIED check in the ED.

1.2.3 Strategies of CIED check in the Emergency Department

Alternate methods of service delivery have been reported in the literature, including read-only device interrogation by ED personnel (37, 42) and use of CIED reader technology for remote assessment.(36, 39, 40) Both strategies can be beneficial with reduced response time when compared to that needed for attendance of device specialist, as well as providing the ability to quickly triage patients who require more urgent intervention. However, such strategies cannot replace a traditional CIED interrogation service as reader technology is limited to select CIED manufacturers, interpretation of the checks is not always real-time and CIED reprogramming is not possible. It has been reported that mobile phone-facilitated video conferencing from a CIED specialist can be used by ED personnel to guide device reprogramming(43), however there is risk of misinterpretation of data when interrogation is performed by less-experienced operators, particularly for more complex devices. Nevertheless, effective strategies are required to handle these ad-hoc CIED checks in the ED that can impose a significant burden on the healthcare service,

especially after-hours when on-site technical support capable of performing the interrogation and interpretation is of limited availability.

1.2.4 Peri-MRI scans CIED checks

There is a growing number of patients with a CIED in-situ and it is estimated that 75% of pacemaker patients shall need an MRI over their lifetime(44). Most current generation CIEDs are suitable for MRI scan provided that certain conditionality criteria is met.(45) Although there are some barriers, most CIED patients are eligible to have an MRI scan for a variety of indications. However, CIED interrogation and reprogramming is required for each of these MRI scans which presents scheduling and logistical challenges for cardiology services and radiology departments.

1.2.5 Barriers and challenges for MRI scan of CIED patients

The key barriers limiting CIED patient access to MRI scan include; suitability of implanted system, radiology department protocols and resource availability. There are historical safety concerns regarding electromagnetic interference and adverse interactions by the potentially hazardous MRI environment.(44, 46) Manufacturers have been able to develop specific hardware that accommodates the MRI environment(47), which has shown to be safe when performed under controlled conditions.(48) Multiple manufacturers were able to produce MRI-conditional leads and pulse generators each with unique specification.(49) These CIEDs are classified as MRI-conditional with the requirement for dedicated MRI mode reprogramming and specific MR scanner conditions including limits on static field strength, gradient slew rate, RF fields, and anatomical limits.(46, 49) In general, most CIED systems have been approved for scanning with

1.5T, gradient slew rate ≤200 T/m/s, a maximal SAR ≤2 W/kg, and a limited number and length of imaging sequences, with allowance for full-body scanning including thorax and cardiac structure.(45, 50) However, an MRI-conditional system cannot comprise mismatched battery and lead/s, either from different manufacturers or non-conditional components or have any abandoned leads in-situ, so the CIED hardware must be assessed for suitability prior to any MRI scan in additional the required interrogation for performance evaluation and mode reprogramming.(45)

The barrier of suitable hardware is diminishing with some mis-matched systems shown to be safe for MRI scan(51) and some manufacturers being able to achieve retrospective approval for MRI-conditional status of older generation leads through demonstration of safety.(52) Furthermore, safety concerns for MRI scans in patients with older generation or legacy CIEDs have also been lowered with a recent meta-analysis reporting no significant adverse events in over 7,000 MRI scans for patients with non MRI-conditional CIEDs.(53) As a result of large studies investigating MRI scans in patients with non MRI-conditional CIED systems(54, 55), there was Class IIa recommendation from the 2017 Heart Rhythm Society (HRS) expert consensus statement for these MRI scans provided institutional protocols are in place.(45) Patient information documents have also been published and are available in an effort to assist acceptance of MRI scans and address common CIED patient concerns.(56) As a result of the large body of evidence supporting that non-MRI conditional and 'mis-matched' CIEDs are indeed safe for MRI scan, there has been a Joint British Society consensus recommendation published in 2022 for MRI of CIEDs(57), which has defined a "Lower" risk category classification for MRI scan of "mismatched CIEDs" and "MR unlabelled pin plug with MR conditional" system. These were both given level of evidence 'class

C', defined as "consensus of expert opinion based on clinical experience or case series". Subsequently, guidelines have been updated and now permit MRI scan of non-MRI-conditional systems, as published in September 2022 by the European Heart Rhythm Association (EHRA) in collaboration with the HRS, Latin America Heart Rhythm Society (LAHRS) and Asian Pacific Heart Rhythm Society (APHRS) in their consensus on prevention and management of interference due to medical procedures in patients with CIED(58). The consensus states that "In patients with non-MRI-conditional CIED systems, MRI may be performed in special settings (ICD generator, PM-dependent patients, recently implanted CIED, epicardial leads)." Additionally, "CIED-trained personnel need to be available onsite with the appropriate device programmer during the MRI scan in higher-risk situations (PM-dependent and ICD patients, devices including surgical epicardial leads, abandoned leads, lead extenders/adaptors) in non-MRI-conditional systems". Furthermore, "Remote monitoring is encouraged after MRI scans, especially for non-MRI-conditional CIED systems and in patients at risk (ICD generator, PM-dependent patients, epicardial LV leads)". These guideline updates have immediately increased the number of patients with a CIED insitu suitable for MRI scan, which will create a larger demand for MRI related services.

1.2.6 Demand for MRI scan of CIED patients

Recent studies have shown that in patients with MRI-conditional CIEDs, MRI scans occurred at up to 7 per 100 patient-years.(59, 60) Locally, the Australian Department of Health data of Medicare statistics show annual increases in the number of MRIs conducted, with more than 1.45 million performed nationally in the 2020-21 financial year (FY).(61) This increase will continue with the Australian government committing to invest $66 million over four years, from 2022–23 to 2025–

26 with an aim to deregulate and expand access to Medicare funded MRI services.(62) As more patients with CIED systems that are suitable for MRI scan, it is expected that the demand for services to facilitate MRI scans for CIED patients will increase. Although cardiology services are invariably required to facilitate CIED assessment, MRI mode reprogramming and follow-up, there is little data on the impact of workload and workflow in fulfilment of CIED requirements for MRI scans.

1.2.7 Workflow implications for MRI scan of CIED patients

To allow MRI-conditional CIEDs to be safely scanned, manufacturers of CIEDs provide specific instructions as part of their conditions of use. These instructions include a full evaluation of the CIED and leads, with activation of MRI program settings including disabling advanced pacing algorithms, as well as tachyarrhythmia detection and therapies in ICD systems.(50) The choice of pacing rate and mode (asynchronous or inhibited) will depend on the patient's characteristics, such as pacing dependence, which need to be evaluated for each patient.(63) Furthermore, considerations of haemodynamic implications from device reprogramming are required for patients with a cardiac resynchronisation therapy (CRT) device, so expertise and vigilance is required when scanning patients with MRI-conditional approved CIED.(64) Guidelines therefore recommend development of a standardised institutional workflow in collaboration with institutional experts in MR imaging and a cardiologist with expertise in CIEDs.(45) A number of publications have presented suggested protocols.(64, 65) In a recent study, a team-based approach operating at a single location was able to markedly improve volume and decrease waiting times for MRI examinations on CIED patients.(66) Additionally, guidelines recommend that reporting of CIED evaluation performed both prior to and after MRI scan be documented and

preferably embedded in an electronically traceable workflow(45). Fulfilment of these requirements are resource intensive, however there is scarce literature available on their workflow impact.

1.2.8 Workflow optimisation for MRI scan of CIED patients

CIED manufacturers are working to remove barriers to workflow efficiency for MRI scans. One manufacturer has introduced a novel MRI conditional pacing system with the capability to switch automatically to asynchronous mode in the presence of a strong magnetic field.(67) Another manufacturer has integrated a similar automated feature for their CIEDs in the form of a dedicated MRI sensor, that can be enabled up to two weeks prior to MRI scan to facilitate flexible scheduling, which will switch the CIED to an MRI programming mode when in the MRI environment field.(68) Both design features allow the CIED to detects the absence of the MR environment and revert to pre-scan settings shortly after exiting the magnetic field. Another vendor has introduced a portable handheld CIED remote control device, which can be used by radiology department personnel to activate and deactivate MRI mode of certain CIEDs in the MRI suite.(46) This technology requires enabling of pre-programmed MRI settings during a prior CIED interrogation. Each of these features avoids the need for post-scan CIED interrogation, allowing follow-up evaluation to be via home or remote monitoring report transmission for optimised workflow. Recently, another manufacturer reported the use of a novel remote access software embedded in CIED programmer for a remotely logged-in operator to perform the CIED evaluation and MRI mode reprogramming.(69) They reported this could be performed safely, securely and with time saving estimated by CIED specialist field representative's travel time, although the possibility of cybersecurity breach using any remote programming platforms remains a primary

concern.(70) As any given radiology department is likely to have multiple brands of CIED referred for MRI scan, systems to implement each of these brand specific technologies is required. However, as there is a scarcity of granular data on the demand of peri-MRI CIED checks, it is difficult to project how these technologies can benefit clinical workflow and provide potential cost savings.

1.3 THE BURDEN OF CIED REMOTE AND HOME MONITORING TRANSMISSIONS

In recent times, the utilisation of remote and home monitoring platforms has transformed the clinical follow-up of patients with CIED.(71) The ability for CIEDs to transmit data to follow-up clinics without the need for programmer interrogation has provided alternative workflow design options for unscheduled CIED services, as has been described. A meta-analysis published in 2015 of randomised control trials (RCT) demonstrated that remote monitoring and in-office follow-up showed comparable overall outcomes related to patient safety and survival, with a potential survival benefit in RCTs using daily transmission verification.(72) Moreover, a multicentre randomised trial of heart-failure patients with ICD, found that use of remote monitoring significantly reduced emergency department visits and urgent in-office visits for heart failure, arrhythmia or ICD-related events.(73) Importantly, it has been reported that in the vast majority of pacemaker follow-ups the device programming is unchanged suggesting that read-only remote follow-up is suitable.(74) Due to the clinical evidence for remote monitoring of CIEDs, the HRS guidelines gave a Class 1A recommendation for a strategy of remote CIED monitoring and interrogation to be combined with at least annual in-clinic interrogation rather than a calendar-based schedule of in-person CIED evaluation alone.(17) Application of a remote monitoring protocol without in-office interrogations in a large multicentre prospective study has been shown

safe and efficient in reducing hospital visits and staff workload.(75) Although there are conflicting reports regarding the cost-utility of adopting remote monitoring into clinical practice(76-78), the COVID-19 pandemic has seen significant increase in its use specifically for patients with PPM and ILR.(79) The Cardiac Society of Australia and New Zealand (CSANZ) issued a 2022 Position Statement(80) on the Follow-Up of CIEDs, declaring that Remote monitoring of CIEDs is the standard of care and should be offered to all patients when possible, and that a hybrid of in-person checks and remote monitoring of CIEDs individualised according to patient and device circumstances is recommended.

The implications for such recommendations are not without significant consequences on workload. Indeed, the CSANZ 2022 Position Statement(80) on the Follow-Up of CIEDs, identified that there is an increasing burden on the workforce contributed by MRI, perioperative management and hazard alerts from CIEDs, and this needs to be factored into the resourcing of a CIED service. As an example, the burden of alerts transmitted by ILR is known to be disproportionately far greater than for ICDs or PPM.(18) This emphasizes that resources need to be allocated with consideration of what is needed to manage the service safely and effectively. Among the many ILR transmissions that are known to generate a large portion of false-positive episode alerts(19) which require clinicians to perform manual adjudication of obtained rhythm strips that requires additional time consideration. Regarding this issue for ILRs, optimal device technology is desperately required, and will be discussed in the following sections, with potential to reduce the false alert burden that is occupying valuable healthcare resources.

1.3.1 The evolution of Implantable Loop Recorder technology

Continuous rhythm monitoring by subcutaneous ILR is a useful tool for evaluating the causes of symptoms that may be related to cardiac arrhythmias, including palpitations light-headedness, syncope/pre-syncope and neurological diagnoses such as transient ischemic attack or cryptogenic stroke.(81-83) The first implantable event loop recorder introduced in 1990 were built on a pacemaker platform with poles for electrocardiographic (ECG) signal detection placed on the generator case.(83) This was later replaced by the leadless device which proved a useful strategy of prolonged monitoring for patients with problematic syncope(84) and the inclusion of detection algorithms allowed more widespread ILR use.(85) Technological advancements and device miniaturisation saw the introduction of the insertable cardiac monitor (ICM) with an injectable delivery system for simplified implantation and increased patient acceptance.(83, 86, 87)

Early experience from ICM usage in a controlled clinical trial and a real-world registry demonstrated that miniaturised ICM can be easily inserted with very low incidence of adverse events.(88) The addition of automated device-based algorithms designed to detect AF has now expanded the use of ICMs for AF monitoring.(89, 90) In a large randomised control trial, ECG monitoring with an ICM was shown superior to conventional follow-up with Holter for detecting AF after cryptogenic stroke.(91) Although ICM is widely accepted as a reliable continuous monitoring method for AF detection, they remain inferior to PPM for AF detection(92), with various known limitations.(93) Consequently, the many false-positive episodes captured by these devices which require manual rhythm adjudication contribute to a large and growing workload burden.

1.3.2 Electrogram signals on insertable cardiac monitor tracings

Review of the literature has identified a number of studies conducted to identify factors impacting the effectiveness of ICM for heart rhythm monitoring. Pre-implant mapping of the left anterior chest region has been used to assess impact on R-wave amplitude of ILR tracings.(94-96) Although preimplant mapping was determined to be non-essential prior to implant(94), it has also been reported that if ILR implant location is chosen only by the height of the R-wave amplitude in the supine position, the device electrodes could be located in an area where amplitude varies by changing body positions, which could lead to false detections.(95) Although the authors determined that R-wave amplitudes change depending on body positions, the minimum amplitude value they report was estimated to be greater than ILR manufacturer-recommended value for adequate sensing.(95) Another study in a paediatric cohort similarly reported that the sensed R-wave amplitude of ICM was acceptable based on the minimum R-wave sensing threshold recommended by the manufacturer, regardless of body surface area, method of implantation, and/or the presence of congenital heart disease.(96) However, they reported that in the setting of low numbers there was a trend towards greater R-waves seen for smaller body surface area and that P-waves were able to be detected for those with greater R-wave amplitude.(96) The ability to obtain P-waves is of particular importance for decerning AF episodes captured by ICM, with new ICM algorithms for AF detection incorporating P-wave for enhanced efficacy.(97) Incoherence of R-R intervals as detected by patterns in a Lorenz plot have been used by ICM algorithms for AF detection but the inclusion of P-wave evidence scoring with programmable aggressiveness and sensitivity has shown reduced inappropriate episode capture with minimal reduction in AF detection sensitivity.(97) However, as P-waves may not always be

discernible, additional algorithm improvements have been required with the software now modified to better discern runs of ectopy and sinus arrhythmia.(98) More recently, artificial intelligence filtering has been applied to tracings obtained by ILR, but false positives of AF detection remains an issue.(99) Ultimately the effectiveness of such algorithms and the ability for clinicians to accurately discern periods of AF by comparison with rhythm strips require that adequate electrogram signal amplitude is obtained by ICM.

The miniaturisation of ICM has seen a reduction in the device's sensing vector length for most models. The BioMonitor 2 (Biotronik Inc, Berlin, Germany) ICM was able to retain a longer sensing vector by the design incorporation of a sensing antenna.(100) It has been shown that the R-wave amplitude was not changed by different body position and an enhanced AF detection algorithm was later included in the following BioMonitor 2 iteration.(101) This ICM design demonstrated AF detection sensitivity of 96% with a positive predictive value of 82% compared to AF detected by concurrently in-situ pacemaker.(102) The R-wave obtained for BioMonitor was larger than that reported for the Medtronic Reveal LINQ (Medtronic Inc, Minneapolis, MN, USA), and false-positive detections were reduced although not eradicated with the BioMonitor 2.(20) The antenna feature has been retained in the new generation BioMonitor III design to maintain a longer sensing vector.(103) Little data exists on the electrogram sensing of these new generation ICM. However, the literature suggests that ICM sensing vector length, as well as patient posture, body size and implant location may impact on electrogram amplitude of tracings obtained by ICM. Adequate electrogram amplitude on ICM strips may be particularly desirable for certain patients for accurate rhythm diagnosis and may assist in managing the growing workload burden associated with ILR follow-ups.

1.4 TECHNOLOGY APPLICATION FOR HEART RHYTHM ASSESSMENT

The ability of implantable technology to detect arrhythmia has improved, but there is growing interest in the application of digital wearable technology for continuous rhythm monitoring. Until recently, arrhythmia diagnosis was primarily by 12-lead ECG and 24-hour Holter ECG in the clinical setting, but the duration of these tracings may be too short for detection of paroxysmal arrhythmias such as AF. Patient owned handheld digital technology devices are now quite common which presents an opportunity for their utility in arrhythmia monitoring and detection. However, many such digital device types exist, each with varying integrated technology features or pairable hardware options, so their best practical application in arrhythmia management has been difficult to establish despite the collaborative efforts of experts.(104)

In recent times, there has been an explosion of literature regarding various digital technology for arrhythmia monitoring with a particular focus on AF detection.(105, 106) Since AF can be asymptomatic or subclinical with the first presentation being ischaemic stroke, there exists a need to detect silent AF in the general population given that AF exerts stroke risk independent of other often-associated cardiovascular abnormalities.(107) The identification of AF can allow appropriate intervention and management, with anticoagulation therapy and aggressive risk factor modification able to curtail the significant morbidity and mortality. (108, 109). However, the accuracy of AF detection by these devices is variable and the majority do not provide an ECG strip as they are based on Photoplethysmography (PPG).(22) This creates a risk of false-positive

detection with inappropriate therapy or false-negatives with missed opportunity for therapy intervention.

1.4.1 Digital technology for heart rhythm adjudication

There are a variety of digital technologies available for AF detection, but not all capture ECG strips. PPG technology is a non-ECG method of AF detection which uses an optical sensor in the form of light-emitting and light-sensitive photodiodes to passively measure changes in blood flow.(110) PPG is available on modern smart phones through applications using the built-in camera,(111, 112) and is also incorporated in many smartwatches and fitness bands that are colloquially referred to as “wearables”. (110, 113, 114) These devices allow longitudinal pulse data known as a tachogram to be analysed by real-time algorithm for assessment of pulse irregularity and variability that may be due to potential irregular heart rhythms such as AF. PPG technology is particularly attractive for AF detection due to low cost, convenience, simplicity and broad accessibility but lacks an ECG tracing for manual adjudication. One study using an automated AF detection algorithm performed a direct comparison and reported similarly high sensitivity and specificity of 96% (95% CI 89%-99%) and 97% (95% CI 91%-99%) for PPG signal versus 95% (95% CI 88%-98%) and 97% (95% CI 91%-99%) for single-lead ECG.(111) However, this comparison was after removing insufficient quality measurements which remains an issue for PPG, as noise artifact from movement during activity limits utility. In many studies evaluating PPG technologies, it has been paired with ECG recordings, such as patch monitoring (115), simultaneous Holter (116) or single-lead ECG capture (112), allowing rhythm strips to be obtained to confirm that irregular pulse detections are due to AF.

The ability to capture single-lead ECG is a feature of many dedicated “handheld” devices, such as the MyDiagnostick and Kardia AliveCor devices.(117) These devices are often connected to a smartphone with a paired application using an automated algorithm to identify arrhythmia. High sensitivity and specificity of AF detection by automated algorithm assessment of single-lead ECG tracing has been demonstrated by validation assessment of patients known to have AF.(118) Consequently, many of the newer generation “wearables” are now designed to capture single-lead ECG allowing both automated algorithm assessment and rhythm strip manual adjudication. The Kardia Band can achieve an ECG tracing by a circuit between the detector on the inner and outer sides of the watch band.(119) Similarly, the Apple Watch (series 4 onwards) achieves this through a circuit between the detector on the watch back and the digital crown.(120) Multiple other technology companies now produce wearable devices with United States Food and Drug Administration (FDA) approval for heart rhythm monitoring, including the Samsung Galaxy Watch and France-based Withings Scanwatch (both using ECG) and Google-owned Fitbit which uses PPG. The ECG tracings from these wearable devices have high fidelity, and can even be positioned to obtain many of the standard vectors of a 12-lead ECG.(121) Other new digital devices for rhythm assessment can simultaneously record multiple ECG leads, such as the KardiaMobile 6L and Istel HR-2000, allowing additional tracings for manual rhythm adjudication as well as automated algorithm assessment.(122) Many of these technologies have been assessed for their ability to detect AF, but their utility specifically for community AF screening is less well established.

1.4.2 AF screening and digital technology

Although the impact of AF and its sequalae is significant, there remains uncertainty regarding the appropriateness of opportunistic screening for AF.(23) The practice of screening for AF suitably fulfils public health principles deemed necessary for appropriate disease screening.(123) In particular, screening in the form of opportunistic pulse palpation or ECG rhythm strip is recommended by the European Society of Cardiology (ESC) in all patients 65 years or older contacting health services.(109) Previously there have been arguments against screening due to cost-effectiveness.(124) Certainly systematic and secondary screening after stroke or systemic embolism is broadly supported.(125) However, guidelines are now recognising the utility of cost effectiveness of readily available digital devices for AF screening and their potential broader utility.(126) For example, the increased consumer use of digital wearables and smart devices that can serve as non-invasive, ambulatory heart rhythm monitoring and provide consumers real-time feedback may support health seeking behaviours.(105) Large AF screening programs have been successfully conducted using the Apple(110) and Huawei(114) digital devices which delivered notifications to users alerting them of the need to seek further medical review of their rhythm. In resource scarce settings, where medical resources are limited, applications which can provide automated heart rhythm adjudicating may be particularly useful. Although there may be concerns regarding feasibility of using digital devices in remote communities less familiar with technology, a previous study in rural India described the successful use of a smartphone monitoring protocol to screen members of the community for AF.(112) More locally in remote and regional Australia, one study used a handheld smartphone ECG device and was able to detected AF in thirty out of 619 Aboriginal people.(127) However, only four of these individuals were not previously known to have AF,(127) so the utility of digital technology for screening in resource poor setting where AF is not already known remains a gap in the literature. Importantly, when applying digital technology for AF screening in such resource scarce settings it is critical that

the technology selected be optimal for maximal yield with minimal limitations. Acknowledging the unknowns, there is a need for reporting of experience using digital technology for AF screening in resource scarce settings which can be valuable for guiding future public health resource planning.

1.4.3 AF in sub-Saharan Africa

Sub-Saharan Africa is a developing region encumbered by resource scarcity, but with a population undergoing epidemiological transition. The Global Burden of Diseases (GBD) 2010 study reported the sub-Saharan Africa region has made overall progress in reducing mortality and prolonging life since 1970.(128) However, sub-Saharan Africa has been considered a unique global region as about half of the cardiovascular disease present has been due to causes other than atherosclerosis.(129) Some sub-Saharan areas are gradually adopting Westernised lifestyle and developing a wave of new cardiovascular risk factors(130) which usually are associated with affluent communities. Indeed, we have seen the impact of this in the Australian and Asia-Pacific region with the consequences for AF.(131) It has been anticipated that the sub-Saharan African population risk of cardiovascular disease will likely transition to being more attributable to recognised modifiable traditional risk factors, including smoking, history of hypertension or diabetes, obesity, unhealthy diet, lack of physical activity, excessive alcohol consumption, raised blood lipids and psychosocial factors.(132) The GBD 2010 study estimated that absolute cardiovascular disease burden has increased in sub-Saharan Africa since 1990, with the largest relative increases in burden being for AF and peripheral arterial disease, with age-standardized rates increasing 16% and 27%, respectively.(129) Additionally, this landmark study reports that

cardiovascular disease deaths in sub-Saharan Africa occur at younger ages on average than in the rest of the world.(129)

Healthcare in this region is being double challenged by the growing burden of lifestyle risk factors, whilst communicable diseases common of the developing world persists, and concerningly both contribute to the development of AF.(133) Although the reported prevalence of AF has been lower in Africa than in the developed world, it is expected to increase significantly over the coming decades for this reason. A recent systematic review identified from 72 studies that the sub-Saharan community-based prevalence of AF was 4.3% and 0.7% in individuals aged ≥40 years and aged ≥70 years, respectively.(134) This study also reported the prevalence of AF ranged between 6.7% and 34.8% in patients with ischemic stroke, between 9.5% and 46.8% in those with rheumatic heart disease (RHD), between 5% and 31.5% in patients with dilated cardiomyopathy.(134) A separate meta-analysis of the incidence and prevalence of AF in RHD reported about one-third of patients with RHD have AF, with an incidence which almost triples every five years after diagnosis.(135) Certainly, it is known that patients with AF in Sub-Saharan Africa tend to be younger and have a higher prevalence of RHD than patients with AF in other regions.(133) However, the importance of modifiable risk factors cannot be dismissed and lifestyle interventions can be effective in AF management.(136) Consequently there remains many unknowns about the burden of AF in sub-Saharan African and a need for advances in arrhythmia care.(137, 138)

1.4.4 AF in Ethiopia

The sub-Saharan region of Ethiopia has had substantial improvements in health over the last three decades as reported by the GBD 2019 Ethiopia subnational analysis.(139) However, the progress across the country has not been uniform, with disparity between the highest and lowest socio-demographic index regions and cities increasing by 54% between 1990 to 2019.(139) Much of the literature pertaining to AF prevalence from Ethiopia is from analyses of hospitalisations and hospital-based data. In the urban Ethiopian region of Addis Ababa, AF was reportedly present for 46.8% of 500 patients with RHD in a retrospective chart review.(140) In a contrasting low-socioeconomic region, a study in west Shewa of Ethiopia surveyed a rural in-hospital population of 54 patients diagnosed with AF, and reported 39% had RHD and that the patient age was younger than the African urban population.(141) Another study from the northwest of Ethiopia reported high prevalence (28.7%) of AF among stroke patients(142). Also from this region it was reported that 26 of 208 stroke patients died in-hospital, with AF being the second most prevalent risk factor (36.5%) behind hypertension (56.7%).(143) Additionally in this region, poorer outcomes of patients with AF were associated with anti-thrombotic undertreatment.(144) One recent study from the Ethiopian Jimma regions reported an AF prevalence of 4.3% in a community-based cross-sectional study in 634 adults, and noted that 19 out of 27 participants with AF were in need of anticoagulation to prevent risk of stroke.(145) Despite these few published reports, there remains a scarcity of data on AF in Ethiopian with little data from community-based cross-sectional investigation. Given the recommendations for Ethiopian federal and regional health policy makers to address the health progress disparity issue, (139) community AF screening using low-cost digital technology may be of great utility to assess burden and impact of AF in Ethiopia and assist with engineering strategies geared to reduce morbidity and mortality.

1.5 SUMMARY

The evolving landscape of technology-assisted medicine provides new opportunities for healthcare delivery and service improvements. Significant gap in our knowledge is evident from the above review of technology integration into clinical workflow for patients with heart rhythm disorders, particularly with regards to technology application for improved CIED workflow, CIED hardware design and the utility of digital devices for arrhythmia screening (Chapters 4, 5, 6 and 7). The overall purpose of this thesis is to investigate clinical services for heart rhythm disorders which require optimisation and identify opportunities for improvement via implementation of emerging technology (Chapters 2 and 3), with an aim to provide maximal value for healthcare funding. It is hypothesized that there are clinical workflow inefficiencies and challenges that could benefit from the application of emerging technologies in the field of heart rhythm disorders.

Statement of Authorship

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Should we check it? assessing interrogation of cardiac implantable electronic devices in the emergency department - The CHECK-ED study: Implications for service planning and care delivery

2 ABSTRACT

Background: Requests from the Emergency Department (ED) for cardiac implantable electronic device (CIED) checks constitute a large workload for cardiac electrophysiology services. We sought to determine the yield of, and clinical characteristics associated with, clinically relevant (remarkable) issues from ED CIED checks.

Methods: Consecutive CIED checks from our ED over a 12-month period were studied. A remarkable issue (RI) was defined as arrhythmia relating to the presentation or device/lead issue requiring reprogramming or intervention. The association between the presenting complaint and an RI was assessed using regression analysis. Multivariable regression model was used to identify pre-specified patient-level characteristics that were predictive of a RI.

Results: A RI was found in 28% (n=98) of 354 ED CIED checks for 306 patients (76±16 years, 59% male). Most patients had no RI (n=224, 73%). One third of checks occurred after-hours and these had a higher yield of RIs than those during routine clinic hours (35% vs 23%, p=.018). Presenting with a perceived ICD shock was predictive of a RI (odds ratio (OR) 6.0, 95% CI=1.8-20.0). Syncope/presyncope was 5-fold less likely to be predictive of a RI (OR 0.19, 95%CI=0.13-0.28) despite being the most common indication for CIED check (51%, n=180 checks). Only history of AF was predictive of RI while advancing age was predictive of not finding a RI.

Conclusion: Almost three-quarters of ED CIED checks did not yield any RI. Patient-reported ICD shock and history of AF were predictive of RI, while syncope/presyncope was not. New models of care especially during after-hours, may help to reduce the burden on cardiac electrophysiology services and healthcare costs.

2.1 INTRODUCTION

The number of patients with a cardiac implantable electronic device (CIED) is increasing.(6, 14) Requests from the emergency department (ED) for CIED check can be directly related to concerns regarding CIED function or other undifferentiated symptoms such as syncope or palpitations. These ad-hoc CIED checks in the ED impose a significant burden on the healthcare service, especially when they occur after-hours, when on-site technical support capable of performing the interrogation and interpretation is unavailable. Recently, remote CIED interrogation technology has been utilised in some centres with early experience showing reduced response time to CIED checks in the ED and potential to alleviate the burden of these requests.(40) However, such technology cannot completely replace in-person CIED check as it is limited to only some CIED manufacturers and interpretation of the checks is not always real-time.

It remains unknown whether any patient or clinical characteristics are predictive of detecting clinically relevant issues from CIED checks. Such information will assist in clinical triaging of the urgency of CIED checks and service planning, which may potentially be cost saving to the healthcare system. We hypothesise that majority of CIED checks in the ED do not detect any clinically relevant issues and a high proportion of after-hours CIED checks can be safely scheduled

till the next working day. Here, we sought to characterise CIED checks in the ED over a 12-month period and to determine the clinical predictors of detecting clinically relevant issues.

2.2 METHODS

The CHECK-ED (Should we **CHECK** it? Assessing interrogation of cardiac implantable electronic devices in the **E**mergency **D**epartment; Australian New Zealand Clinical Trials Registry ACTRN12619000607178) study evaluated consecutive CIED checks performed in the ED of our tertiary referral institution over a 12-month period up until 4th September 2017. This single-centre retrospective study has approval from the institutional Human Research Ethics Committee.

All CIED interrogations were requested by ED physicians. CIED checks were classified as permanent pacemaker (PPM), implantable cardioverter-defibrillator (ICD) and implantable loop recorder (ILR), with cardiac resynchronization therapy devices included as ICD or PPM based on the presence or absence of defibrillator therapy. We defined after-hours as any occasion after 5pm or before 8am on a weekday or anytime on Saturdays or Sundays. Remarkable issues (RIs) were defined as an arrhythmia with or without anti-tachyarrhythmia therapy related to the ED presentation or a device-related issue requiring re-programming or lead/device revision procedure. RIs were correspondingly classified as newly diagnosed atrial arrhythmia, sustained ventricular arrhythmia, or system issue. Specifically, non-urgent CIED reprogramming such as routine optimisation of sensing or pacing parameters to reduce pacing burden and battery drain were not included as RIs. Similarly, known chronic atrial or non-sustained arrhythmias were not included as RIs. We extracted data from the time-logged reports consisting of the interpretation

of the CIED checks and the exported CIED PDFs from our electronic health record system. Patient characteristics and the presenting symptoms were also retrieved from the electronic health records. The presenting symptom was classified as follows: palpitations, chest pain, syncope/presyncope, dyspnoea, ICD therapy, or others (non-cardiac symptoms).

Statistical analysis

Continuous variables are reported as mean ± standard deviation (SD) or median and interquartile range (IQR) where appropriate. Non-continuous variables are presented as numbers and frequency. Patient clinical characteristics were compared using the unpaired Student t-test or Chi-squared tests. The impact of presenting complaint on finding an RI was assessed using binary logistic regression and expressed as odds ratio (OR) with 95% confidence interval (CI). Further, a multivariable binary logistic regression model was used to identify patient-level characteristics as predictors of RIs. This was adjusted for age, gender, atrial fibrillation, ischaemic heart disease and congestive cardiac failure which were selected *a priori* by expert clinician consensus. All statistical analyses were undertaken using SPSS Statistics (version 25, IBM Corp, Armonk, NY, USA) and a two-tailed p-value of <0.05 was considered statistically significant.

2.3 RESULTS

A total of 354 CIED checks were performed in the ED over the 12-month period, comprising 222 (63%) PPM, 100 (28%) ICD and 32 (9%) ILR checks. CIED checks were performed for 306 patients with 33 of these patients having multiple ED visits during the study period. The mean age of the patients was 76 ± 16 years and 59% were male. Table 1 shows the patient demographic and clinical characteristics according to CIED type. The patients requiring ICD checks were younger

and more often male with history of ischaemic heart disease, congestive heart failure, obstructive sleep apnoea, smoking and structural heart disease. The patients needing PPM checks were older and more likely to have hypertension, hypercholesterolaemia, atrial fibrillation (AF) and malignancy. The patients needing ILR checks were less likely to have cardiovascular risk factors or cardiac conditions.

Remarkable issues

A RI was found for 28% (n=98) of the 354 total CIED checks. As shown in the central figure, three-quarters of the RI (n=73) were due to 'arrhythmia episodes', and the remaining RI were due to 'programming issues' (n=14) and 'device issues' (n=11). Among the 'programming issues', there were three occasions warranting reversal of a programming change performed recently at their routine device follow-up clinic that had since caused symptoms. Among the 'device issues', there were seven occasions of lead dysfunction, including four occasions of failure to capture (due to damage or dislodgment), two occasions of sensing failure and one occasion of phrenic capture due to LV lead displacement. The 98 checks with RI came from 82 different patients, 14 of whom had more than one ED presentation requiring CIED check. The most repeat presentations by a single patient with RI on each check was five, and this patient also had one presentation without an RI noted. Comparisons of the patient characteristics for those with and without an RI is shown in Table 2. Patients with RI were more likely to have a history of AF, known structural or congenital heart disease and repeat ED presentations. ICD accounted for the most checks with an RI (n=49) followed by PPM (n=45) and ILR (n=4), leading to significantly higher yield of RI (50% vs. 46% vs. 4% respectively, $p<0.0001$; Figure 1a). A total of 127 CIED checks (36%) were performed after-hours. Compared to checks during regular hours, a significantly greater proportion of after-hours checks had RIs (35% vs 23%, $p=0.018$; Figure 1b).

Of the RIs, n=45 were due to newly diagnosed atrial arrhythmias, n=33 were due to sustained ventricular arrhythmias and n=20 were due to device/system issues requiring immediate reprogramming, with six of these requiring urgent intervention for battery depletion or lead dislodgment. Non-urgent device reprogramming was performed in n=8 checks which did not meet RI criteria. The type of RI differed significantly by CIED type with the majority of RI in ICD due to ventricular arrhythmias (65%) while newly diagnosed atrial arrhythmias accounted for the most RIs in PPM (69%) and ILR (75%) (Figure 2; $p<0.001$). Majority of ED CIED checks were requested for patients who presented with syncope/presyncope (n=180, 51%), while chest pain, dyspnoea, palpitations, and ICD shock complaint accounted for only 13%, 12%, 8%, and 6% respectively. The yield of detecting any RIs was lowest for checks performed for syncope/presyncope and highest for checks performed for ICD shock ($p<.0001$; Figure 3, top panel). ICD shock presentation was mostly in keeping with ventricular arrhythmias on CIED check while at least half of the RIs for each of syncope/presyncope, dyspnoea and palpitations were due to atrial arrhythmias (Figure 3, bottom panel).

Predictors of remarkable issues

Using binary logistic regression, the impact of presenting complaint on finding an RI is shown in Figure 4A. Presenting symptom of syncope/presyncope was 5-fold less likely to be predictive of a RI (OR 0.19, 95% CI 0.13-0.28) despite being the most common indication for ED CIED checks. In contrast, presenting complaint of ICD shock was the only positive predictor of RI (OR 6.0, 95% CI 1.8-20.0). The multivariable binary logistic regression model with predetermined variables (Figure 4B) showed that previous history of AF was the only positive predictor of RIs (OR 2.17, 95% CI

1.3-3.6) while advancing age was predictive of not finding any RI from ED CIED checks (OR 0.98, 95% CI 0.98-0.99).

2.4 DISCUSSION

Requests for CIED interrogations from the ED present a significant unplanned clinical workload by nature of patient presentations. This study found that fewer than one in three of these checks detected clinically relevant or remarkable issues, while 35% of all ED CIED checks occurred after-hours. Most remarkable issues identified were due to arrhythmia episodes with a low yield of system or device issues. Specifically, only 6 out of 354 (1.7%) checks required urgent device intervention due to battery or lead issues. Notably, despite syncope/presyncope being the most common patient complaint that led to CIED checks in the ED, it was associated with the lowest yield of detecting a RI and with odds ratio of 0.19 by logistic regression analysis. Our findings have important implications on service provision and call for improved triaging of ED requests for CIED checks.

CIED checks in the ED

The demand for CIED checks from the ED is likely to increase with the ageing population and increasing number of CIED implants.(6, 14) Little data exist regarding outcomes of CIED checks in the ED with existing published works limited to “read-only” remote CIED interrogation technology, encompassing a variety of clinical settings (ED and peri-operative areas) and reported according to specific device manufacturer.(36, 40) Mittal and co-workers evaluated 509 Boston Scientific remote checks (n=294, 58% from ED) with arrhythmias detected in 59 and lead/device issues in 14 checks. Only 53 (10%) of their checks were classified as clinically

urgent.(36) Ahmed and co-workers evaluated 6135 Medtronic remote transmissions from EDs with 9.9% demonstrating significant arrhythmias and device/lead issues.(40)

Our study found an overall yield of 28% for detecting clinically relevant or remarkable issues from CIED interrogations in the ED over a 12-month period. These are higher than reported by others and appears to be driven by arrhythmias, with device/lead issues at similarly low rates (<10%). The low rates of device/lead issues suggest potential utility of remote CIED interrogation technology in clinical settings such as the EDs whereby "read-only" information would facilitate timely patient management. This may be particularly useful during after-hours when qualified physiologists capable of performing CIED checks are not on site. However, in-person CIED checks are indispensable and carry the advantage of instantaneous device reprogramming that can help to alleviate symptoms due to inappropriate device/lead issues in some situations.

Prioritising CIED checks from the ED

The majority of device interrogations in the present study were for PPM as compared to those for ICD or ILR. However, the proportion of ICD checks with a RI was statistically greater than those for either PPM or ILR checks. Symptoms of presyncope or syncope was the most common clinical indication for requesting a CIED check but yielded a very low rate of RI at just 16%. This is not dissimilar to the study by Ahmed et al where the yield of clinically relevant events for presenting complaints of presyncope or syncope was 6.5%.(40) In our study, logistic regression analysis affirms that presenting complaint of ICD shock was the only positive predictor of a RI. Presentations with symptoms of syncope/presyncope was five-fold less likely to be predictive of a RI. Our data suggest that physicians should continue to maintain a lower threshold for requesting CIED checks in the ED for ICD-related presentations, particularly when ICD shock is

suspected. In contrast, remote interrogation may be a suitable initial alternative for PPM and ILR checks, if available and depending on patient symptoms. Due consideration of urgency is needed particularly for in-person PPM and ILR checks, to minimise unnecessary after-hours call backs to the ED.

Optimising CIED service delivery

This study demonstrates a low overall yield (28%) for identifying significant clinical issues in an unselected group of patients presenting to an ED and where CIED interrogation is requested. The requirement for immediate CIED intervention was even lower at 1.7%. This would support the use of an initial strategy of remote interrogation if available, with in-person CIED interrogation by programmer reserved for those instances where remote interrogation is not possible or where urgent device reprogramming is required. Remote home monitoring is now recommended as part of routine CIED follow-up and is widely utilised, and has been shown to be cost-effective and provide earlier detection of clinical events along with reduced ED presentations in selected populations of patients with CIEDs.(17, 72, 73, 77) However, “read-only” remote CIED interrogation technology is vendor specific and unavailable for some CIED manufacturers. The use if ED-initiated remote device interrogation requires qualified personnel to interpret the remotely transmitted data and report the findings back to the ED. Institutions need to make prior arrangements for these systems to work seamlessly in their EDs. With a minimum or basic training, “read-only” in-person CIED interrogation can be performed by onsite ED staff and this has been reported to be safe and efficient.(37, 42) This strategy achieved CIED check results sooner, and with similar 30-day outcomes, when compared to CIED checks performed by specialist CIED technicians needing to return-to-site.(38) Potentially, ED personnel undertaking “read-only” device checks could also be guided by specialist CIED technicians or physicians

through video conferencing for urgent device reprogramming.(43) Given the many options for CIED checks in the ED, effective institutional protocols are required to ensure adequate resource allocation and workflow efficiency for timely care for patients with CIEDs. The complexity of CIED checks cannot be underestimated and appropriate follow-up checks by specialist CIED technicians or physicians would need to be arranged after the ED visit.

Study Limitations

Our data is a retrospective analysis of the outcomes from CIED checks in the ED at our institution with a few noted limitations. First, the data was sourced from medical records and the clinical details available was dependent on the quality of record keeping. Second, we were only able to analyse CIED checks which were performed and therefore patients with CIED who presented to the ED but did not receive CIED checks were not accounted for in this analysis. Last, while we reported on the yield of RI from CIED checks, it is not possible to define how a "negative" check would have assisted in expediting patient discharge and preventing unnecessary hospitalisation.

2.5 CONCLUSIONS

CIED checks requested from the ED have low yield of RI, with only 1.7% of device/lead issues requiring urgent device intervention. Patient reported ICD shock and history of AF were predictive, while syncope/presyncope was not predictive of a RI. Effective institutional protocols to prioritise urgency of CIED checks are required to optimise resource allocation and workflow efficiency for the timely care for patients with CIEDs in the ED, especially during after-hours.

2.6 TABLES & FIGURES

Table 1 - Baseline patient characteristics by CIED type

	PPM (n=197)	ICD (n=77)	ILR (n=32)	P-value
Age in years, mean ± SD	82 ± 11	66 ± 18	65 ± 22	<0.0001
Male, n (%)	101 (51)	63 (82)	17 (53)	<0.0001
Hypertension, n (%)	126 (64)	40 (51.9)	13 (40.6)	0.018
Diabetes mellitus, n (%)	39 (19.8)	15 (19.5)	4 (12.5)	0.615
Congestive heart failure, n (%)	25 (12.7)	18 (23.4)	0 (0)	0.004
History of stroke or transient ischaemic attack, n (%)	26 (13.2)	7 (9.1)	5 (15.6)	0.550
Ischaemic heart disease, n (%)	61 (31)	43 (55.8)	7 (21.9)	<0.0001
Obstructive sleep apnoea, n (%)	11 (5.6)	13 (16.9)	2 (6.3)	0.010
Hypercholesterolemia, n (%)	79 (40.1)	25 (32.5)	6 (18.8)	0.049
Atrial fibrillation, n (%)	77 (39.1)	28 (36.4)	3 (9.4)	0.005
Smoking - active or past, n (%)	20 (10.2)	17 (22.1)	3 (9.4)	0.025
Malignancy - active or past, n (%)	27 (13.7)	6 (7.8)	1 (3.1)	0.118
Known structural or congenital heart disease, n (%)	29 (14.7)	27 (35.1)	3 (9.4)	<0.0001

Table 2 - Baseline patient characteristics by presence or absence of remarkable issues

	RI (n=82)	No RI (n=224)	P-value
Age, years	75 ± 16	76 ± 16	0.36
Male, n (%)	48 (58.5)	132 (58.9)	0.95
Patient with repeat presentations, n (%)	14 (17.1)	19 (8.5)	0.03
Hypertension, n (%)	54 (65.9)	125 (55.8)	0.11
Diabetes, n (%)	18 (22)	40 (17.9)	0.42
Congestive heart failure, n (%)	14 (17.1)	29 (12.9)	0.36
History of stroke or transient ischaemic attack, n (%)	13 (15.9)	25 (11.2)	0.27
Ischaemic heart disease, n (%)	32 (39)	79 (35.3)	0.55
Obstructive sleep apnoea, n (%)	11 (13.4)	15 (6.7)	0.06
Hypercholesterolemia, n (%)	35 (42.7)	75 (33.5)	0.14
Atrial fibrillation, n (%)	40 (48.8)	68 (30.4)	0.003
Smoking - active or past, n (%)	12 (14.6)	28 (12.5)	0.62
Malignancy - active or past, n (%)	5 (6.1)	29 (12.9)	0.09
Known structural or congenital heart disease, n (%)	22 (26.8)	37 (16.5)	0.043

FIGURE LEGENDS

Figure 1: Remarkable issues by (A) device type and (B) occasion of presentation

CIED: cardiac implantable electronic device, ICD: implantable cardioverter-defibrillator, ILR: implantable loop recorder, PPM: permanent pacemaker, RI: remarkable issue

Figure 2: Type of remarkable issue by device type

ICD: implantable cardioverter-defibrillator, ILR: implantable loop recorder, PPM: permanent pacemaker

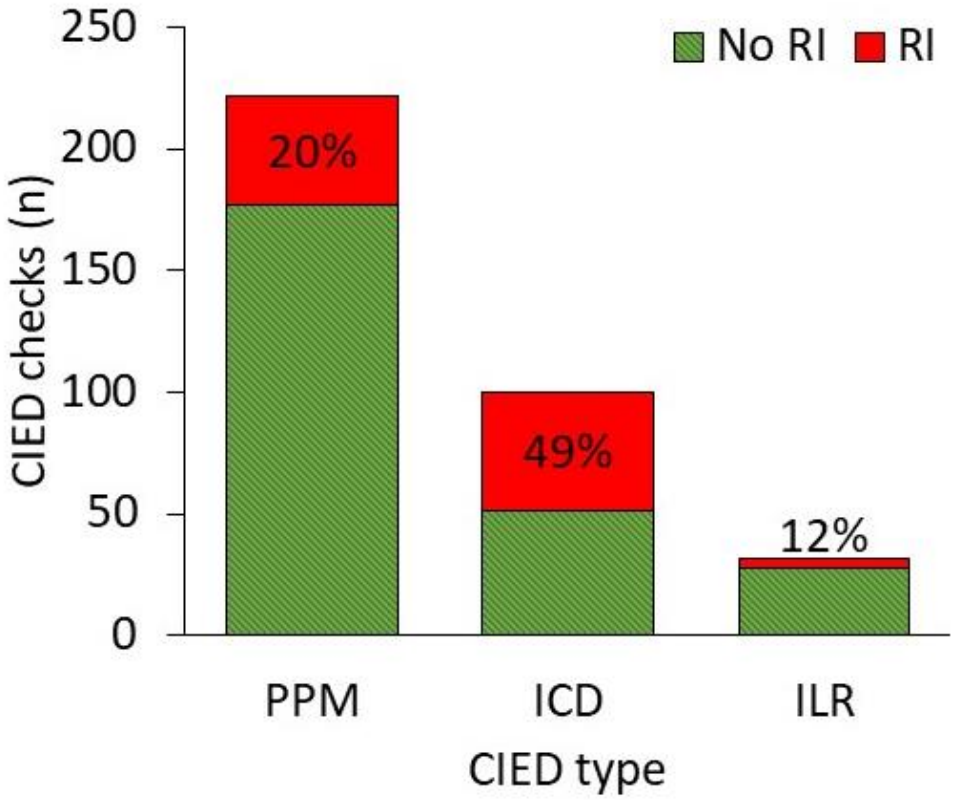
Figure 3: Yield (A) and type (B) of remarkable issues per presenting indication for CIED check

Figure 4: Predictors of remarkable issues. (A) CIED type and presenting complaint; (B) Clinical parameters

Central Figure: Summary

CIED: cardiac implantable electronic device, ICD: implantable cardioverter-defibrillator, ILR: implantable loop recorder, PPM: permanent pacemaker, RI: remarkable issue

Figure 1: Remarkable issues by (A) device type and (B) occasion of presentation



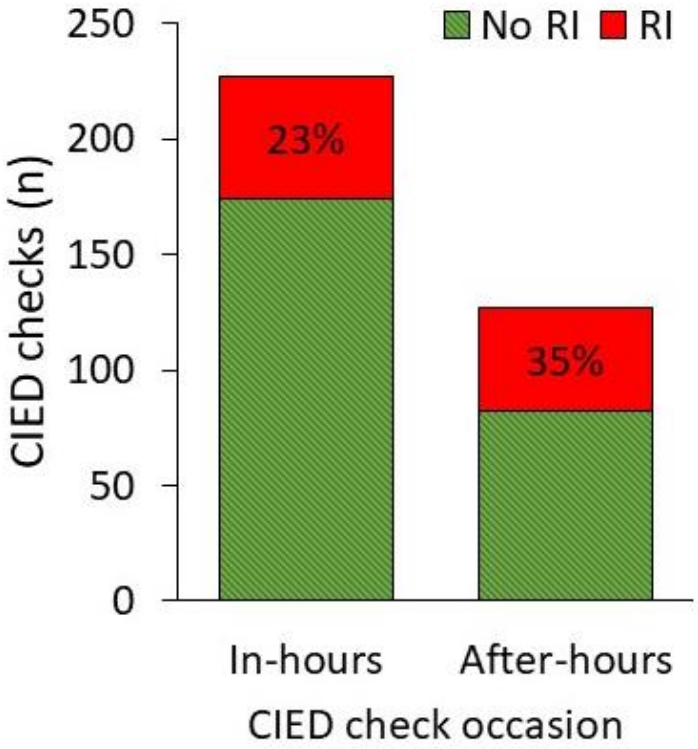


Figure 2: Type of remarkable issue by device type

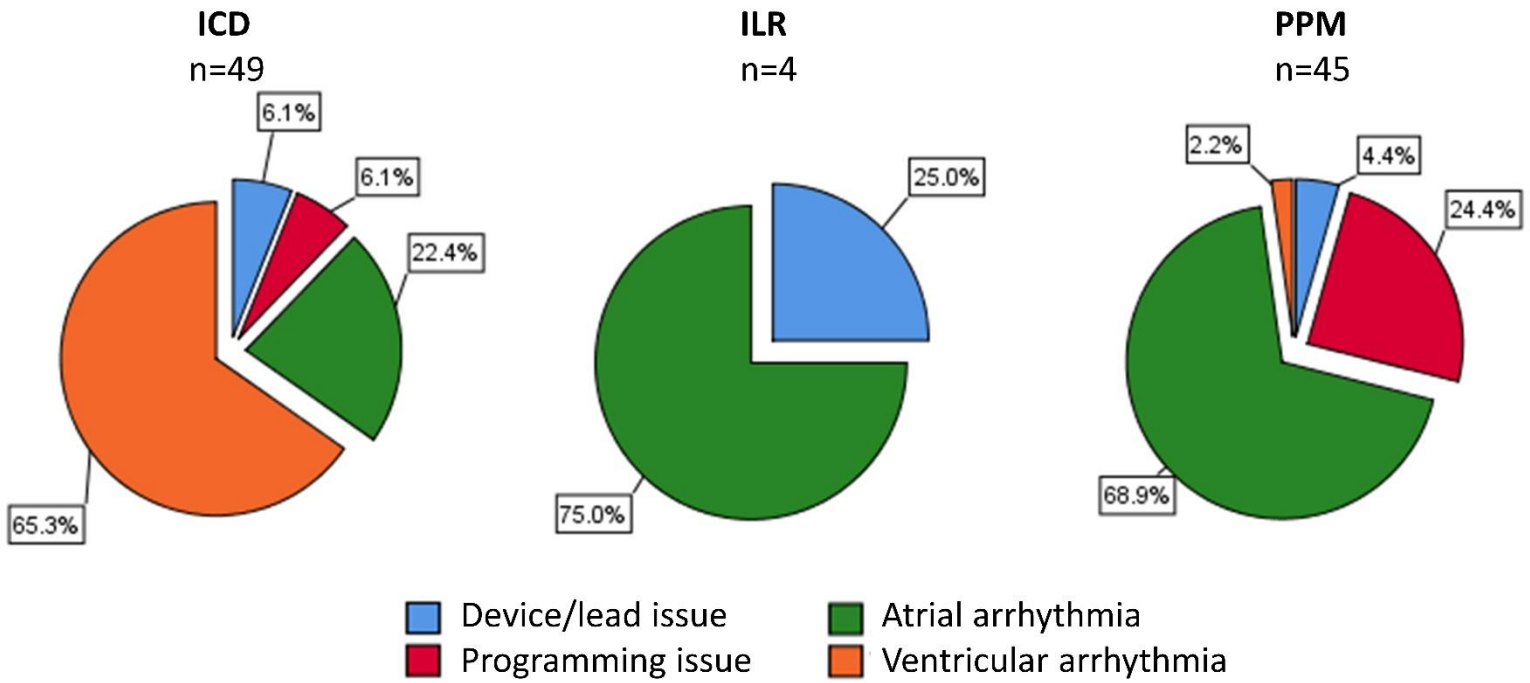


Figure 3: Yield (A) and type (B) of remarkable issues per presenting indication for CIED check

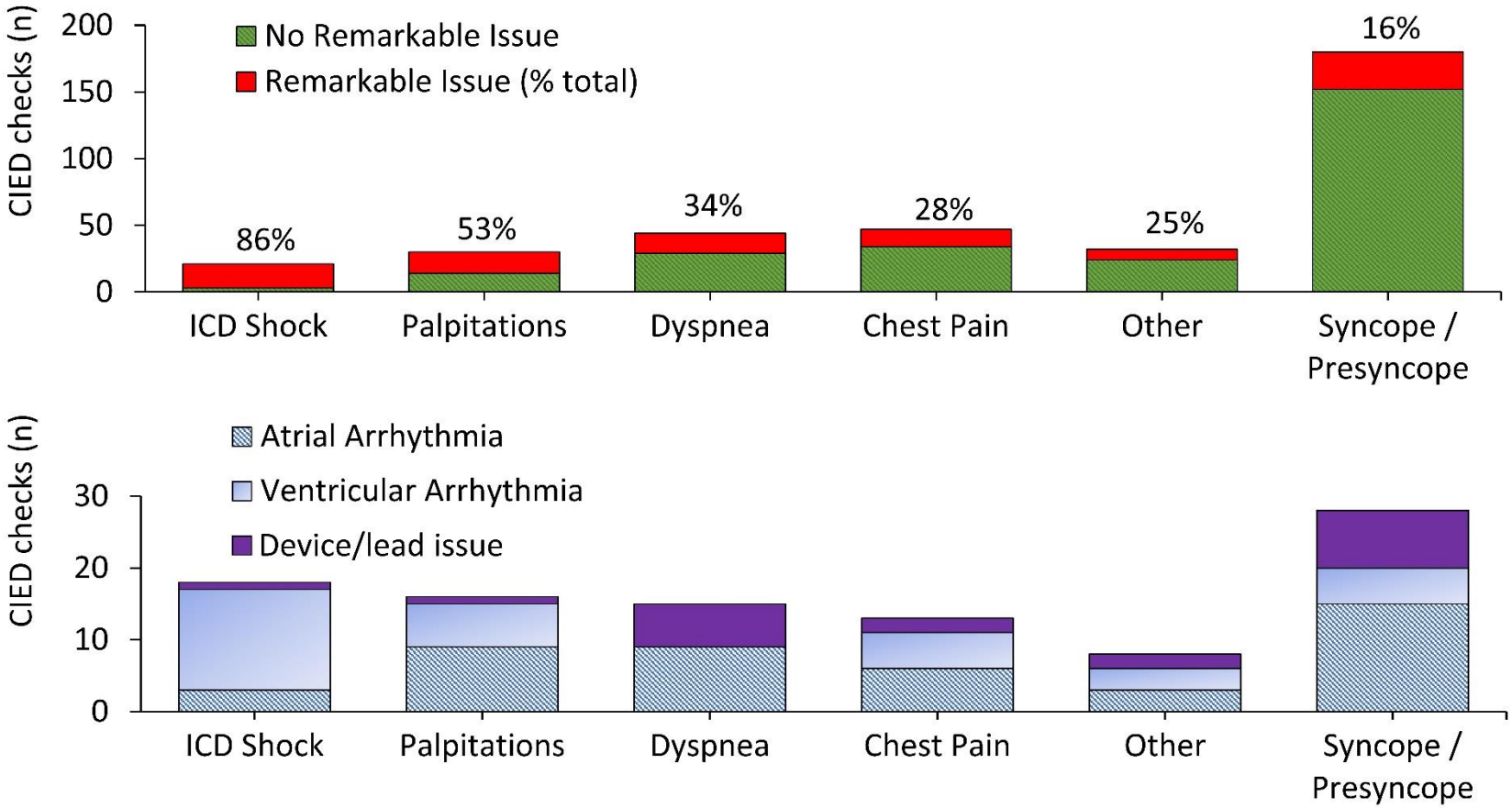
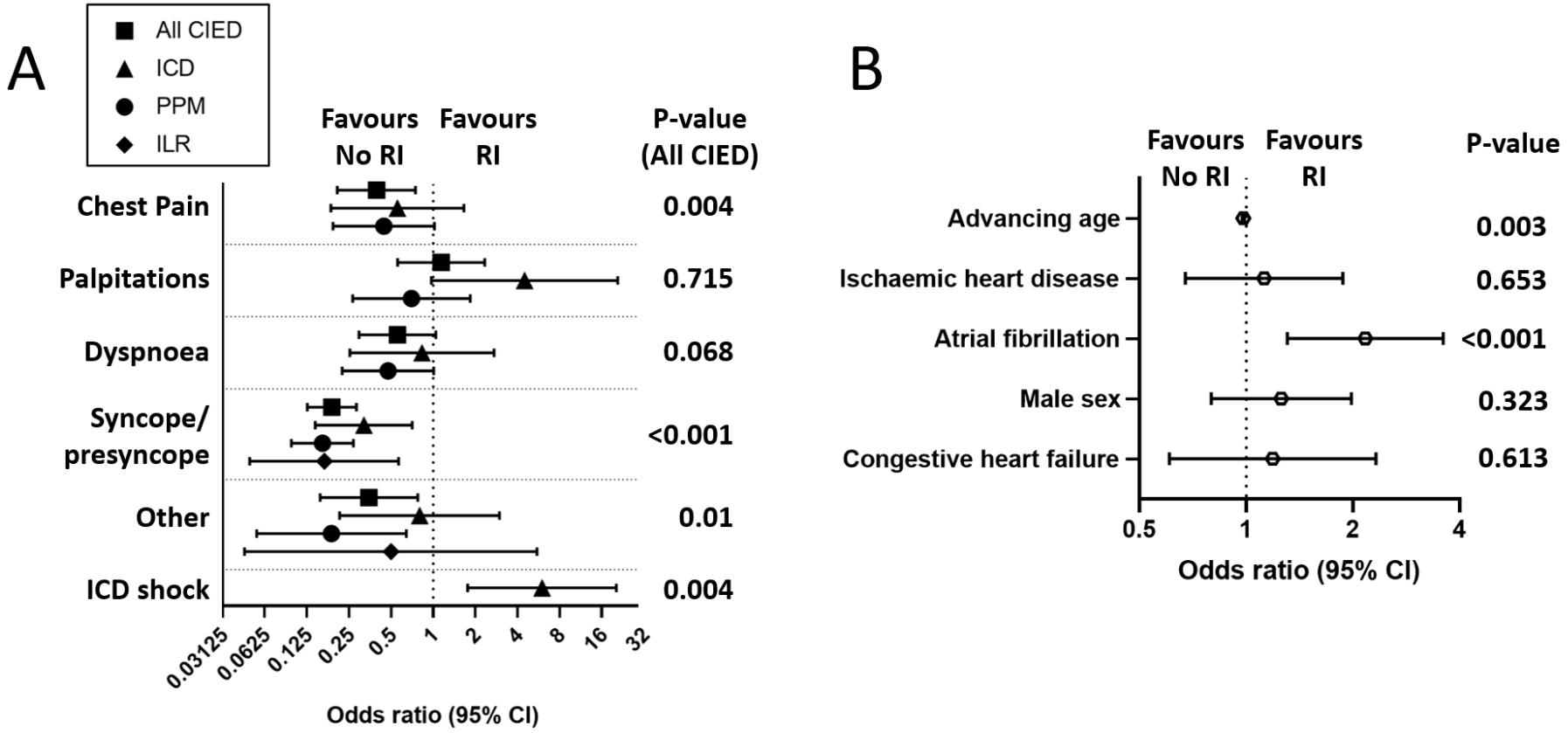
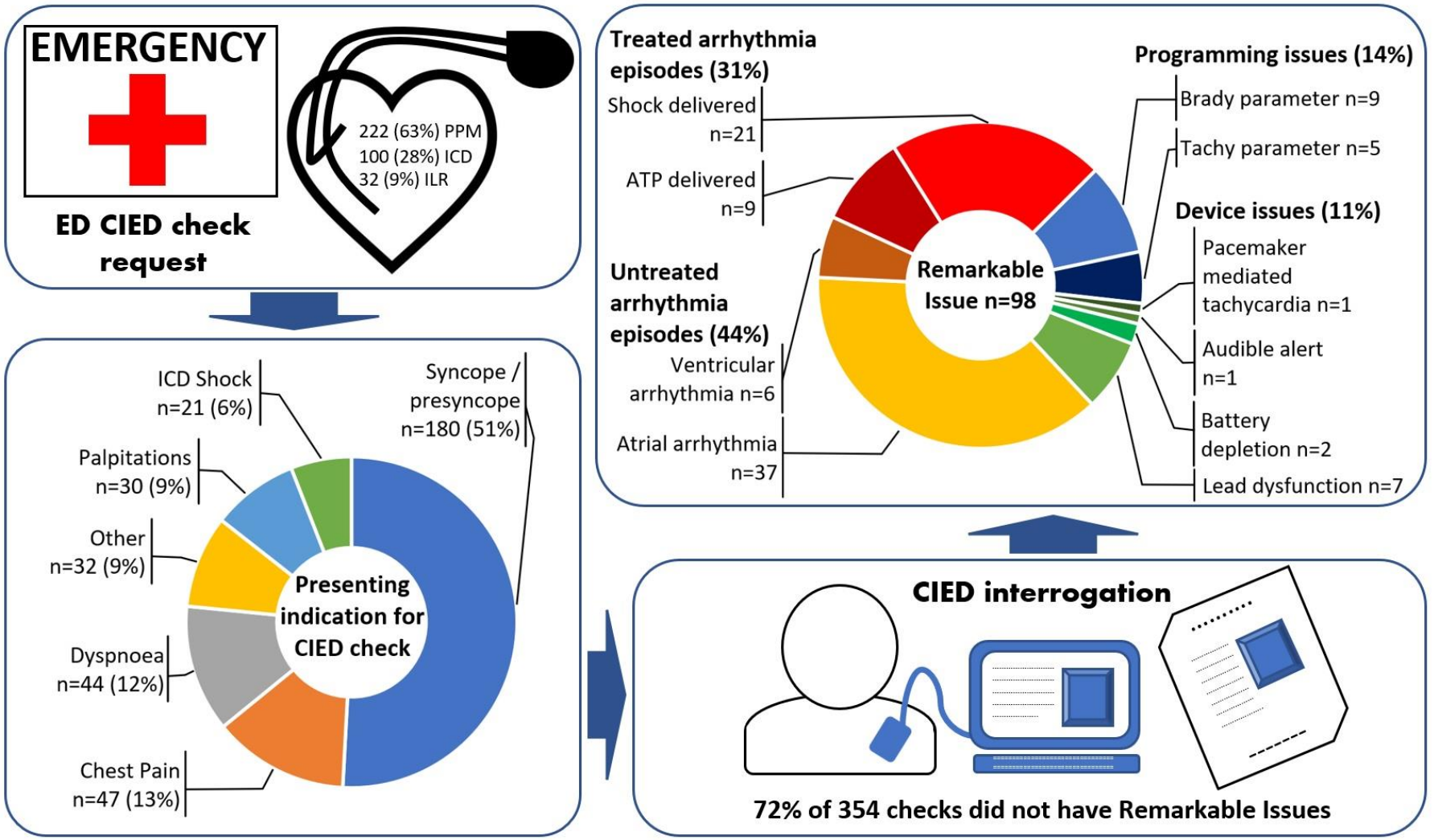


Figure 4 - Predictors of remarkable issues: (A) CIED type and presenting complaint; (B) Clinical parameters



Central Figure



CHAPTER THREE – CHECK-MRI STUDY

AUTHORSHIP STATEMENT

Statement of Authorship

Title of Paper	The burden of cardiac implantable electronic device checks in the peri-MRI setting: The CHECK-MRI study
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Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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The Burden of Cardiac Implantable Electronic Device Checks in the Peri-MRI Setting: The CHECK-MRI Study

3 ABSTRACT

Background: Most modern cardiac implantable electronic device (CIED) systems are now compatible with magnetic resonance imaging (MRI) scans. The requirement for both pre- and post-MRI CIED checks imposes significant workload to the cardiac electrophysiology service. Here, we sought to determine the burden of CIED checks associated with MRI scans.

Methods: We identified all CIED checks performed peri-MRI scans at our institution over a 3-year period between July 1st 2017 to June 30th 2020, comprising 3 separate financial years (FY). Device check reports, MRI scan reports and clinical summaries were collated. The workload burden was determined by assessing the occasions and duration of service. Analysis was performed to determine cost burden/projections for this service and identify factors contributing to the workload.

Results: A total of 739 CIED checks were performed in the peri-MRI scan setting (370 pre- and 369 post-MRI scan), including 5% (n=39) that were performed outside of routine hours (weekday <8am or >5pm, and weekends). MRIs were performed for 295 patients (75 ± 13 years old, 64% male) with a CIED (88% permanent pacemaker, and 12% high voltage device), including 49 who had more than one MRI scan. The proportion of total MRI scans for patients with a CIED in-situ increased each FY (from 0.5% of all MRIs in FY1, to 0.9% in FY2, to 1.0% in FY3). The weekly workload increased (R^2=0.2, P<.001), but with week-to-week variability due to ad hoc scheduling (209 days with only 1 MRI vs. 78 days with ≥2 MRIs for CIED patients).

The projected annual cost of this service will increase to $161,695 in 10 years for an estimated annual 546 MRI scans for CIED patients.

Conclusions: There is an increasing workload burden and expense associated with CIED checks in the peri-MRI setting. Appropriate budgeting, staff allocation and standardisation of automated CIED pre-programming features among manufacturers are urgently needed.

3.1 INTRODUCTION

The number of patients with a cardiac implantable electronic device (CIED) is rising due to expanded implant indications and ageing population.(6) Most current generation CIEDs are compatible with magnetic resonance imaging (MRI) scans provided that certain conditions are fulfilled.(45) The barriers of safety concerns for MRI scans in patients with older generation or legacy CIEDs have been lowered with a recent meta-analysis reporting no significant adverse events in over 7,000 MRI scans for patients with non MRI-conditional CIEDs.(53) Further, MRI scans in patients with non MRI-conditional CIED systems have received Class IIa recommendation from the 2017 Heart Rhythm Society expert consensus statement provided institutional protocols are in place.(45) The Australian Department of Health data of Medicare statistics show an 18% rise in the number of MRIs conducted between 2017 to 2019, with more than 1.45 million performed nationally in the 2020-21 financial year (FY).(61) This increase will continue with the Australian government committing to invest $66 million over four years, from 2022–23 to 2025–26 with an aim to deregulate and expand access to Medicare funded MRI services.(62) Recent studies showed that in patients with MRI-conditional CIEDs, MRI scans occurred at up to 7 per 100 patient-years.(59, 60) Taking into considerations the millions of patients with non MRI-conditional CIED systems

worldwide, cardiac electrophysiology units are facing an increasing workload for the requisite peri-MRI scans CIED checks.

However, there remains a scarcity of data on the impact of workload and workflow in fulfilment of CIED requirements for MRI scans. We hypothesize that the workload burden for peri-MRI CIED checks is increasing with significant economic burden. In this study, we sought to delineate the burden of peri-MRI CIED checks in our institution over a 3-year period and determine the patient, CIED, scheduling and MRI related factors associated with this workload. We also undertook costing analysis to determine the current and projected economic burden associated with peri-MRI CIED checks.

3.2 METHODS

We identified all CIED checks performed pre- and post-MRI scans at our institution between July 1st 2017 and June 30th 2020. Our institutional cardiac electrophysiology protocol for peri-MRI CIED checks include ascertainment of compatible CIED parameters, appropriate pre-scan programming based on patient's pacing dependency, disabling tachyarrhythmia therapy, and activation of MRI mode prior to the scan. This is followed by re-programming the CIED back to pre-scan parameters after ensuring satisfactory CIED function after the scan. All CIED interrogations are performed by trained CIED physiologists/physicians and all CIED reports are uploaded to the electronic medical record (EMR) system. All CIED reports, MRI scan reports and patient clinical summaries were collated for this retrospective analysis. Additionally, we accessed data of the total number of MRI scans performed during the study period using coding information from de-identified institutional administrative database. This

data was used to perform costing analysis on the current and projected expenses for providing CIED checks in the peri-MRI settings. A detailed methodology for this analysis is provided in the Supplementary Appendix 1. This study was approved by institutional human research ethics committee (approval #13213) and was prospectively registered (Australian New Zealand Clinical Trials Registry - ANZCTR #12620000866909).

The occasion of service for CIED checks in the peri-MRI setting was determined from the date and time of these checks logged on the EMR and verified with the time stamps on the generated CIED PDF reports. After-hours was defined as between 5pm and 8am on weekdays and any time on weekends. The clinical burden of each individual MRI was defined by addition of two specific time periods (shown in central figure). Firstly, each CIED patient requires approximately 30 minutes of preparation prior to MRI which include, (1) confirmation of MRI-conditional CIED hardware, (2) exclusion of abandoned/capped CIED hardware in-situ on chest X-ray, (3) CIED interrogation with assessment of sensing, impedance and threshold for each individual lead, as well as assessment of underlying rhythm and appropriate MRI-scan mode selection, (4) completion of manufacturer-specific radiology-authorisation paperwork. Secondly, there is a time interval identified by EMR timestamped reports entered both Pre- and Post- MRI of the CIED interrogations, as shown in central figure. The CIED workload for one MRI scan is the total of these two time periods. The workload burden was calculated weekly for the total hours spent by the cardiac electrophysiology unit for fulfilment of all peri-MRI CIED checks.

We also collected from our EMR the following information for our analysis: 1) Clinical factors including patient characteristics and co-morbidities; 2) CIED-related information including

device type, brand, year of implant and the programming mode for MRI; 3) MRI-related factors including indication for scans, body region scanned, occasion of scan and number of sequences performed. This information was used to determine factors associated with the clinical workload. Details on cost calculation for peri-MRI CIED checks are included in Supplementary Appendix 2. The following assumptions were used; (I) the service will continue to grow, (II) service capacity of MRI department is finite, (III) demand for MRI scans of patients with a CIED continues to increase, (IV) there is no change in department protocol (i.e. do not begin scanning patients with "non-conditional" CIEDs), (V) the need for specialist staffing requirement will remain, (VI) salary is per current enterprise bargaining agreement, (VII) and wage conditions remain unchanged (CPI increases, penalty rates).

Statistical analysis

Continuous variables were summarized using mean ± standard deviation for normally distributed data, or median and interquartile range (IQR) where appropriate. Categorical variables are presented as count and percentages. Comparisons were performed using ANOVA test for continuous variables and Chi-square test or Fishers exact for categorical variables. Logistic regression analysis was used to identify factors associated with longer MRI scan intervals. Linear regression analysis was used to assess change in workload burden over the course of the study. Univariate and multivariate logistic regression was used to identify factors associated with weeks of heavy workload burden defined as exceeding the median weekly workload duration of 200 minutes. As it is anticipated that MRI-scan, patient, CIED and/or scheduling factors may impact MRI-scan interval and workload burden, variables from each of these categories were included in univariate analysis with factors significant at $p<0.05$ level included in multivariate logistic regression analysis. Analysis was conducted using SPSS

Statistics (version 25, IBM Corp, Armonk, NY, USA) and a two-tailed p-value of <0.05 was considered statistically significant.

3.3 RESULTS

There were 739 CIED checks performed for a total of 370 MRI scans scheduled for patients with CIEDs during the 3-year period. Only one MRI scan was cancelled due to failure to meet MRI conditionality criteria with pre-MRI CIED check showing high pacing threshold. The most common indications for MRI scans were cerebrovascular event (n=137), trauma (n=133), investigation for systemic illness/infection (n=32) and cardiac structure & function (n=25). MRI scans were undertaken at the following body regions (Figure 1): brain (n=238), spine (n=52), limbs (n=26), heart (n=25), abdomen (n=14), pelvis (n=12) with 2 aborted prior to imaging and one cancelled due to CIED issue. During the study period, MRI scan for patients with CIEDs occurred on 287 separate days (26.2% of the 1,095 days over 3-years) with most of these days having only a single MRI performed (n=209, 72.8%). Fridays had the most MRI scans performed (n=120, 32.4%), with the busiest day having five separate MRI scans requiring ten CIED interrogations. Thirty-nine (5.3%) of the peri-MRI CIED checks were performed after-hours, including five occasions of MRI scans performed on the weekend. The 739 CIED checks were performed for 295 patients (64% male, mean age 75.2 ± 12.8 years) with 49 (16.6%) having had more than one MRI scan during the study period. The most MRIs for a single patient was seven separate scans. The patient characteristics are detailed in Table 1 with high prevalence of hypertension, cardiac arrhythmias, cerebrovascular diseases, and diabetes mellitus.

Outcome of CIED checks

There were 258 (87.5%) permanent pacemakers (PPMs) and 37 (12.5%) implantable cardioverter-defibrillators (ICDs), with a total of four cardiac resynchronization systems. The median CIED implant duration at the time of first MRI scan during the study period was 726 (IQR 250 – 1396) days, with the oldest device at 10.1 years old. All CIEDs were MRI-conditional systems with no abandoned, epicardial or fractured leads. CIEDs were mostly programmed to asynchronous pacing mode (n=313, 85%) with pacing disabled in the remaining 56 devices during the MRI scans. Post-MRI checks revealed only one lead malfunction, with a right ventricular lead sensing issue (amplitude reduced from 4.9mV to 2.3mV immediately; and subsequent 483 new-onset short V-V intervals noted at 1 month check), but with no other significant pacing thresholds or lead impedance changes noted. There were four occasions of new-onset atrial arrhythmias detected post-MRI scans check with three of these patients having pre-existing history of atrial fibrillation.

Clinical burden of MRIs for CIED patients

The number of MRI scans for CIED patients trended higher during the study period, with an increasing proportion of outpatient scans being performed (Figure 2A). Each MRI scan required a pre- and post-MRI CIED check, except for the one cancelled scan. Accordingly, peri-MRI CIED checks increased from 16 during the first FY quarter to 100 by the 8th quarter of the study, with the trend increasing until a decline in the final 2 quarters due to COVID-19 restrictions on clinical activity (Figure 2B). During the study period, total institutional MRI scan burden increased each year, from 12,050 in FY17/18 to 15,720 in FY18/19 and 16,744 in FY19/20 (Supplementary Appendix 2). The proportion of MRI scans for CIED patients requiring device checks also increased each year from 0.5% (n=66) to 0.9% (n=138) and 1.0% (n=166) respectively (Supplementary Appendix 2). The proportion of these peri-MRI CIED checks for

outpatients increased each year (central figure), from 23% (n=15 of 66) in FY17/18 to 37% in both FY18/19 (n=51 of 166) and FY19/20 (n=61 of 138).

Peri-MRI time burden of CIED checks

The median time interval from completion of the pre-MRI scan CIED check report to completion of the post-MRI scan CIED check report was 70 minutes (IQR 53 - 92). Of the 369 MRI scans, 75% (n=276) had pre- to post-MRI intervals of between 30 - 90 minutes, and only 9% (n=33) exceeded 120 minutes. The 75th percentile was used to define a long interval duration, but logistic regression did not identify any specific feature associated with having long interval between pre- to post-MRI scan CIED check (Supplementary Appendix Table S2) although MRI scan of the head region was significantly associated with not having a long interval duration.

Weekly burden of peri-MRI CIED checks

The peri-MRI CIED workload over the 3-year study was 661 hours (total 39,671 minutes), with a median of 200 minutes/week (IQR 92 – 404). The weekly workload burden for peri-MRI checks of CIED increased throughout the study as shown by linear regression ($p<.001$, Figure 3). Week-to-week variability in workload was noted with an overall increasing trend from less than 2 hours/week at the start of the study, up to approximately 7 hours/week by the end of the study. Univariate analysis identified patient, CIED, scheduling and MRI-scan related factors that were associated with high workload burden (Table 2). The only independent predictors in multivariate analysis were for weeks when MRI scans were performed for patients aged >75 years, newer generation CIEDs implanted after 2016 and occasions with long pre- to post-MRI CIED checks intervals (Table 2).

Economic burden of peri-MRI CIED checks

The calculated cost of providing peri-MRI CIED checks was $15,442, $32,275 and $39,760 for the 1st, 2nd and 3rd financial year respectively. The projected annual cost of this service will increase to $100,538 and $161,695 in 5 and 10 years respectively for an estimated 379 and 546 MRI scans per annum for patients with CIED patients as detailed in supplementary appendix.

3.4 DISCUSSION

This single-centre study of peri-MRI CIED checks over a 3-year period found an increasing number of MRI scans being performed for patients with CIEDs resulting in increased clinical workload and significant projected economic burden. There is marked week-to-week variability in the peri-MRI workload burden for CIED checks which highlights the challenge of appropriate resource allocation for this service with '*ad-hoc'* demand. Notably, 5.3% of these peri-MRI CIED checks were performed after-hours and we found that weeks with the highest workload burden were associated with MRI scans for older patients, newer generation CIEDs and longer MRI-scan intervals. In the setting of a growing workload burden, strategies are required to minimize its impact on the already over-stretched healthcare system.(146)

Rising burden of peri-MRI checks for CIED patients

Limited administrative data of MRI scans in select patients with CIEDs has shown an increasing proportion of MRI-conditional systems being implanted locally with low numbers of MRI scans performed in these patients up until 2015.(147) The data from our study confirms that among

an overall increasing number of MRI scans being performed, there is a growing proportion of patients with CIEDs. Although quarterly increases in the number of peri-MRI CIED checks were impacted by COVID-19 restrictions towards the end of our study period, the activity remained greater than any six-month period prior to 2019. The rising burden of peri-MRI CIED checks is in keeping with overseas experience where 28.5% of mostly North Americans patients with an MRI-conditional CIED system underwent a clinically indicated MRI scan during mean follow-up of only 26.6 months in a prospective large-scale multicentre study (n=2,629).(148) Consequently, the projected burden of MRI scans in patients with CIEDs and its associated cost over the next decade will require appropriate resource allocation to keep up with the projected service demand. As MRI scanning of patients with non-conditional legacy devices is likely to increase soon, even more resources will be required to ensure adherence to guideline recommended scanning and CIED checks protocol.(54, 55)

Variable peri-MRI CIEDs workflow: Need for improved service protocol

Mullane, et al. (68) reported an average MRI exposure time of 40.8 minutes as detected by internal sensors in CIEDs (n=2,197) of patients having clinically indicated MRI scans. In our study, the median time from completion of pre- to post-MRI CIED checks was 70 (IQR 53 – 92) minutes. The long and variable intervals between these checks represents potential reduced clinical productivity for the cardiac physiologists, especially when ad-hoc or unscheduled MRI scans are required for patients with CIEDs. To this end, several manufacturers have introduced specific programming solutions to improve peri-MRI CIEDs workflow efficiency allowing for pre-programming of pacing parameters that can be activated with a handheld device or automatically turned on in the presence of a strong magnetic field environment (Figure 5).(46, 67, 68) Not only could these features reduce the need for pre-MRI CIED checks,

the automatic reversion to normal pacing parameters post MRI scans and utilization of remote monitoring system to transmit a post-MRI scan report could further reduce the manual post-MRI CIED checks. However, these features tend to vary by device models and brands with different requisites regarding time window for pre-programming that may render scheduling for these not always possible and resulting in under-utilization. Some MRI units may prefer the affirmation of manual CIED checks and not all units utilize these automated features routinely. Standardization of these automated MRI programming features among device brands and models would help streamline these CIED checks. The use of remote access software imbedded in CIED programmers for MRI mode reprogramming has previously been explored and reported by one manufacturer, but issues exist regarding cybersecurity limiting the uptake of this strategy in clinical workflow.(149) However, there is a scope for protocol driven implementation of these CIED features that would allow for more flexible scheduling of MRI scans and improved efficiency of peri-MRI CIED checks.

Several other strategies could be considered from the service provision aspect to improve workflow efficiency. First, prior screening of CIEDs and patients' suitability for MRI scans is paramount to ensure appropriate patient selection. Second, dedicated scheduling of MRI list for patients with CIEDs on the same day or even by CIED manufacturers can allow more efficient use of CIED clinicians' time. Third, scheduling of MRI scans should be avoided outside of business hours to minimise waiting times and additional expenses related to overtime rates. Last, a team-based approach operating at dedicated MRI facility for patients with CIEDs is required as others have shown it markedly improved volume and reduced waiting times for MRI examinations in these patients.(66) Taken together, although improved protocol, scheduling and automated CIEDs pre-programming checks are useful to improve service

delivery, there will remain a growing workload burden which requires appropriate allocation of clinician resources by healthcare services.

Study Limitations

Our single-centre data provides findings from a real-world experience but variability in practices between different healthcare services would need to be taken into consideration. The use of retrospectively obtained data is a limitation but this would not have impacted on the increasing trend seen over the study period. The workload burden we have reported underestimates the overall clinical impact imposed by MRI scanning in patients with CIEDs as we have not incorporated pre-MRI assessment of patient and CIED suitability that is done by referring physician and Radiology department prior to Cardiology involvement. Similarly, we have not included occasions of CIED checks which were requested to determine MRI conditionality prior to even requesting for an MRI scan.

3.5 CONCLUSIONS

This study provides previously unreported evidence of an increasing workload and workflow burden imposed by fulfilment of CIED requirements in the peri-MRI scan settings. Appropriate budgeting and allocation of staffing resources is required and standardization of automated CIEDs pre-programming features across manufacturers in the peri-MRI scan setting will help to reduce the impact of the ever-increasing number of patients with CIEDs needing MRI scans

3.6 TABLES & FIGURES

Table 1: Baseline characteristics

		Patients, n=295 (%)
Age		median 77 (IQR 69 – 85) years old
Male		189 (64.0)
CIED		median 2 (IQR 1 - 4) years in-situ
Type	Permanent Pacemaker	258 (87.5)
	Implantable cardioverter-defibrillator	37 (12.5)
Brand	Medtronic	158 (53.6)
	Boston Scientific	48 (16.3)
	Abbott / St Jude	45 (15.2)
	Biotronik	44 (14.9)
Medical History		
	Hypertension	146 (49.5)
	Atrial Fibrillation	117 (39.7)
	Dyslipidaemia	86 (29.2)
	Diabetes Mellitus	83 (28.2)
	Ischaemic Heart Disease	82 (27.8)
	Stroke of transient ischaemic attack	72 (24.5)
	Gastrointestinal Disease	62 (21.1)
	Neurological Disease	62 (21.1)
	Cancer	49 (16.7)
	Valvular Heart Disease	49 (16.7)
	Osteoarthritis	46 (15.6)
	Respiratory disease	43 (14.6)
	Congestive Heart Failure	37 (12.6)
	Renal Failure	35 (11.9)
	Rheumatological Disease	26 (8.9)
	Endocrine Disease	24 (8.2)
	Haematological Disease	18 (6.2)
	Obstructive Sleep Apnoea	16 (5.5)
	Venous thromboembolism	16 (5.5)
	Peripheral Vascular Disease	11 (3.8)

Table 2: Factors associated with high burden (>200minutes) of weekly peri-MRI CIED checks workload

		Univariate			Multivariate		
Category	**Factor** (occurred during week)	**OR**	**95% C.I.**	**P value**	**OR**	**95% C.I.**	**P value**
Patient	Aged >75years	30.2	4.0 - 227.2	.001	17.1	2.0 - 144.1	.009
CIED	Implantable cardioverter-defibrillator	3.4	1.5 - 7.7	.003	1.7	0.6 - 4.7	.33
	Implant date after 2016	27.2	3.6 - 205.0	.001	12.6	1.5 - 104.2	.019
Scheduling	After-hours	3.5	1.1 - 11.6	.04	3.1	0.6 - 16.3	.19
	Outpatient elective MRI	5.7	2.2 - 14.7	>.001	3.0	0.9 - 10.0	.079
MRI	Head region	19.7	2.6 - 148.8	.004	5.9	0.5 - 67.5	.15
	Heart region	1.3	0.5 - 3.3	.644	-	-	-
	Pre- to Post-MRI interval of longer than median (>70minutes)	16.3	3.7 - 70.6	>.001	7.2	1.5 - 35.3	.016

FIGURE LEGENDS

Figure 1: MRI scans performed for CIED patients by anatomical region of interest.

Figure 2: Burden of MRI scans for CIED patients each quarter during the study period, A) MRI scans performed for inpatients and outpatients, B) number of CIED checks required.

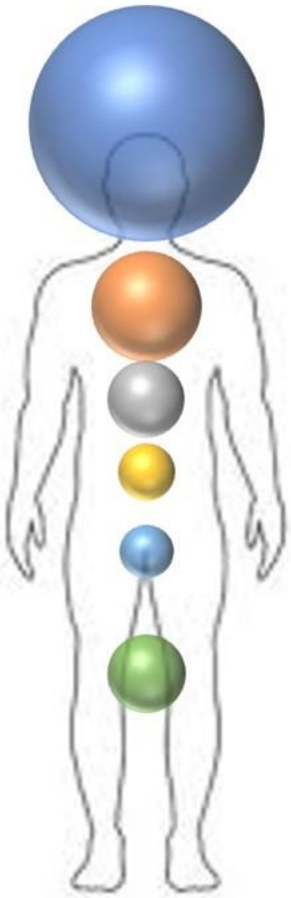
Figure 3: Workload burden per week for fulfilment of CIED conditionality to facilitate MRI scans throughout study period.

Figure 4: Service provision costing and projection.

Figure 5: Manufacturer specific CIED workflow options for MRI scan.

Central figure: Study summary.

Figure 1: MRI scans performed for CIED patients by anatomical region of interest.



Head, 238 (64.3%)

Spine, 52 (14.1%)

Heart, 25 (6.8%)

Abdomen, 14 (3.8%)

Pelvis, 12 (3.2%)

Limb/s, 26 (7.0%)

Not performed, 3 (0.8%)
- aborted prior to imaging, 2
- abandoned due to CIED, 1

Figure 2: Burden of MRI scans for CIED patients each quarter during the study period, A) MRI scans performed for inpatients and outpatients, B) number of CIED checks required.

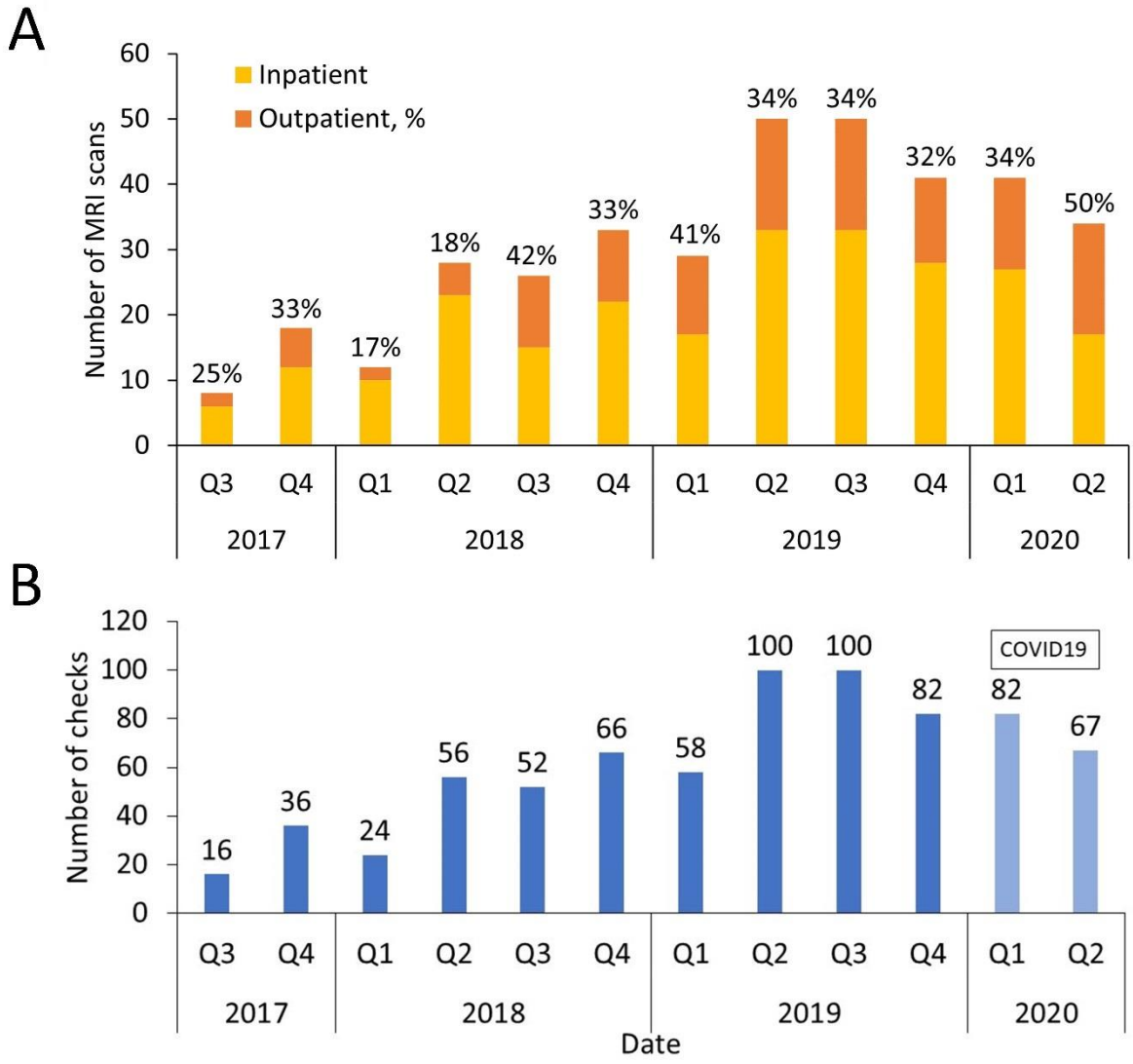


Figure 3: Workload burden per week for fulfilment of CIED conditionality to facilitate MRI scans throughout study period.

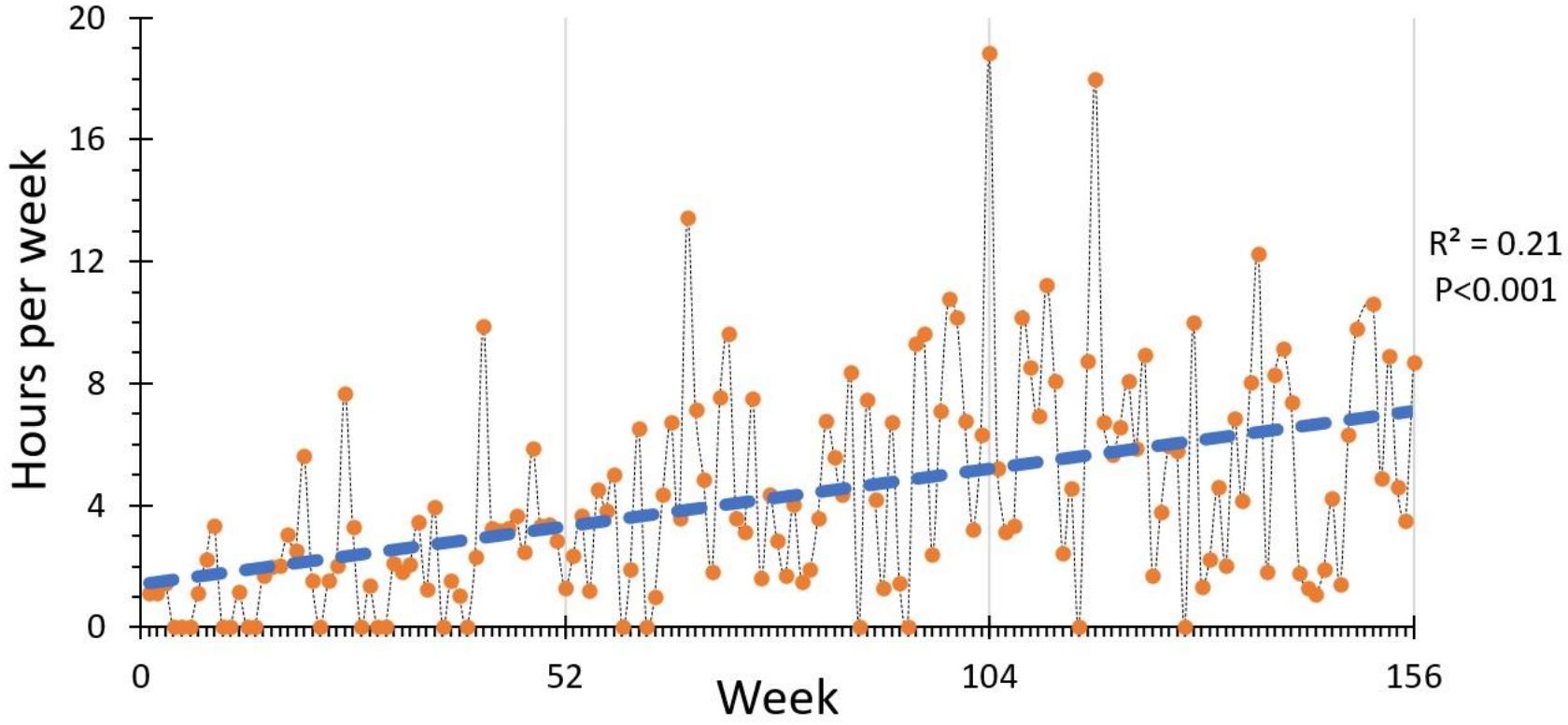


Figure 4: Service provision costing and projection.

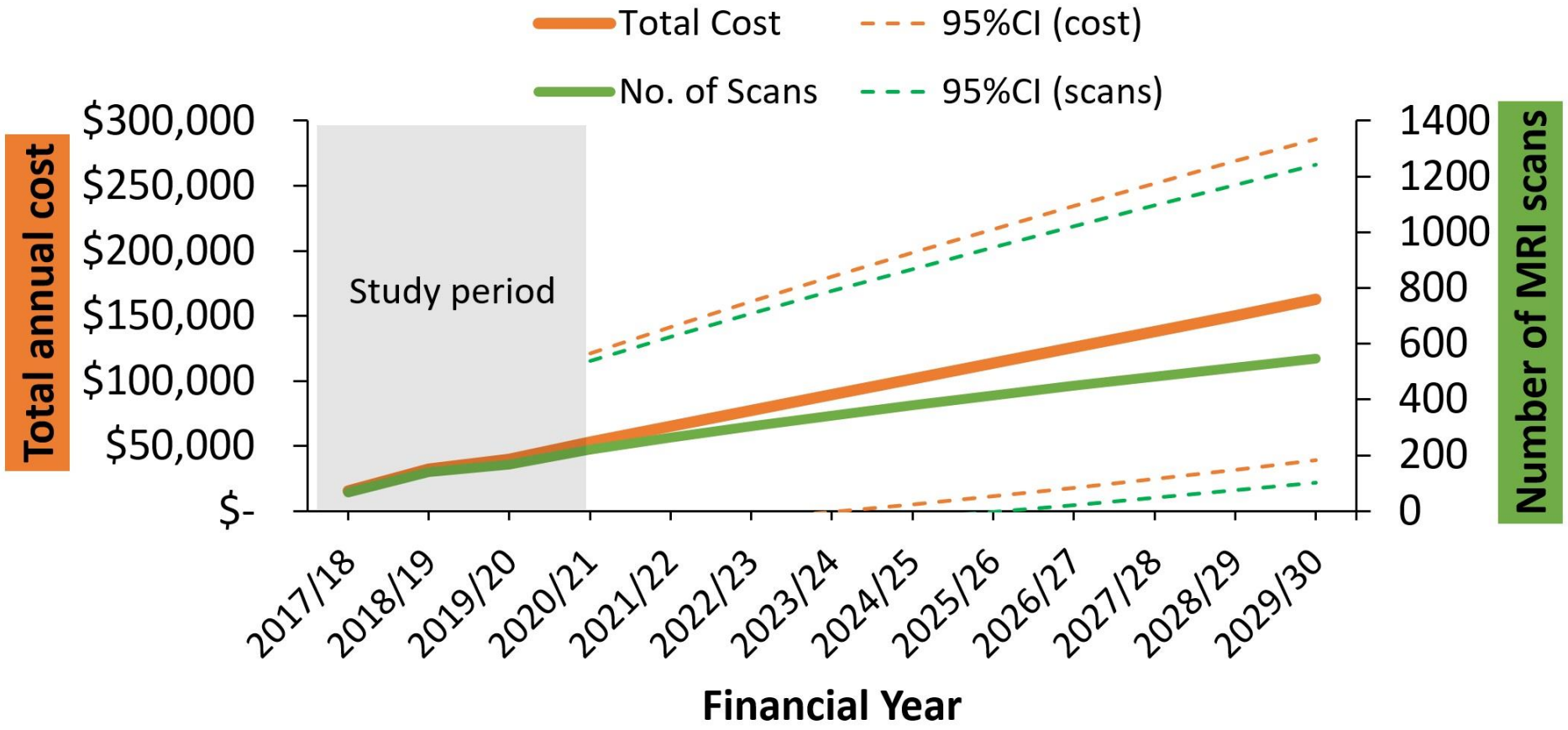


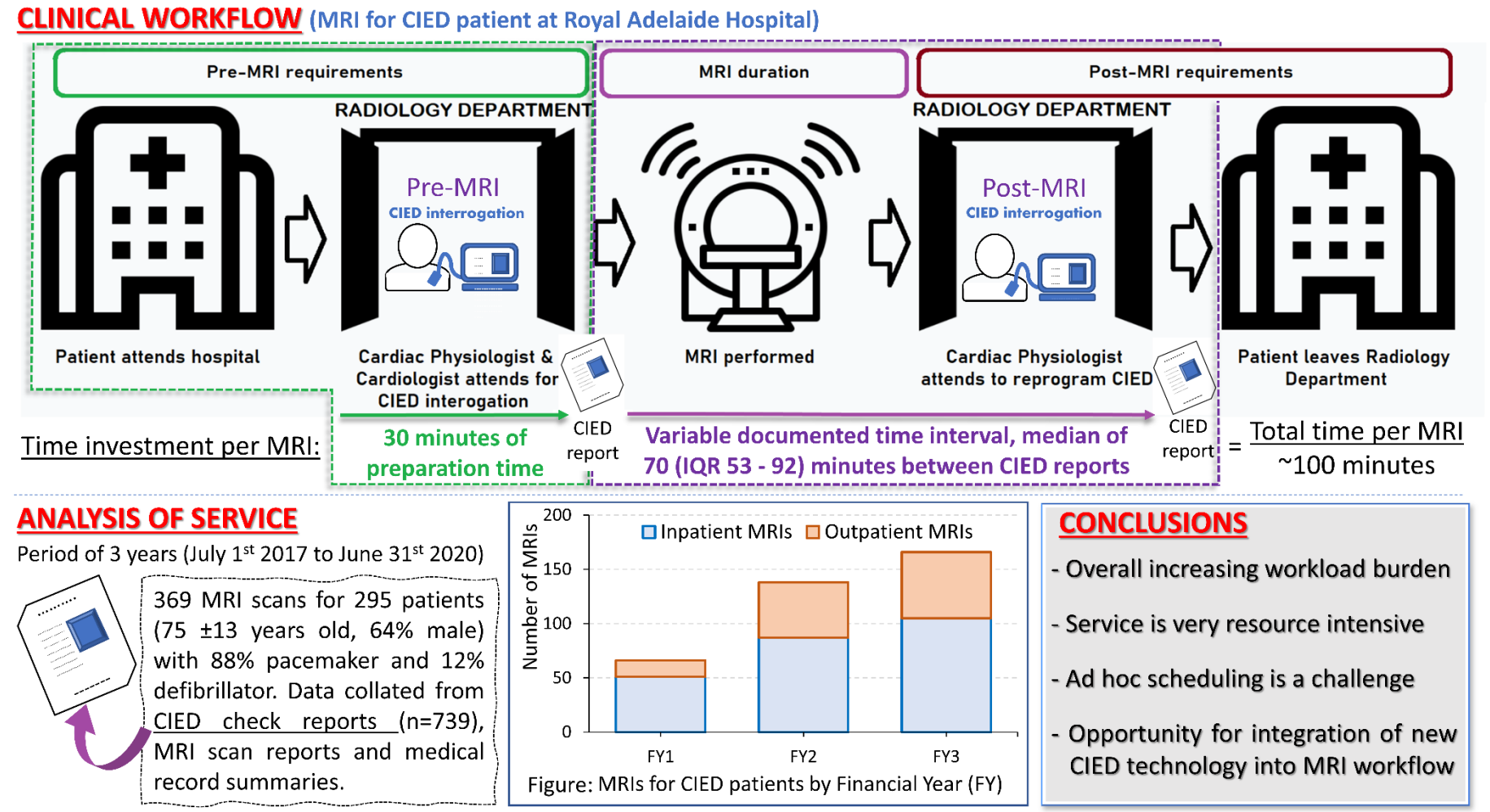
Figure 5: Manufacturer specific CIED workflow options for MRI scan.

Manufacturer	Online product listing of available devices and leads	Programmer interrogation to facilitate MRI conditionality	**Pre-MRI** mode activation options other than programmer interrogation	**Post-MRI** mode dis-enable options other than programmer interrogation	Post-MRI check options other than programmer interrogation
Medtronic Surescan™	https://www.medtronic.com/us-en/healthcare-professionals/mri-resources/	At occasion of MRI-scan only	✖ N/A	☑ ICD or CRT-D only; Timeout*	
Abbott/St. Jude MRI ready	https://mri.merlin.net	Interrogation required to "Setup MRI Activator", or At occasion of MRI-scan "Setup for MRI Now"	 SJM MRI Activator™ handheld device Model EX4000	☑ SJM MRI Activator™ Model EX4000	
Biotronik ProMRI™	https://www.promricheck.com	Interrogation to enable MRI AutoDetect with in 14 days of MRI scan, or at occasion of MRI-scan manual activation of MRI mode	ProMRI® MRI AutoDetect, switches to MRI AutoDetect sensor will switch to the MRI programming mode only when the MR environment field is detected within 14 day window of activation.	☑ If MRI AutoDetect is used, the CIED sensor will detect absence of MRI environment post scan and restore settings.	
Boston Scientific ImageReady™	https://www.bostonscientific.com/imageready/en-US/model-lookup.html	At occasion of MRI-scan only "Enable MRI Protection"	✖ N/A	☑ Programmable Time-out window, between 3 – 48hours	
Microport/Sorin AutoMRI™	https://www.crm.microport.com/therapies/automri	Interrogation required for MRI mode to be set to 'Auto' and time window for strong magnetic field detection is set (up to 48 hours)	AUTOMRI™ Patient enters MRI: Device detects strong magnetic field and automatically switches to asynchronous mode	☑ 5 minutes after MRI: Device automatically switched back to initial settings	

* : SureScan Timeout in defibrillation and CRT-D systems is a safety feature to ensure patients are not sent home without programming MRI SureScan "OFF." When programmed into SureScan mode the 6-hour timeout is activated; when this timeout period ends the device automatically returns to the pre-scan settings.

Central figure

CHECK-MRI study central figure



3.7 SUPPLEMENT

Appendix 1: Methods (costing analysis)

The Cardiac Physiologist (CIED clinician) expense was taken from Allied Health Professional (AHP) annual rates of salary in the current public sector salaried enterprise bargaining agreement (EBA). To ensure that a fair representation of the skill levels of the Cardiac Technicians that undertake the CIED check, the annual rates for five Classification levels: AHP201, AHP203, AHP206, AHP301 and AHP304 were collated. The Cardiologist expense was taken from Consultant rates were taken from South Australian Salaried Medical Officers Association. The single classification of MD029G was used for the Consultant costs. At the time of analysis, both the AHP and the Medical EBA had expired, and there are no annual salary rates published beyond 2021 for both groups. For the Consultant group, a comparison of the annual salaries effective April every year showed an annual rate of increase in salary of 2.5% per annum.

The Annual Rate for each Classification was divided by 52.1786 (to provide the weekly rate) then divided by the standard hours worked of 37.5 to produce the Base Hourly Rate. Other payroll costs including superannuation, leave provisions, allowance and penalties were calculated as a percentage of the Base Hourly Rate. For the AHP Classifications an average rate of 13% for On-Costs was then applied to the Base Hourly Rate to provide a Total Hourly Cost. For the Consultant, an On-Cost rate of 65% was applied. This higher rate occurs due to the Allowances paid to Consultants.

The Australian Bureau of Statistics has published a 1.6% Annual percentage change for the Consumer Price Index (CPI) at June 2021. While CPI is a factor in the setting of annual salaries, the study has chosen to use a 2.5% increase in Consultant salaries when modelling future years. Similar comparison on the Annual Rate for the AHP staff showed an average increase of 1.98% per annum. The study has chosen to use a 2% increase in AHP salaries when modelling future years.

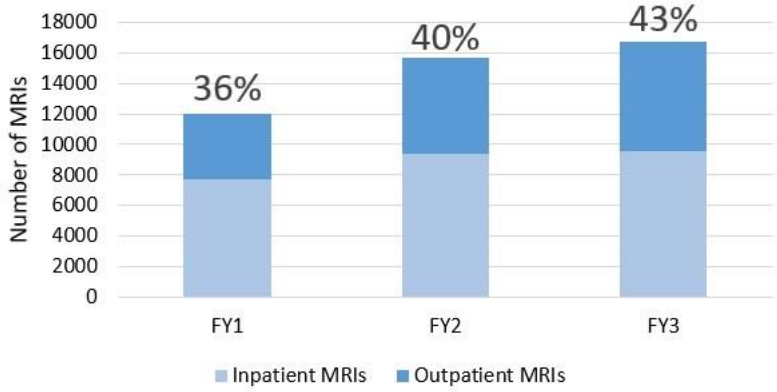
Our data indicated that most of the work was undertaken during normal working hours (95%) with ~5% undertaken outside of normal hours. Staff are paid at penalty rates for any work outside of normal hours. It was shown that 4.5% of all work was undertaken either after hours on Monday to Friday or on Saturday, falling into the Overtime at Time and a Half category, and 0.5% of all work was being undertaken on Sundays (considered Overtime at Double Time). For each year in the 10-year Projection, the annual number of scans expected was allocated across “Normal”, “OT @ 1.5” and “OT @ 2” at the appropriate rate. There is a minimum three hour call after hours and on weekends, and AHP clinicians called in to undertake a CIED check will receive a minimum of three hours pay at the appropriate penalty, and there is then relevant recall rates for medical Consultants.

Analysis of the variance in cost of the upper and lower limits of the Pre- to Post-MRI checks of CIED reflecting time allocation of the Cardiac Physiologist was undertaken, however the Standard Error of 1.98 minutes drives a $10,362 (<0.9%) variance in the estimated Total Cost of the service provision, which is not considered material.

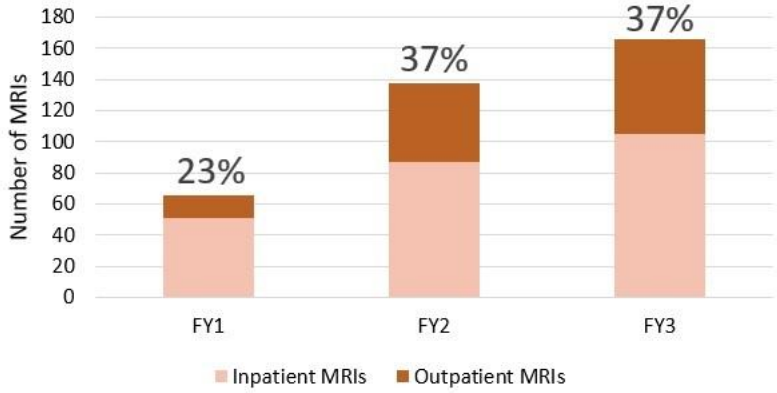
Logarithmic projection (Appendix3) of the number of MRI scans was performed as well as the percentage of those who will be for patients that have CIED insitu. This was used to estimate the number of future expected peri-MRI CIED checks, allowing projection of the annual cost (Figure 4, and detailed in Appendix table S1 panel A and B).

Appendix 2 (administrative coding data)

A



B



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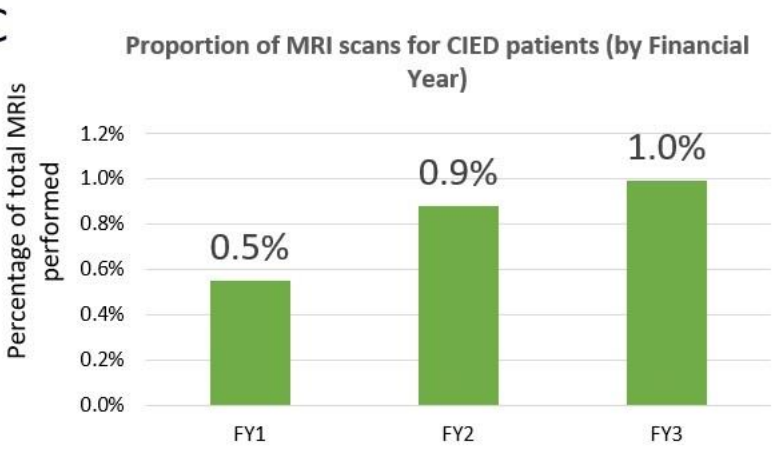
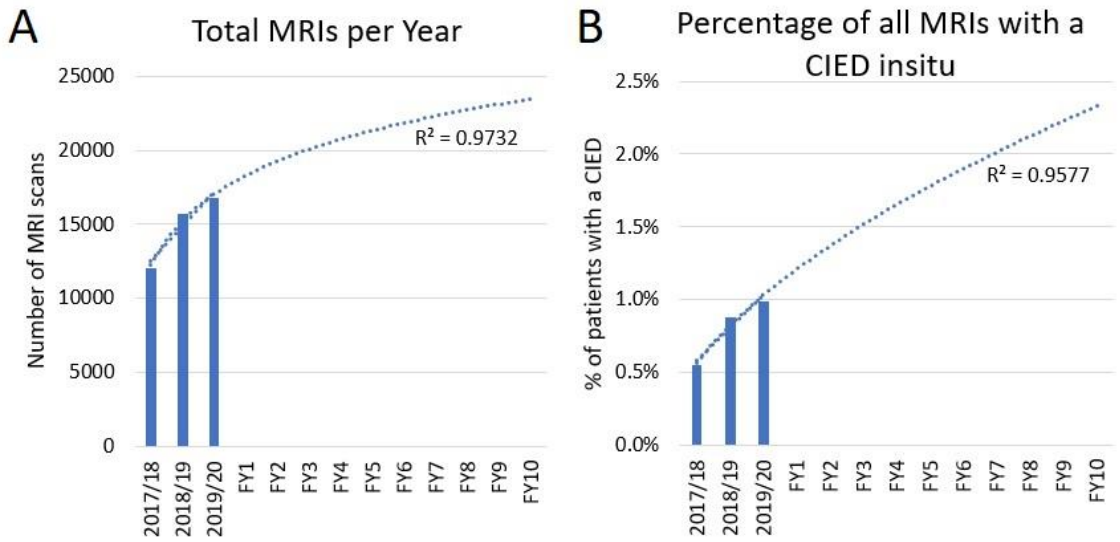


Appendix 3 (service modelling for costing projection)



Table

Year	Total MRI service All MRIs (modelling graph A) "Value ***T***"	Annual difference	Annual Δ proportion	CIED patients Percentage of MRI patients who have CIED (modelling graph B) "Value ***P***"	No. of MRI Scans for CIED patients, formula = ***T*** x ***P***
2017/18	12050	-	-	0.5%	**66**
2018/19	15720	3670	30.5%	0.9%	**138**
2019/20	16744	1024	6.5%	1.0%	**166**
2020/21	18296	1552	9.3%	1.2%	**221**
2021/22	19274	978	5.3%	1.4%	**264**
2022/23	20073	799	4.1%	1.5%	**304**
2023/24	20748	676	3.4%	1.6%	**342**
2024/25	21334	585	2.8%	1.8%	**379**
2025/26	21850	516	2.4%	1.9%	**414**
2026/27	22312	462	2.1%	2.0%	**449**
2027/28	22729	418	1.9%	2.1%	**482**
2028/29	23111	381	1.7%	2.2%	**514**
2029/30	23461	351	1.5%	2.3%	**546**

Table S1. Cost projections. Panel A, Total annual service cost calculations

Year	MRI scans			Applicable pay rates			Combined expense at each pay rate (addition of AHP and Consultant wage, see table B below)			Total cost
	No. of MRI Scans from modelling	Delta No. of MRI scans	% Increase	Normal, 1.0x rate (95% of occasions)	Penalty* A, 1.5x (4.5% of occasions)	Penalty# B, 2.0x (0.5% of occasions)	Normal 1.0x rate (95% of occasions)	Penalty* A, 1.5x rate (4.5% of occasions)	Penalty# B, 2.0x rate (0.5% of occasions)	Provision of service, 100% (all occasions of service)
2017/18	**66**			63	3	zero	$ 12,540.98	$ 2,129.92	zero	**$ 15,441.82**
2018/19	**138**	72	109%	131	6	1	$ 26,307.01	$ 4,307.19	$ 889.45	**$ 32,274.57**
2019/20	**166**	28	20%	158	7	1	$ 32,890.95	$ 5,158.70	$ 911.18	**$ 39,759.75**
2020/21	**221**	55	33%	210	10	1	$ 44,712.14	$ 7,510.44	$ 928.02	**$ 53,964.05**
2021/22	**264**	43	19%	251	12	1	$ 54,932.76	$ 9,211.37	$ 947.41	**$ 65,925.30**
2022/23	**304**	40	15%	289	14	2	$ 64,370.32	$ 10,922.17	$ 1,925.63	**$ 78,061.73**
2023/24	**342**	38	13%	325	15	2	$ 74,039.93	$ 11,927.92	$ 1,961.57	**$ 88,788.67**
2024/25	**379**	37	11%	360	17	2	$ 83,884.65	$ 13,779.64	$ 1,998.28	**$ 100,537.85**
2025/26	**414**	35	9%	394	19	2	$ 93,902.28	$ 15,699.28	$ 2,035.80	**$ 112,529.08**
2026/27	**449**	34	8%	426	20	2	$ 103,846.53	$ 16,846.73	$ 2,074.13	**$ 123,675.95**
2027/28	**482**	33	7%	458	22	2	$ 114,196.52	$ 18,892.49	$ 2,113.29	**$ 136,128.14**
2028/29	**514**	32	7%	489	23	3	$ 122,979.58	$ 19,974.25	$ 3,208.72	**$ 147,088.38**
2029/30	**546**	32	6%	518	25	3	$ 135,124.73	$ 22,316.82	$ 3,291.29	**$ 161,694.52**

Panel B, Cost of support for each MRI scan (by applicable specialist rate)

Year	AHP wage rate (Technician/Physiologist)			Medical Consultant (Cardiologist)		
	If normal (1.0x rate)	If penalty* A (1.5x rate)	If penalty# B (2.0x rate)	If normal (1.0x rate)	If penalty* A rate	If penalty# B rate
2017/18	$ 88.44	$ 397.98	$ 530.63	$ 110.62	$ 312.00	$ 348.30
2018/19	$ 90.19	$ 405.87	$ 541.16	$ 110.62	$ 312.00	$ 348.30
2019/20	$ 91.95	$ 413.76	$ 551.68	$ 116.22	$ 323.20	$ 359.50
2020/21	$ 93.79	$ 422.03	$ 562.71	$ 119.13	$ 329.01	$ 365.31
2021/22	$ 95.66	$ 430.48	$ 573.97	$ 123.19	$ 337.14	$ 373.44
2022/23	$ 97.57	$ 439.08	$ 585.45	$ 125.16	$ 341.07	$ 377.37
2023/24	$ 99.53	$ 447.87	$ 597.16	$ 128.29	$ 347.33	$ 383.63
2024/25	$ 101.52	$ 456.82	$ 609.10	$ 131.50	$ 353.74	$ 390.04
2025/26	$ 103.55	$ 465.96	$ 621.28	$ 134.78	$ 360.32	$ 396.62
2026/27	$ 105.62	$ 475.28	$ 633.71	$ 138.15	$ 367.06	$ 403.36
2027/28	$ 107.73	$ 484.78	$ 646.38	$ 141.61	$ 373.96	$ 410.26
2028/29	$ 109.88	$ 494.48	$ 659.31	$ 141.61	$ 373.96	$ 410.26
2029/30	$ 112.08	$ 504.37	$ 672.49	$ 148.78	$ 388.30	$ 424.60

*** Penalty A: Overtime Saturday, has minimum 3hours call-back fee. # Penalty B: Overtime Sunday, has minimum 3hours call-back fee.**

Table S2: Factors associated with long pre- to post-MRI CIED checks intervals (>92minutes; 75th percentile)

		Univariate		
Category	**Factor**	**OR**	**95%CI**	**P value**
Patient	Male gender	1.15	0.69 1.90	0.60
	Aged >75years	1.37	0.85 2.22	0.19
	Multiple MRIs during study	0.96	0.58 1.59	0.88
CIED	CIED insitu >2years	1.26	0.78 2.04	0.35
	ICD	0.46	0.19 1.13	0.09
	Medtronic	0.81	0.50 1.30	0.39
	Asynchronous programming	1.71	0.77 3.83	0.19
Scheduling	After-hours	2.73	0.89 8.35	0.08
	Outpatient MRI	0.86	0.52 1.42	0.56
MRI scan	Head region	0.49	0.30 0.80	0.004
	Heart region	0.56	0.19 1.68	0.30
	More than 4 sequences noted in MRI report	1.31	0.81 2.10	0.27

Statement of Authorship

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Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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Impact of device length on electrogram sensing in miniaturized insertable cardiac monitors

4 ABSTRACT

Background: Little data exists on electrogram sensing in current generation of miniaturized insertable cardiac monitors (ICMs).

Objective: To compare the sensing capability of ICM with different vector length: Medtronic Reveal LINQ (~40mm) vs. Biotronik Biomonitor III (BM-III, ~70mm).

Methods: De-identified remote monitoring transmissions from n=40 patients with BMIII were compared with n=80 gender and body mass index (BMI)-matched patients with Reveal LINQ. Digital measurement of P- and R-wave amplitude from calibrated ICM electrograms was undertaken by 3 investigators independently. Further, we evaluated the impact of BMI and gender on P-wave visibility.

Results: Patients in both groups were well matched for gender and BMI (53% male, mean BMI 26.7 kg/m2; both p=NS). Median P- and R-wave amplitude were 97% & 56% larger in the BM-III vs. LINQ [.065 (IQR .039-.10) vs. .033 (IQR .022-.050) mV, p<.0001; & .78 (IQR .52-1.10) vs. .50 (IQR .41-.89) mV, p=.012 respectively). The P/R-wave ratio was 36% greater with the BM-III (p<.001). The 25th percentile of P-wave amplitude for all 120 patients was .026mV. Logistic regression analysis showed BM-III was more likely than LINQ to have P-wave amplitude ≥.026mV (OR 7.47, 95%CI 1.965-29.42, p=.003), and increasing BMI was negatively associated with P-wave amplitude ≥.026mV (OR .84, 95%CI .75-.95, p=.004). However, gender was not significantly associated with P-wave amplitude ≥.026mV (p=.37).

Conclusion: The longer ICM sensing vector of BM-III yielded larger overall P- and R- wave amplitude than LINQ. Both longer sensing vector and lower BMI were independently associated with greater P-wave visibility.

4.1 INTRODUCTION

Implantable loop recorders are useful for longer term diagnosis and monitoring of heart rhythm disorders. Miniaturization of implantable loop recorders has led to the current generation of insertable cardiac monitors (ICMs).(83) The reduction in device size and simplification of implant procedure with dedicated insertion tools have allowed the insertion to be performed “in-office”.(150) Recent studies have shown that these ICMs are capable of high fidelity electrocardiogram recording with adequate signal amplitude for reliable sensing.(86, 103) However, the positive predictive value for ICM adjudicated atrial fibrillation (AF) events has been shown to be as low as 32.8% for patients with cryptogenic stroke, 59.5% for those with known AF, and 69.4% for those who have undergone AF ablation.(99) Newer ICM algorithms incorporating P-wave filtering and detection, in addition to irregularity and incoherence of R-R intervals, have proven more effective at detection of AF.(90, 97) Consequently, improved P-wave amplitude may potentially improve accuracy of atrial arrhythmia detection and reduce false alerts.(97)

Others have shown larger R-wave amplitude with longer sensing vector in older generation non-injectable loop recorders.(20) Little data exists on electrogram sensing in current generation of miniaturized ICMs. Here, we aim to compare the sensing capability of the Reveal LINQ (Medtronic, Minneapolis, MN, USA; sensing vector of ~40mm) and Biomonitor III (BM-III, Biotronik, Berlin, Germany; sensing vector of ~70mm) in terms of both P- and R-wave

amplitude as well as P-wave visibility (Figure 1).(83, 103) Further, we aim to evaluate the patient variables that may impact on P-wave sensing in these miniaturized devices with different sensing vector length.

4.2 METHODS

Data Collection

Forty-four subjects with BM-III implanted as part of the first-in-human BIO|CONCEPT.BIOMONITOR III study who had a remote monitoring transmission during sinus rhythm from the Biotronik Home Monitoring service were included. Four of these patients were excluded as height and weight data were unavailable to determine body mass index (BMI). We then matched these 40 patients, by gender and BMI and in a 1:2 ratio to subjects with sinus rhythm electrograms from their Reveal LINQ identified via our institution's Medtronic Carelink Home Monitoring service. The process did not take into account patients' co-morbidities and all remote monitoring PDFs were anonymized for subsequent electrogram analysis. This study has local institutional Human Research Ethics Committee approval (Ref 12327).

Data Analysis

The electrograms were randomly assigned to each investigator (n=40 per investigator at 1 BM-III:2 Reveal LINQ ratio). Additionally, n=12 (6 LINQ and 6 BM-III) electrograms from each investigator were re-assessed by a different investigator to determine inter-observer variability (Figure 2). Electrogram analysis was undertaken using the DigitizeIt© (V2.3.3, Braunschweig, Germany) digital analysis software. Gain settings were not adjusted from the

nominal setting (either 0.1mV or 1mV scale for LINQ, vs. variable 0.2mV scale for BM-III). Among the 80 Reveal LINQ, 30 were utilizing the first-generation software (implanted between June-2014 and March-2017) and 50 were utilizing newer generation TruRhythm^{TM} software (implanted between April-2017 and September-2019). All electrograms with their calibration plots were uploaded as image files into the software and analyzed independently by three investigators (BMP, RT and EJ). Following calibration of both the X-axis for duration (milliseconds, ms) and Y-axis for amplitude (milliVolts, mV), measurements were performed for 5 consecutive sinus beats. P-wave was measured from baseline to peak amplitude and QRS was measured from peak-to-peak (Figure 3). P-wave visibility was also assessed in a separate analysis by three electrophysiologists independently (KRT, GDY & CXW) and classified as 'visible', 'partially visible' or 'not visible'.

Statistical Analysis

Distribution of continuous variables were tested for normality with the Shapiro-Wilk test. Continuous data are expressed as means ± standard deviation, or median and interquartile range (IQR), and analysed for statistical differences by student's t-test, Mann Whitney U-test or Kruskal-Wallis test (ANOVA) with Sidak's adjustment for multiple comparisons. Categorical data are presented as percentages and analysed by Chi-square test. Inter-observer measurement variability was assessed using intraclass correlation analysis. BMI categories were defined as normal (up to 25 kg/m^2), overweight (>25 to 29.9 kg/m^2) and obese (≥30kg/m^2). Spearman's correlation analysis was used to evaluate association between BMI and P-wave amplitude. Logistic regression analysis was performed to assess the association of sensing vector length, gender and BMI with the dependent variable of P-wave amplitude

≥25th percentile. All statistical analysis was undertaken using SPSS (Version 27, IBM, Armonk, NY). A two-tailed P value of <0.05 was considered statistically significant.

4.3 RESULTS

The 120 patients (n=80 with Reveal LINQ and n=40 with BM-III) included in this analysis were well matched for gender (53% males for each; p=NS) and BMI (26.71 vs. 26.65 kg/m^2 for Reveal LINQ vs. BM-III respectively; p=NS). There were no significant differences in baseline characteristics, implant indication, co-morbidities, or arrhythmia history between groups (Table 1). Intra-class correlation analysis showed that inter-operator reproducibility of P-wave and R-wave measures were very good (ICC 0.91 and 0.88 respectively, both P<0.001).

Electrogram Amplitude

The overall median P-wave amplitude of the 120 patients was 0.041 (.026-.064) mV. Median P-wave amplitude was 97% larger with the BM-III as compared to Reveal LINQ (Figure 4A, .065(.039-.10) vs. .033(.022-.050) mV; p<.0001). Specifically, 7.5% (3/40) of BM-III and 33.8% (27/80) of LINQ patients had P-wave amplitude below the 25th percentile (.026 mV). Median R-wave amplitude was 56% larger with the BM-III (Figure 4B, .78(.52-1.10) vs. 0.50(.41-.89) mV; p=.012). The P/R-wave ratio was 36% greater with the BM-III (Figure 4C, p<.001). The average P/R-wave ratio for BM-III had P-wave of only 10% that of the R-wave, which maintains sufficient P- and R-waves differentiation.

Impact of Gender and BMI on electrogram amplitude

There was no difference in R-wave amplitude between gender (p=.65). R-wave amplitude differed for BMI categories with smaller R-waves seen for obese BMI compared to overweight

BMI and normal BMI patients [.427 (.300-.651) vs. .612 (.468-.950) vs. .663 (.427-1.115) mV; p=.046]. The median P-wave amplitude was larger in males than females (Figure 5A, .046 (.027-.72) vs. .034 (.022-.050) mV, p=.03). Similarly, P-wave amplitude differed for BMI categories, with smaller P-waves seen for obese BMI compared to overweight BMI and normal BMI [.026 (.019-.042) vs. .041 (.027-.068) vs. .043 (.032-.063) mV; p=.043).

Impact of sensing vector length on P-wave amplitude

The P-wave amplitude was larger in the BM-III than Reveal LINQ although this was only statistically significant in male (difference .040 (.021-.059) mV, p<.001; Figure 5B) but not in female patients (difference .022 (.002-.045) mV, p=.178). A significant negative association between increasing BMI and P-wave amplitude was evident for the Reveal LINQ but not for the BM-III (Spearman's rho -.306, p=.006 and -.138, p=.4 respectively; Figure 6). Logistic regression analysis showed BM-III was more likely than Reveal LINQ to have P-wave amplitude ≥.026mV (OR 7.47, 95%CI 1.97-28.42, p=.003), and increasing BMI was negatively associated with P-wave amplitude ≥.026mV (OR .84, 95%CI .75-.95, p=.004). However, gender was not significantly associated with P-wave amplitude ≥.026mV (p=.37).

P-wave visibility

Independent adjudication undertaken by three electrophysiologists found P-wave to be 'not visible' or 'partially visible' in 16.3-48.8% of Reveal LINQ and 5.0-27.5% of BM-III electrograms (Table 2). Interobserver reliability of P-wave visibility assessment had an intraclass correlation coefficient of .81 (95%CI .74-.86). Overall P-wave visibility was better with the BM-III vs. Reveal LINQ (85.8 vs. 71.2%, p=.002). There were 17 Reveal LINQ traces with 1mV scale, all having R-wave >0.9mV amplitude, which were adjudicated to have 'not visible' or 'partially

visible' P-waves in 47.1-88.2%. The proportion with 'not visible' or 'partially visible' P-waves was significantly greater with the 1mV as compared to those with fixed 0.1mV Reveal LINQ traces (Table 2). P-wave visibility was found to be improved with the newer-generation TruRhythm^{TM} software version of the Reveal LINQ (Table 2), but this remains inferior when compared to the BM-III (76.0 vs. 85.8%, p=.043). The minimum P-wave amplitude in traces with adjudicated visible P-waves were .016mV for the BM-III, .016mV for the Reveal LINQ (0.1mV scale) and .041mV for the Reveal LINQ (1mV scale). These translated to minimum P/R-wave ratio of 1.5 vs. 3.7 vs. 3.5% respectively.

4.4 DISCUSSION

This study evaluated the sensing capability of latest generation miniaturized ICMs with principal finding of larger P- & R-wave amplitude and greater P-wave visibility with the longer sensing vector of the BM-III as compared to the Reveal LINQ. Additionally, we found that increasing BMI, female gender and shorter sensing vector of the Reveal LINQ device were independently associated with lower P-wave amplitude. It is well established that signal amplitude correlates with inter-electrode spacing as seen in precordial, epicardial and intracardiac mapping studies and the differences between the two ICMs can be accounted for by the ~30mm difference in their sensing vector.(151-153) Although more work is needed to incorporate P-wave detection into automated device algorithms, larger P-wave amplitude is likely to facilitate improved atrial arrhythmia discrimination either manually or using artificial intelligence..

Sensing capability of ICMs

The miniaturization of devices has led to the latest generation of 'injectable' ICMs with dedicated insertion tools. These ICMs are capable of high-fidelity electrocardiogram recording with adequate signal amplitude as compared to previous generation implantable loop recorders with mean R-wave amplitude ranging between ~0.6 to 1 mV.(86, 100, 103, 154) However, data on P-wave amplitude is more limited with studies mainly reporting on P-wave visibility. Specifically, P-wave was found to be detectable in 48% of Reveal LINQ tracings from a paediatric cohort (mean age 11.8 years old), in 100% of CONFIRM RX tracings from 29 paediatric patients (median age 8 years old) and in close to 90% of all sinus rhythm cardiac cycles from BM-III tracings (mean age 64 years old).(96, 103, 155) Our study adds to the existing literature by providing comparative P-wave amplitude measurements and P-wave visibility data between ICMs of different vector length.

Prolonged rhythm monitoring with ICM is now an established indication for atrial fibrillation (AF) detection in patients with embolic stroke of undetermined source following the landmark CRYSTAL-AF (Cryptogenic Stroke and Underlying Atrial Fibrillation) study.(91) The AF detection algorithm is known to vary according to device manufacturers with criteria such as cycle length variability, probability score and Lorentz plot.(89, 90, 93) However, the automated arrhythmia detection ability of ICMs is known to be improved when there is incorporation of P-wave detection in the algorithm.(97) Notably, the inclusion of a P-wave filter leveraging on the evidence of a single P-wave between two R-waves, applied after the original R-R interval pattern–based algorithm, improved the performance of the AF detection algorithm in Reveal LINQ.(90) Further, larger P-wave amplitude may also aid deep neural network filtering to improve artificial intelligence based solution that has recently been shown to have higher positive predictive value in AF detection.(99) Taken together, improved

AF detection may help to reduce the high incidence of false positive alerts (up to 86%) as well as a disproportionately high burden of alerts from implantable loop recorders as compared to pacemakers and implantable cardioverter-defibrillators.(18, 156, 157) Naturally, improved P-wave visibility will also aid clinician's interpretation of other atrial arrhythmias such as atrial flutter and tachycardia.

Impact of gender and BMI on ICM signals

The impact of body composition on sensing amplitude from ICMs has been examined in earlier studies. Data from the Reveal LINQ suggests a direct relationship between BMI and sensed R-wave where R-wave amplitude was lower with higher BMI.(93) In the older generation BioMonitor 2 ICM with longer device length of 88mm, BMI did not impact on R-wave amplitude or P-wave visibility.(101) Our data adds to the existing literature as we found a weaker correlation between P-wave amplitude and increasing BMI with longer sensing vector of the BM-III as compared to the Reveal LINQ. We also observed significantly smaller P-wave amplitude in female patients, which may reflect anatomical and body composition limitations when compared to males. As there was no significant difference between baseline clinical characteristics of the patient groups, it is unlikely that our observed difference in P-wave amplitude and visibility was due to underlying clinical factors.

Impact of home monitoring software calibration on P-wave visibility

Electrograms were downloaded from respective home monitoring platform with nominal gain settings. The gain settings of Reveal LINQ were found to be fixed at either 0.1mV or 1mV scale. All 1mV scale traces had R-wave amplitude greater than 0.9mV, which significantly impacted the P-wave visibility, requiring a minimum P-wave amplitude of 0.041mV as compared to only

0.016 mV for 0.1mV scale traces. However, the gain settings of the Reveal LINQ could be manually adjusted on the home monitoring platform prior to exporting of the report to improve P-wave visibility. In comparison, the BM-III traces had variable scale which automatically optimized to the P- and R-wave amplitude to provide better visibility. This allowed a minimum P/R-wave ratio as low as 1.5% as compared to the 3.5-3.7% in the Reveal LINQ for better P-wave visibility.

Clinical Implications

Our study shows that the longer sensing vector of the BM-III provides superior P-wave amplitude which may improve P-wave visualization for better rhythm discrimination in the clinical setting. Incorporation of P-wave information in automated arrhythmia detection algorithm is needed as this is not being used by all device manufacturers. Improved P-wave detection may translate into improved AF detection and reduced remote monitoring false alerts, which has demonstrated significant clinical burden in the face of growing ICM use. Further prospective studies are needed to determine the clinical impact of larger ICM P-wave amplitude on atrial arrhythmia detection and discrimination.

Study Limitations

Our data is limited by the small number of patients with an implanted BM-III and its retrospective design. Further, we do not have information on patients' cardiac structural/functional data as well as device implant location/orientation, which may also affect P- and R-wave amplitude. Further, we did not evaluate the impact of increased sensing amplitude on the adjudication of arrhythmia episodes.

4.5 CONCLUSION

The BM-III with longer sensing vector achieved larger overall P- and R-wave amplitude compared to the Reveal LINQ. Additionally, increasing BMI and the shorter sensing vector of the Reveal LINQ device were independently associated with lower P-wave amplitude.

4.6 TABLES & FIGURES

Table 1: Baseline patient characteristics

	Biomonitor III, n=40	Reveal LINQ, n=80	P-value
Age in years, median (IQR)	66 (54-74)	67 (49-72)	0.47
Body mass index in kg/m^2, median (IQR)	27 (25-28)	27 (25-28)	0.99
Implant indication			
AF monitoring, n (%)	11 (27.5)	16 (20.0)	0.36
Palpitations, n (%)	0 (0.0)	7 (8.8)	0.09
Syncope/presyncope, n (%)	23 (57.5)	44 (55.0)	0.79
Cryptogenic stroke, n (%)	6 (15.0)	13 (16.2)	0.86
Medical history			
Heart failure, n (%)	2 (5.0)	7 (8.8)	0.46
Ischemic heart disease, n (%)	5 (12.5)	12 (15.0)	0.71
Hypertension, n (%)	21 (52.5)	42 (52.5)	0.99
Dyslipidemia, n (%)	21 (52.5)	31 (38.8)	0.15
Stroke or transient ischemic attack, n (%)	9 (22.5)	10 (12.5)	0.16
Peripheral vascular disease, n (%)	1 (2.5)	1 (1.3)	0.61
Renal disease, n (%)	1 (2.5)	2 (2.5)	0.99
Sleep disordered breathing, n (%)	2 (5.0)	10 (12.5)	0.20
Diabetes mellitus, n (%)	3 (7.5)	11 (13.8)	0.31
Anemia, n (%)	1 (2.5)	1 (1.3)	0.61
Malignancy, n (%)	3 (7.5)	6 (7.5)	0.99
Arrhythmia history			
Sick sinus syndrome or sinus node disease, n (%)	1 (2.5)	6 (7.5)	0.27
Atrioventricular block, n (%)	4 (10.0)	4 (5.0)	0.33
Atrial fibrillation, n (%)	11 (27.5)	26 (32.5)	0.56
- Paroxysmal, n (%)	7 (17.5)	20 (25.0)	0.38
- Permanent or persistent, n (%)	4 (10.0)	4 (5.0)	0.30
Ventricular tachycardia, n (%)	1 (2.5)	4 (5.0)	0.17

Table 2: P-wave visibility adjudication

Investigator	1		2		3		Combined		P-value
	BM-III (n=40)	**LINQ** (n=80)	**BM-III** (n=40)	**LINQ** (n=80)	**BM-III** (n=40)	**LINQ** (n=80)	**BM-III**	**LINQ**	(BM-III vs. LINQ)
All traces (n=120)									
Not visible	2	6	5	21	1	8	8/120 (6.7%)	35/240 (14.5%)	.038
Partially visible	0	7	6	18	3	9	9/120 (7.5%)	34/240 (14.2%)	.084
Not or *partially visible*	2 (5.0%)	13 (16.3%)	11 (27.5%)	39 (48.8%)	4 (10.0%)	17 (21.3%)	17/120 (14.2%)	69/240 (28.8%)	.002
Fixed scale traces (n=80)									
0.1mV scale (n=63) *Not* or *partially visible*	n/a	5 (7.9%)	n/a	24 (38.1%)	n/a	8 (12.7%)	n/a	37/189 (19.6%)	-
1mV scale (n=17) *Not* or *partially visible*	n/a	8 (47.1%)	n/a	15 (88.2%)	n/a	9 (52.9%)	n/a	32/51 (62.8%)	-
P-value (0.1mV vs. 1mV)		.0006		.0003		.001		.0001	
Reveal LINQ software (n=80)									
1st generation (n=30) *Not* or *partially visible*	n/a	7 (23.3%)	n/a	16 (53.3%)	n/a	10 (33.3%)	n/a	33/90 (36.7%)	-
TruRhythm™ (n=50) *Not* or *partially visible*	n/a	6 (12.0%)	n/a	23 (46.0%)	n/a	7 (14.0%)	n/a	36/150 (24.0%)	-
P-value (1st generation vs. TruRhythm™)		.219		.645		.0514		0.036	

FIGURE LEGENDS

Figure 1: Sensing vector length of the Biomonitor III and Reveal LINQ devices

Figure 2: Study methodology and analysis flow chart

Figure 3: Example of measurements performed in DigitizeIt software. Red calipers show calibration. Green calipers show amplitude measurements. Panel A; Medtronic Reveal LINQ. Panel B; Biotronik Biomonitor III

Figure 4: Median amplitude of (A) P-wave, (B) R-wave and (C) P/R-wave ratio for each ICM type. Whisker denotes 10-90% range

Figure 5: Median P-wave amplitude by (A) gender and (B) gender-ICM type. Whisker denotes 10-90% range

Figure 6: Dot plots of P-wave amplitude across the BMI range

Figure 1: Sensing vector length of the Biomonitor III and Reveal LINQ devices

Figure 2. Study methodology and analysis flow chart

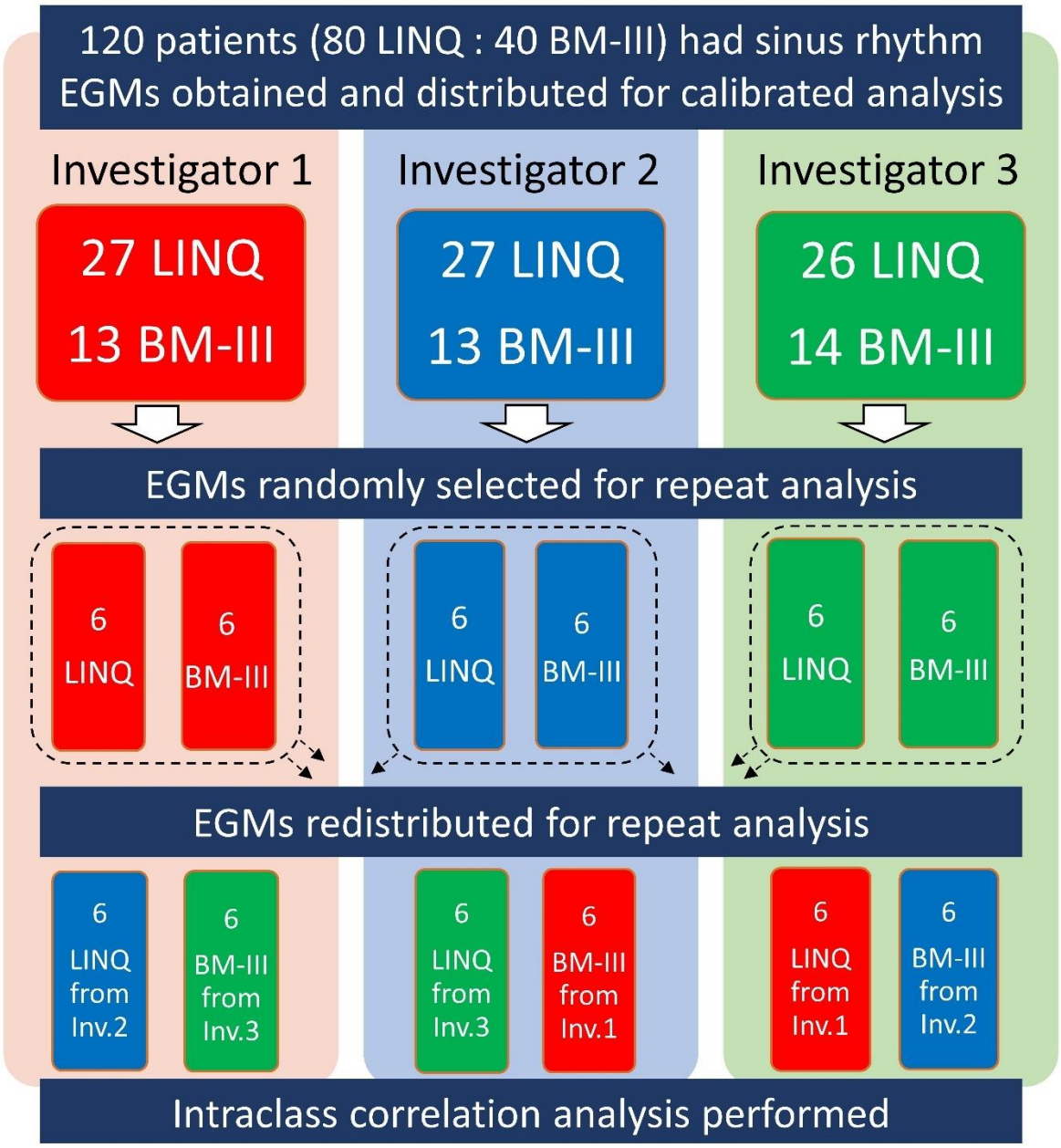


Figure 3. Example of measurements performed in DigitizeIt software

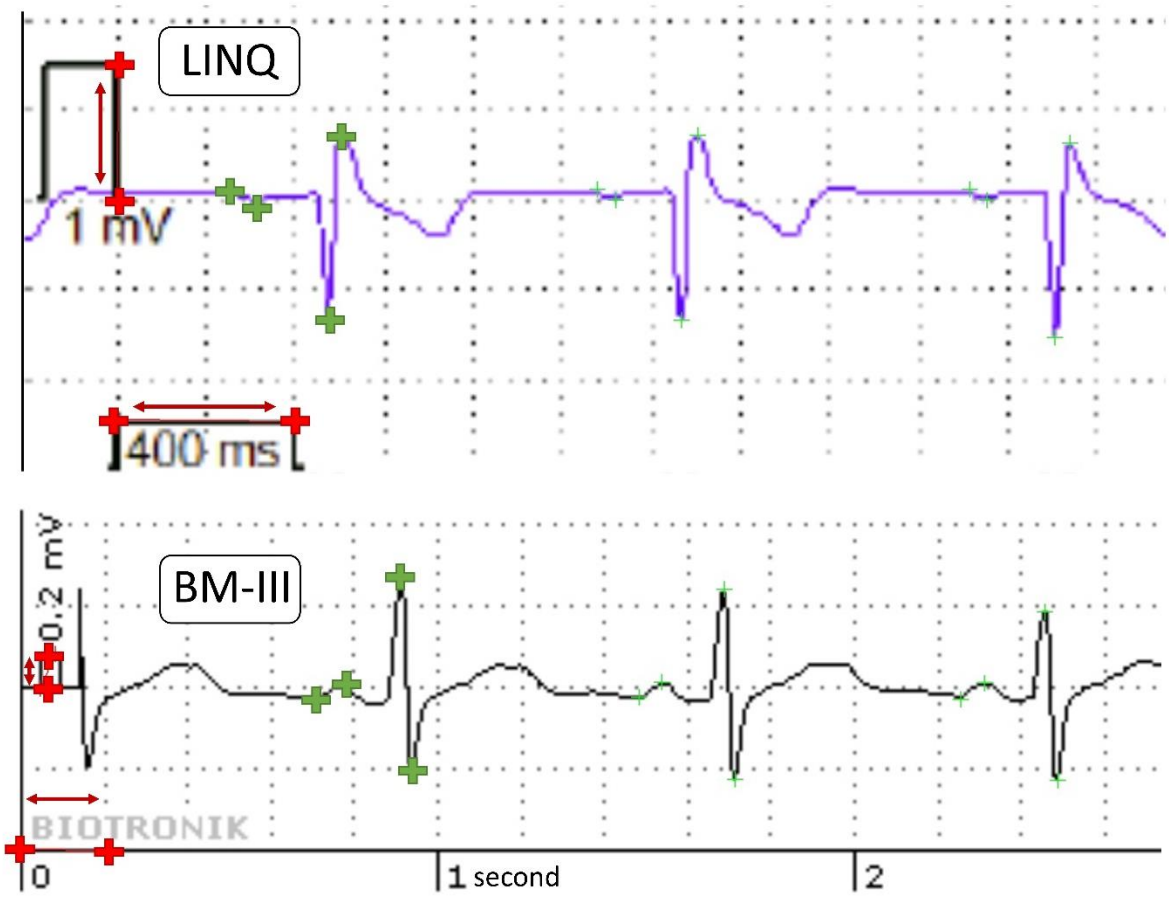
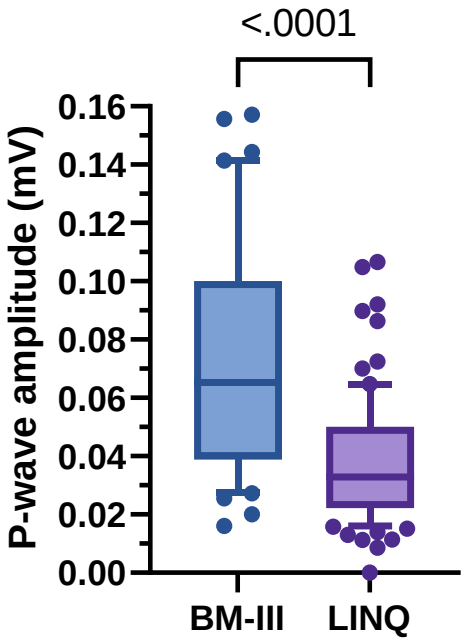
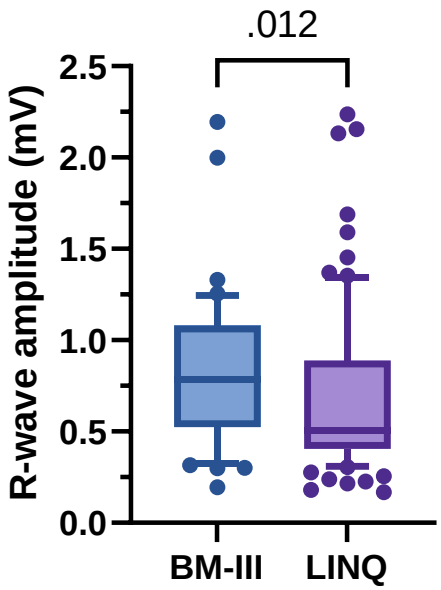


Figure 4. Median amplitude of P-wave (A), R-wave (B) and P/R-wave ratio (C) for each ICM type

A)



B)



C)

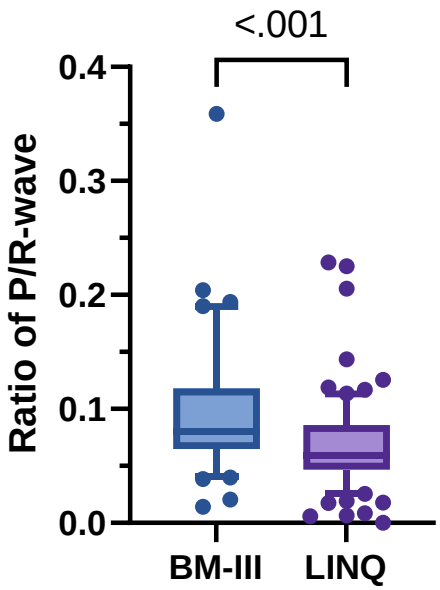
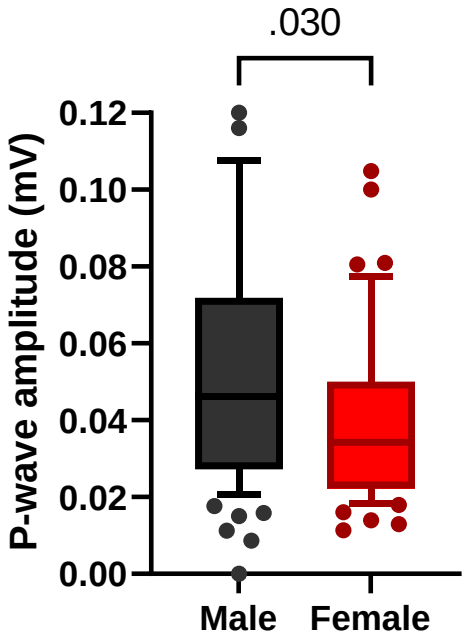


Figure 5. Median P-wave amplitude by (A) gender and (B) gender-ICM type

A)



B)

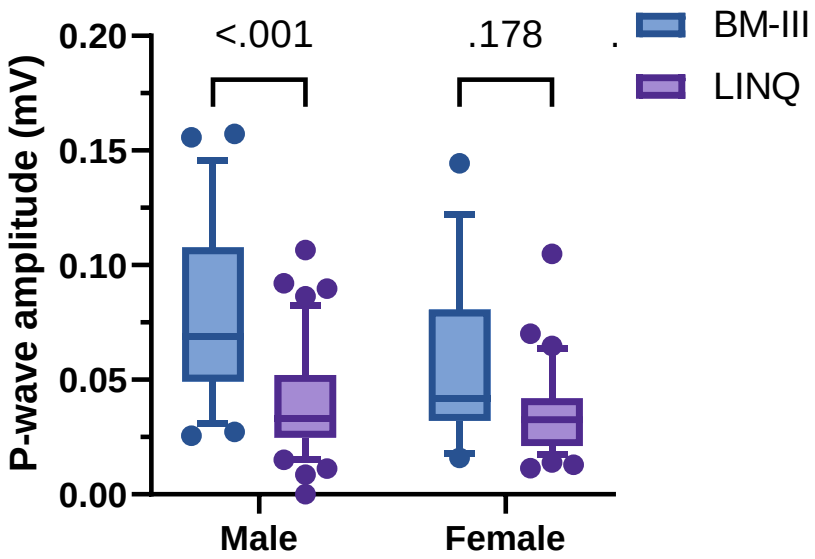
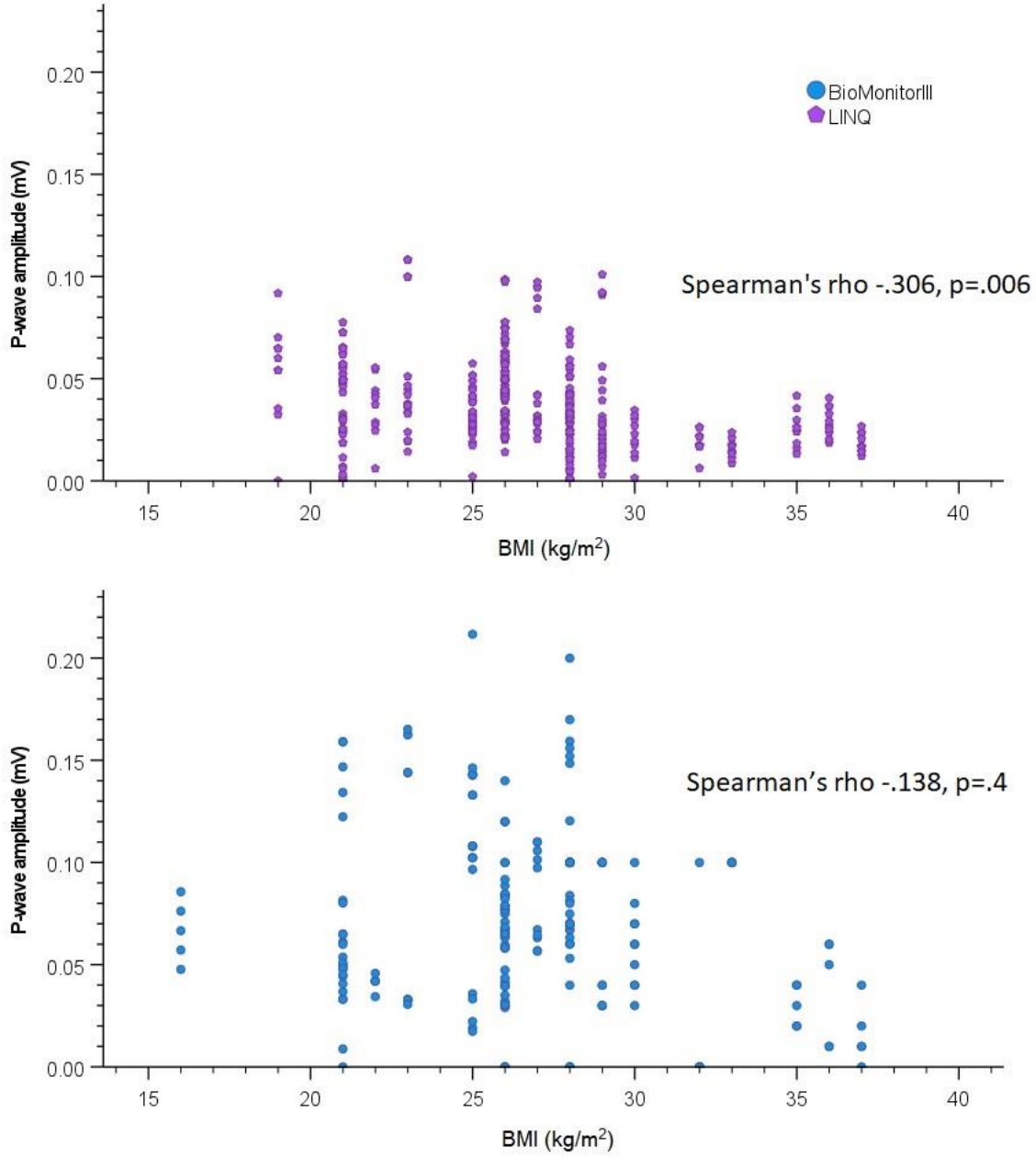


Figure 6. Dot plots of P-wave amplitude across the BMI range



CHAPTER FIVE – CHERCHEZ LE P STUDY

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ii. permission is granted for the candidate in include the publication in the thesis; and

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Factors affecting electrogram sensing in insertable cardiac monitor: Insights from surface EKG mapping analysis

5 ABSTRACT

Background: Fidelity of electrogram sensing may reduce false alerts from insertable cardiac monitor (ICM).

Objective: To assess impact of vector length, implant angle and patient factors on electrogram sensing using surface electrocardiogram (EKG) mapping.

Methods: Twelve separate precordial single-lead surface EKGs were acquired from 150 participants at two inter-electrode distance (75mm & 45mm), three vector angles (vertical, oblique, horizontal) and in two postures (upright & supine). A subset of fifty patients also received a clinically indicated ICM implant in 1:1 ratio (Medtronic Reveal LINQ:Biotronik Biomonitor III). All EKG and ICM electrogram were analyzed by blinded investigators using DigitizeIt software. P-wave visibility threshold was set at >0.015mV. Logistic regression was used to identify factors impacting P-wave amplitude.

Results: A total of 1,800 tracings from 150 participants [44.5% female, median 59 years old] were assessed. Median P- and R-wave were 45% and 53% larger with vector length of 75 vs. 45mm respectively (both $p<0.001$). The oblique orientation yielded the best P- and R-wave sensing while there was marginal difference seen with posture change. Increasing body mass index (BMI) and body fat percentage resulted in lower P-wave amplitude. Multivariate analysis showed obese BMI and horizontal vector angles were negatively associated with P-wave visibility, but 75mm vector length was likely to achieve visible P-waves [OR 2.16 (95%CI

1.69 – 2.77)]. The ICM electrogram sensing mirrored the findings from surface EKG mapping with moderate correlation.

Conclusion: Longer vector length and oblique implant angle yielded the best electrogram sensing and are relevant considerations for ICM implantations.

5.1 INTRODUCTION

The utilization of insertable cardiac monitor (ICM) for long-term heart rhythm monitoring is increasing due to expanding clinical indications, with recent inclusion for atrial fibrillation (AF) detection following embolic stroke of undetermined source.(108) There is a consequent growing workload burden for assessing remote monitoring (RM) alerts from ICMs where a significant proportion are due to false alerts and patient activated symptom alerts.(18) A recent multi-center cohort study reported that 59.8% of ICM RM alerts were false positives, with 97.3% of false-positive non-AF tachycardia alerts due to over-sensing, and 100% of false positive asystole and bradycardia alerts due to under-sensing.(157) Factors responsible for inappropriate sensing remain poorly studied and these may include implant location or orientation, patient's body habitus, ICM sensing vector, ICM detection algorithm and extrinsic factors such as external interference, noise or motion.

Pre-implant electrocardiogram (EKG) mapping to evaluate sensing was recommended with earlier generation implantable loop recorders with variable R-wave amplitude seen with different implant locations and changing body positions.(95) The routine for pre-implant EKG mapping was subsequently abandoned as studies have demonstrated adequate R-wave sensing at V_2-V_3 location (12-lead EKG equivalent) at 45 degrees angle or in the left upper chest area midway between the supraclavicular notch and the left breast area.(94, 158)

Integration of P-wave has been shown in novel ICM algorithm to yield high accuracy for atrial arrhythmia discrimination.(90) However, the data regarding P-wave sensing in current generation miniaturized ICMs remains limited where the sensing vector ranges between ~40 and 70mm. We hypothesize that ICMs with longer sensing vector can record larger P- and R-waves across different postures and implant orientations that are less likely to be impacted by body habitus as compared to those with shorter sensing vector. Therefore, this study aimed to evaluate electrogram sensing using surface EKG mapping in patients with varying body mass index (BMI) at different implant angle and patient posture with vector length of 45 and 75mm.

5.2 METHODS

This study was prospectively registered on the Australian New Zealand Clinical Trials Registry (ACTRN 12620000140954) with institutional Human Research Ethics Committee approval (ID: 12672). We recruited 150 participants (n=50 for each BMI category of 'normal', 'overweight' and 'obese' according to the World Health Organization definition of ≥18.5 to 25, >25 to 30 & >30 kg/m^2 respectively) who were in sinus rhythm and awaiting cardiac investigation at our institution who provided informed consent for a single occasion of research participation. To facilitate comparison of surface EKG measurements with ICM electrograms, we included participants who had clinical indication for ICM implantation (n=25 with Medtronic LINQ and n=25 with Biotronik Biomonitor-III). We obtained baseline clinical parameters using a brief health questionnaire as well as measurements of height, weight and body fat percentage (BF%) using a hand-held impedance monitor (HBF-306C, Omron healthcare, Illinois, United States). Measurements of height and weight were used to calculate body composition metrics

of body surface area (BSA) and body mass index (BMI). Measurements of left atrial size were acquired from available reports of clinically indicated transthoracic echocardiogram (TTE).

Surface EKG measurements

A single-lead EKG event loop Holter (DR200/HE, Northeast Monitoring, Massachusetts, United States) was used for surface EKG measurements with standard electrodes (Red Dot, 3M, New South Wales, Australia). Each participant had 12 separate EKGs obtained at the 4th intercostal space at the left sternal border (interelectrode distance of 45mm & 75mm at vertical, oblique and horizontal orientations in both supine and upright posture; Figure 1A). All EKGs and ICM electrograms were uploaded into DigitizeIt software (V2.3.3, Braunschweig, Germany) for offline analysis by blinded investigators to measure both P- and R-wave amplitude as previously described.(159) Following calibration of both the X-axis for duration (milliseconds, ms) and Y-axis for amplitude (millivolts, mV), measurements were performed for 5 consecutive sinus beats. P-wave was measured from baseline to peak amplitude and QRS was measured from peak-to-peak (Figure 1B). According to previous data, the threshold for readily visible P-wave was taken at >0.015mV.(159)

Statistical Analysis

Distribution of continuous variables were tested for normality with the Shapiro-Wilk test. Continuous data are expressed as mean ± standard deviation, or median and interquartile range (IQR) according to distribution, and analyzed using either student's t-test, Mann Whitney U-test, Kruskal-Wallis test or Friedman test (ANOVA). Categorical data are presented as percentages and analysed by Chi-square or Fisher's exact test. Bonferroni correction was used for multiple comparisons. Participants who additionally received ICM had an

instantaneous supine electrogram collected from the device for comparison to surface EKG recorded from the oblique angle. Intraclass correlation analysis was then performed between the device electrogram and the surface EKG. Using the correlation analysis, extrapolations can then be made from observed EKG amplitude to the likely electrogram amplitude for participants who did not receive ICM. Pearson's or Spearman correlation was used to assess relationship between continuous variables. Additional analysis was performed to determine the impact of clinical variables on signal amplitude, including the participant characteristics of age, gender, medical history, and current medication. BF% was stratified for each gender according to age and BMI categories as, described by Gallagher, et al.(160). Patients were categorized as having BF% either above or below predicted for gender, age and BMI. These body composition metrics were assessed to determine their impact of on the amplitude of different tracings. Logistic regression analysis was performed to assess the association of different variables with the dependent variable of P-wave visibility defined by amplitude of >0.015mV.(159) All statistical analysis was undertaken using SPSS (Version 27, IBM, Armonk, NY). A two-tailed P value of <0.05 was considered statistically significant.

5.3 RESULTS

A total of 1,800 EKG tracings were acquired from 150 participants [55.5% male, median 59 years old (IQR 35-73), median BMI 26.9 kg/m^2 (IQR 23.9-32.3), BSA 2.0±0.3 m^2]. Baseline characteristics of all participants are summarized in Table 1. Female participants were older with smaller BSA but higher BF% (Table 1), but there were no differences seen in comorbidities. The most common baseline characteristic was hypertension (53%). The body composition of the participant cohort is shown in Figure 1C, with BF% and BMI having a

statistically significant correlation (Pearson's r=0.68, p<0.001). When comparing these metrics according to BSA, a statistically significant relationship between participant BMI and BSA was noted (Pearson's r=0.72, p<.001), but BSA had a weaker correlation with participant BF% (Pearson's r=0.227, p=.005). Overall median EKG P- and R-wave amplitude was 0.034 (IQR 0.019 - 0.051) and 0.660 (IQR 0.425 - 0.984) mV respectively. Overall, 80% (n=1,444) of EKG traces had P-wave amplitude greater than the threshold for P-wave visibility (>0.015mV).

Impact of posture, implant angle and Inter-electrode spacing on EKG sensing

Median P-wave amplitude did not differ by posture [supine vs. upright: 0.035 (0.019-0.052) vs. 0.034mV (0.019-0.050) mV; p=0.12, Figure 2A] although R-wave was larger for supine vs. upright posture [0.68 (0.46-1.02) vs 0.63 (0.41-0.93) mV; p=0.009, Figure 2D]. The oblique angle provided the largest R-wave of 0.76 (0.52 – 1.08) mV as compared to both horizontal [0.60 (0.40 -0.91) mV; p<0.001] and vertical orientation [0.60 (0.38-0.92) mV; p<0.001, Figure 2E]. Although the oblique angle yielded the larger P-wave than the horizontal orientation [0.038 (0.022-0.054) vs. 0.029 (0.014-0.044) mV; p <0.001], it was similar to those from the vertical angle [0.036 (0.022-0.055) mV; p=0.9, Figure 2B]. Median P- and R-wave were 45% and 53% larger with vector length of 75 vs. 45mm respectively [0.042 (0.025-0.059) vs. 0.029 (0.014-0.0042) mV and 0.81 (0.56-1.19) vs. 0.53 (0.35-0.75) mV; both p<0.001, Figure 2C & F]. The P/R wave ratio was acceptable for both vector lengths across all implant angles; however, the vertical angle is noted to have more spread of outlier points (Figure 2G).

P-wave visibility

The violin plots in Figure 3 show in detail the P-wave amplitude according to posture, angle orientation and vector length. P-wave amplitude was larger with vector length of 75mm vs. 45mm in both postures and for all orientations (Figure 3, Friedman $p<0.001$). The horizontal angle had the lowest P-wave amplitude for both vector lengths. A P-wave amplitude of >0.015mV was seen more frequently with vector length of 75mm than 45mm (overall 86 vs. 75% respectively, $p<.0001$). The proportion of traces with P-wave amplitude >0.015mV according to different orientations, posture and vector length were significantly different (chi-square $p<0.001$). The oblique orientation at vector length of 75mm demonstrated the highest proportion of P-wave amplitude >0.015mV (90% whilst supine and 88% whilst upright). The horizontal orientation at vector length of 45mm showed the lowest proportion of P-wave amplitude >0.015mV (66% whilst supine and 65% whilst upright). There were 96 participants who had P-wave >0.015mV in all six of their EKG strips recorded at vector length of 75mm while only 68 participants achieved P-wave >0.015mV in all six of their EKG strips recorded at vector length of 45mm.

Impact of body size and composition on EKG sensing

Lower P-wave amplitude was seen with increasing BMI and BF% (Spearman's r=-0.315 and -0.362 respectively, Figure 4A-B). When analyzed according to BMI category, the proportion of participants with P-wave amplitude >0.015mV differed significantly (Figure 4C, $p=0.049$). Pairwise comparison showed significantly lower proportion with P-wave >0.015mV in the obese participants when the vector length was 45mm as compared to 75mm (66% vs. 75%, $p=0.025$). When BMI is considered with different posture, vector length and implant angle, P-wave amplitude in the oblique orientation at vector length of 75mm was least affected by

posture even in the obese category, where its advantage was lost in the horizontal orientation in both posture and when upright in the vertical orientation (Figure 5).

When analyzed according to P-wave visibility, BMI of participants did not differ in those with all 12 EKG tracings having P-wave >0.015mV (44.7%, n=67) and those without (n=83). However, BF% was significantly lower in those with all 12 EKG tracings having P-wave >0.015mV [27.4 (17.3-35.4) vs. 32.5 (22.5-38.0) %, p=0.037], and there was no difference for proportion of females between either of these groups. Overall, 77% (n=116) of participants had BF% above that expected for gender, age and BMI, and P-wave amplitude was found to be smaller in these participants as compared to those with BF% below that expected for gender, age and BMI [0.033 (0.017-0.049) vs. 0.038 (0.023-0.055) mV, p<0.001].

Factors impacting P-wave visibility

Gender, posture and peripheral vascular disease were found to be non-significant factors at the univariate level (Table 2). Multivariate analysis showed that patient characteristics of obese BMI, known paroxysmal AF and heart failure as well as horizontal angle were all negatively associated with having P-wave amplitude >0.015mV, while BF% above expected did not reach statistical significance (p=0.057). In contrast, vector length of 75mm was positively associated with having P-wave amplitude >0.015mV.

Surface EKG vs. ICM sensing

Baseline characteristics of this subgroup of 50 participants are shown in Table 3. There were no significant differences between patients implanted with Reveal LINQ (Medtronic, Minneapolis, MN, USA; sensing vector of ~40mm) or Biomonitor III (Biotronik, Berlin,

Germany; sensing vector of ~70mm) in terms of baseline characteristics, body composition or medical history. Both P- and R-wave amplitude were larger from the Biomonitor III vs. Reveal LINQ subcutaneous electrogram [0.041 (0.028-0.054) vs. 0.022 (0.012-0.036) mV, p=0.003; and 0.64 (0.48-1.07) vs. 0.47 (0.35-0.64) mV, p=0.016; respectively). Although most ICMs had R-wave >0.30mV (Reveal LINQ, n=21 and Biomonitor III, n=23), the P-wave was <0.015mV for nine (36%) of the Reveal LINQ, but only one (4%) of the Biomonitor III. When compared to the EKG from the oblique angle, we found moderate correlation to ICM derived P- and R-wave amplitude [ICC 0.74 (95% CI 0.58-0.84) and 0.80 (95% CI 0.67-0.88) respectively].

5.4 DISCUSSION

This surface EKG mapping study evaluated factors that may impact on electrogram sensing in ICM. First, both longer vector length and the oblique orientation yielded the best P- and R-wave sensing while there was marginal difference seen with posture change. Second, shorter vector length at the horizontal orientation resulted in poorest P-wave visibility. Third, increasing BMI and BF% resulted in lower P-wave amplitude although a longer vector length improved P-wave visibility despite increased BMI. Fourth, lower BF% but not BMI was seen in those with visible P-waves in all 12 EKG tracings. Fifth, multivariate analysis confirmed the positive impact of longer vector length on P-wave visibility while obese BMI, horizontal orientation and known paroxysmal AF and heart failure had a negative impact on P-wave visibility. Last, ICM electrogram analysis confirmed the surface EKG mapping data, with the Biomonitor III achieving larger P- and R-waves due to its longer vector length as compared to the Reveal LINQ (70 vs. 40mm). Taken together, electrogram sensing from ICM is best

achieved in the oblique position with longer device vector length especially in those with larger body composition.

Clinical importance of optimizing ICM sensing

With the increasing use of ICMs due to expanding clinical indications, the burden from ICM RM is significant. Indeed, recent work had found a majority of ICM RM alerts were due to false positives where under- and over-sensing contributed almost 40% of the total number of alerts.(157) Therefore, fidelity of ICM tracings is of great importance in maximizing diagnostic accuracy and minimizing the risk of under- or over-sensing that could lead to false RM alerts. This work affirms previous findings from studies on earlier generation implantable loop recorders that oblique orientation at the V_2-V_3 location provides the best electrogram sensing.

It was previously reported that every 2.5mm reduction in inter-electrode spacing resulted in a 5% reduction in R-wave amplitude. The gain in P- and R-wave with the additional 30mm of interelectrode distance in this study was found to be 45 to 53% which was in keeping with previous work. P-waves on ICM tracings have important diagnostic utility for arrhythmia identification with novel algorithm incorporating them in addition to the standard R-R interval patterns from Lorenz plots to reduce false positives in AF detection due to ectopics.(97, 98) However, the effectiveness of the algorithm are known to be affected by P-wave amplitude fluctuation, baseline noise, rapid rates, or long P-R intervals.(98) As such, identification of the optimal sensing vector to provide the highest amplitude P-wave on ICM tracings will maximize performance of this algorithm.

Our precordial EKG tracings had good correlation with ICM recordings. Previous studies investigating precordial mapping of R-wave prior to implantable loop recorder insertion have recommended the V_2-V_3 location (12-lead EKG equivalent) at 45 degrees angle.(94-96) One study investigating Reveal LINQ implant for paediatric patients reported visible P-waves in 48% of tracings that did not improve with pre-implant mapping.(96) Several recent studies have shown high P-wave visibility with longer sensing vector of the Biomonitor III where P-wave amplitude was found to be larger than ICMs of shorter vector length.(21, 103, 161) Our data supports the benefit of longer sensing vector in the oblique orientation to achieve the best P-wave sensing with superior P-wave visibility of up to 90% that was less likely to be affected by the subject's BMI or BF%.

Impact of body composition and co-morbidities on P-wave sensing

It has previously been reported that obese patients have lower R-wave amplitude on ICM tracings.(162) In another study, higher R-wave amplitude from Reveal LINQ tracings was seen in those with lower BSA and those with higher R-wave amplitude are more likely to have visible P-wave, implying that impact of body composition on ICM electrogram sensing.(96) Our data confirmed the negative impact of increasing BMI and BF% on P-wave amplitude and these are in keeping with previous data from the Framingham Heart Study.(163) Indeed, patients with high P-wave voltage on surface EKG (≥0.2 mV) have greater likelihood of visible P-wave on ICM tracings.(162) The lower P-wave amplitude with obesity can be explained by the impact of subcutaneous fat on EKG acquisition or underlying atrial remodeling including increased abnormal atrial conduction and reduced atrial voltage due to atrial fibrosis as well as increased epicardial adiposity.(164, 165) Data from our multivariate analysis shows the impact of co-morbidities such as paroxysmal AF and heart failure that can negatively impact

on P-wave visibility. This further affirms the possibility of adverse atrial remodeling and fibrosis in these atria that could result in reduced P-wave visibility. As obesity is a major risk factor for AF and ICM is now recommended for AF detection following embolic stroke of undetermined source, strategies to maximize P-wave sensing such as aforementioned choice of longer vector length and oblique implant angle are relevant considerations.(108, 136)

Study Limitations

We have utilized surface EKG to mimic subcutaneous recordings from ICM which has shown good correlation with ICM recordings obtained from a portion of patients. Although the methodology of using surface EKG tracings allowed assessment of multiple sensing vector angles without physical implantation, there is some limitation in their extrapolation to implanted ICM recordings. Patients who received ICM implant where not randomized to their ICM type and although patients of each ICM type were well matched for clinical parameters, we cannot exclude an inherent physician selection bias. We did not have echocardiographic left atria parameters for a proportion of patients and were unable to provide further P-wave analysis according to atrial size.

5.5 CONCLUSION

Longer vector length and oblique implant angle yielded the best electrogram sensing and are relevant considerations for ICM implantations especially in those who are obese and with risk factors for atrial remodeling.

5.6 TABLES & FIGURES

Table 1: Baseline Characteristics

	All, n=150	Female, n=68	Male, n=82	P-value
Clinical parameters				
Age (years)	59 (35 - 73)	65 (40 - 77)	57 (33 - 68)	**0.016**
Height (cm)	169.6 ± 9.6	162.4 ± 6.4	175.5 ± 7.5	**<.001**
Weight(kg)	79.5 (70.8 - 91)	72.5 (60 - 87)	83.5 (75 - 98)	**<.001**
Body Fat (%)	29.3 ± 10.6	35.2 ± 9.6	24.4 ± 8.8	**<.001**
BMI (kg/m^2)	26.9 (23.9 - 32.2)	26.8 (23.7 - 33)	27.5 (24.1 - 32.1)	0.93
BSA (m^2)	2.0 ± 0.2	1.8 ± 0.2	2.1 ± 0.2	**<.001**
Medical history				
Atrial fibrillation	14 (9.3%)	9 (13.2%)	5 (6%)	0.14
Hypertension	80 (53.3%)	32 (47%)	48 (58.5%)	0.16
Diabetes mellitus	21 (14%)	11 (16.1%)	10 (12.1%)	0.48
Heart failure	12 (8%)	7 (10.2%)	5 (6%)	0.35
Ischemic heart disease	16 (10.6%)	6 (8.8%)	10 (12.1%)	0.51
Peripheral vascular disease	9 (6%)	4 (5.8%)	5 (6%)	0.96
Stroke / transient ischaemic attack	39 (26%)	18 (26.4%)	21 (25.6%)	0.98
Medication				
Any cardiac medication	93 (62%)	42 (61.7%)	51 (62.1%)	0.96
Anti-arrhythmic drug	32 (21.3%)	18 (26.4%)	14 (17%)	0.16
Anti-hypertensive agents	62 (41.3%)	29 (42.6%)	33 (40.2%)	0.77
Lipid lowering agents	54 (36%)	26 (38.2%)	28 (34.1%)	0.60
Anticoagulant or anti-platelet agents	57 (38%)	24 (35.2%)	33 (40.2%)	0.53
Reason for cardiac investigation				0.81
Coronary angiogram	16 (10.6%)	7 (10.2%)	9 (10.9%)	0.98
Echocardiogram	9 (6%)	3 (4.4%)	6 (7.3%)	0.51
Electrophysiology study	11 (7.3%)	6 (8.8%)	5 (6%)	0.55
Management of suspected AF	46 (30.6%)	18 (26.4%)	28 (34.1%)	0.37
Holter	21 (14%)	11 (16.1%)	10 (12.1%)	0.49
Syncope	8 (5.3%)	5 (7.3%)	3 (3.6%)	0.47
Stroke investigation	39 (26%)	18 (26.4%)	21 (25.6%)	0.98

Table 2. Univariate and multivariate analysis of factors impacting on P-wave amplitude >0.015mV

Factors		Univariate			Multivariate		
		OR	95% CI	Pvalue	OR	95% CI	Pvalue
Female gender		0.99	0.79 – 1.25	0.94	.	.	.
BF% above expected		0.67	0.49 – 0.90	0.009	0.74	0.54 – 1.01	0.057
Obese BMI		0.53	0.42 – 0.67	<0.001	0.59	0.45 – 0.77	**<0.001**
Supine posture		0.98	0.78 – 1.24	0.91	.	.	.
75mm vector length		2.08	1.63 – 2.64	<0.001	2.16	1.69 – 2.77	**<0.001**
Vector Angle	**Horizontal**	0.53	0.39 – 0.70	<0.001	0.51	0.38 – 0.68	**<0.001**
	Vertical (ref)	.	.	.	.	.	.
	Oblique	0.91	0.67 – 1.23	0.53	0.90	0.66 – 1.24	0.52
Known paroxysmal AF		0.48	0.34 – 0.68	<0.001	0.53	0.36 – 0.77	**<0.001**
Hypertension		0.67	0.53 – 0.85	0.001	0.81	0.63 – 1.04	0.10
Diabetes Mellitus		0.67	0.49 – 0.91	0.01	1.01	0.70 – 1.45	0.98
Heart Failure		0.46	0.32 – 0.66	<0.001	0.59	0.40 – 0.89	**0.012**
Ischaemic Heart disease		0.53	0.38 – 0.73	<0.001	0.73	0.49 – 1.07	0.11
Peripheral Vascular Disease		0.96	0.59 – 1.56	0.87	.	.	.

Table 3. Comparison of clinical parameters for patients receiving ICM

	All ICM patients, n=50	BM-IIIm, n=25	LINQ, n=25	Pvalue*
Clinical parameters				
Age (years)	59 (35 - 73)	65 (58 - 78)	73 (65 - 76)	0.33
Male gender	30 (60%)	15 (60%)	15 (60%)	-
Height (cm)	169.0 ± 9.0	168.0 ± 9.0	170.0 ± 8.0	0.60
Weight (kg)	79.5 (70.6 – 91.0)	85.0 (76.0 – 100.0)	78.0 (72.0 – 89.0)	0.14
Body Fat (%)	32.0 ± 9.7	33.5 ± 9.6	30.6 ± 9.8	0.92
BMI (kg/m^2)	26.9 (23.9 - 32.3)	29.4 (26.1 - 33.5)	27.5 (24.4 - 29.3)	0.13
BSA (cm^2)	2.0 ± 0.2	2.0 ± 0.2	1.9 ± 0.2	0.74
ICM indication				
Transient ischaemic attack / embolic stroke unknown source	31 (62%)	12 (48%)	19 (76%)	0.08
Syncope	16 (32%)	11 (44%)	5 (20%)	0.13
AF management	2 (4%)	1 (4%)	1 (4%)	-
Palpitations	1 (2%)	1 (4%)	-	-
Medical history				
Hypertension	32 (64%)	16 (64%)	16 (64%)	-
Diabetes mellitus	7 (14%)	4 (16%)	3 (12%)	0.68
Ischemic heart disease	6 (12%)	3 (12%)	3 (12%)	-
Known AF	2 (4%)	2 (8%)	-	-
Heart failure	3 (6%)	2 (8%)	1 (4%)	0.55
Peripheral vascular disease	4 (8%)	1 (4%)	3 (12%)	0.30
Medication				
Any cardiac medication	43 (86%)	21 (84%)	22 (88%)	0.68
Anti-arrhythmic drug	7 (14%)	6 (24%)	1 (4%)	**0.048**
Anti-hypertensive agents	28 (56%)	15 (60%)	13 (52%)	0.57
Lipid lowering agents	28 (56%)	11 (44%)	17 (68%)	0.09
Anticoagulant/anti-platelet agents	32 (64%)	12 (48%)	20 (80%)	**0.018**

FIGURE LEGENDS

Figure 1: Data collection. (A) method, (B) measurements, (C) body size of recruited participants

Figure 2: Violin plots for EKG amplitude of P-wave & R-wave and box plots of P/R ratios

Figure 3: Violin plot comparison of P-wave amplitude by vector length, implant angle and posture

Figure 4: Correlation of body composition on P-wave amplitude. (A) Dotplot for BMI. (B) Dotplot for BF%. (C) P-wave visibility by BMI category

Figure 5: Box and whisker plots of P-wave amplitude by BMI category

Figure 1. Data collection. (A) method, (B) measurements, (C) body size of recruited participants

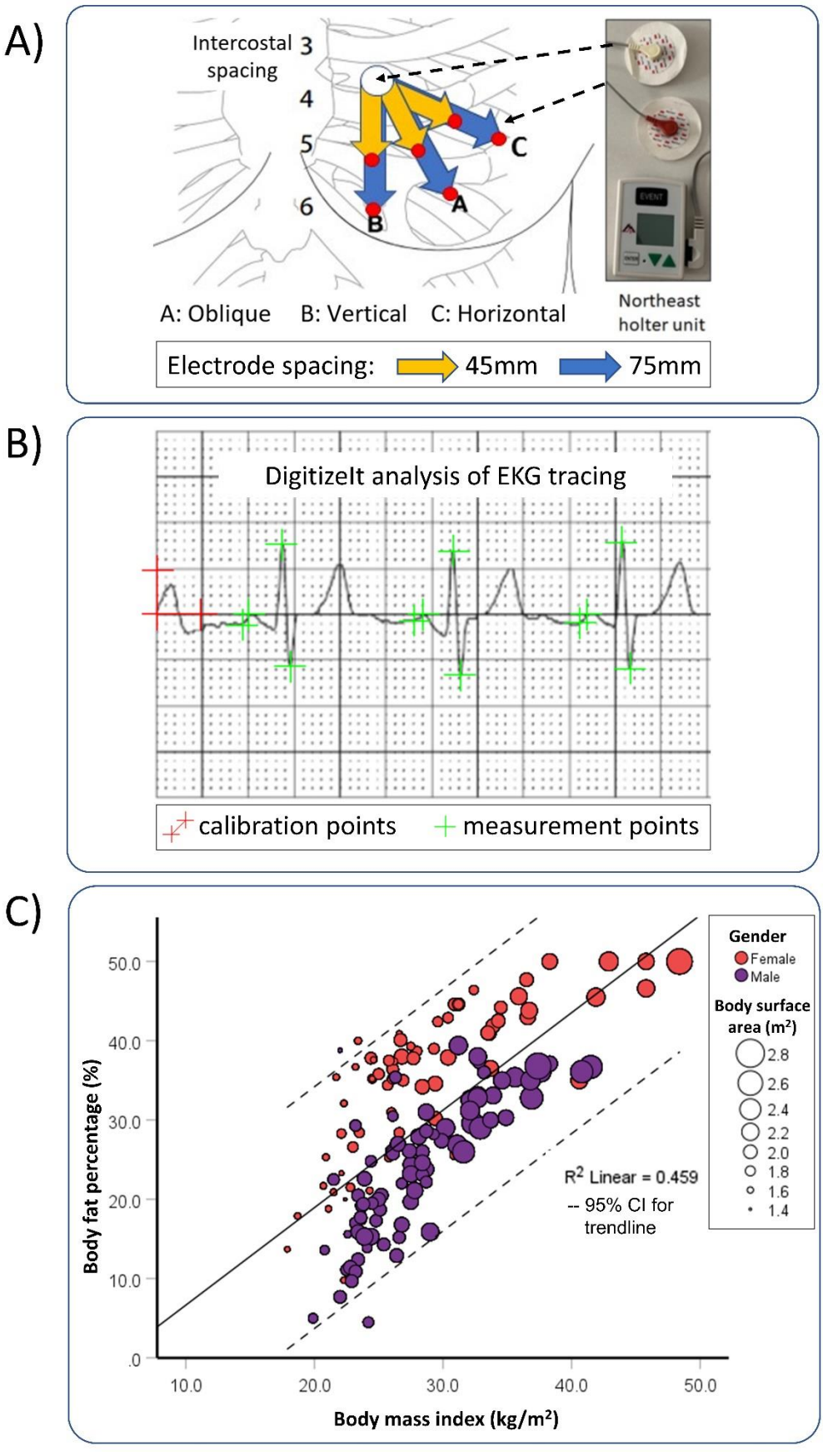
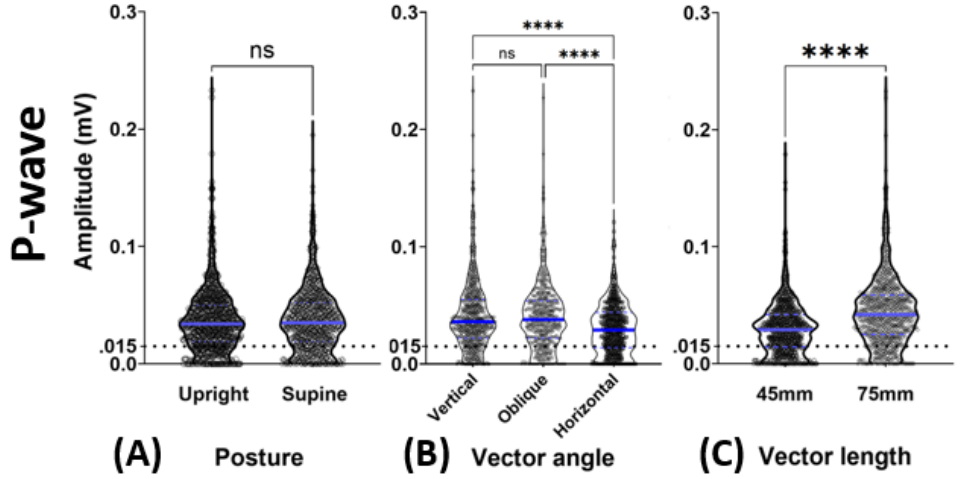
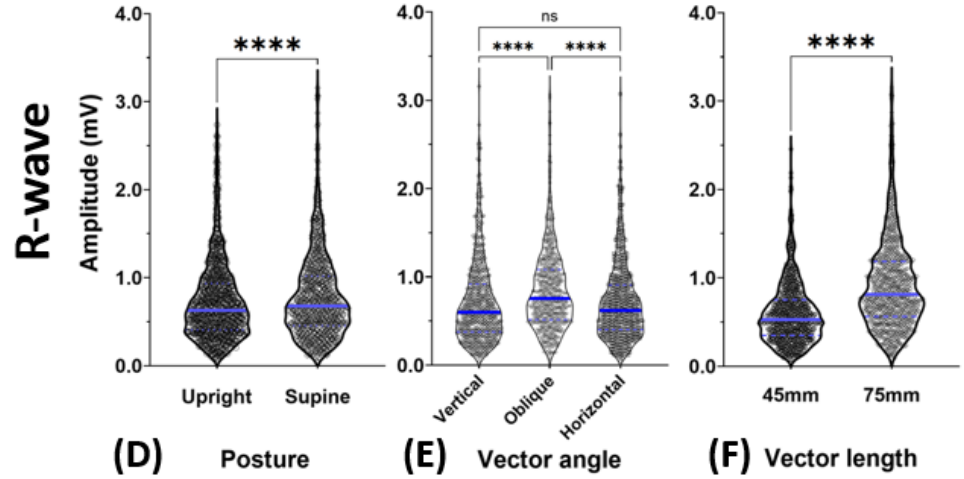


Figure 2. Violin plots for EKG amplitude of P-wave, R-wave and box plots of P/R ratio





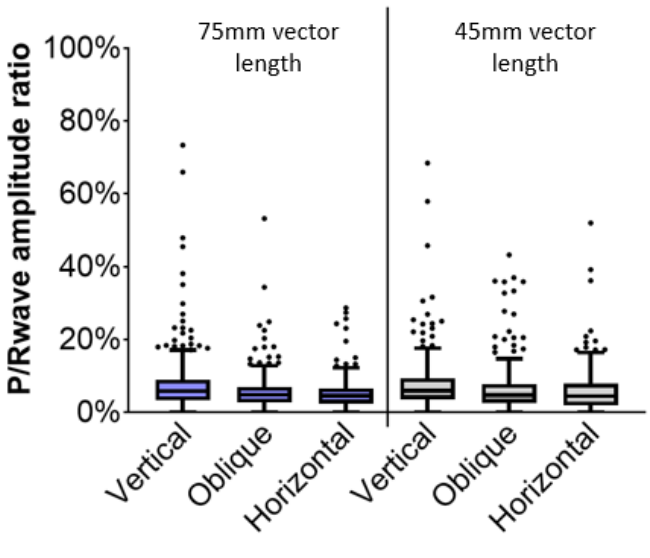
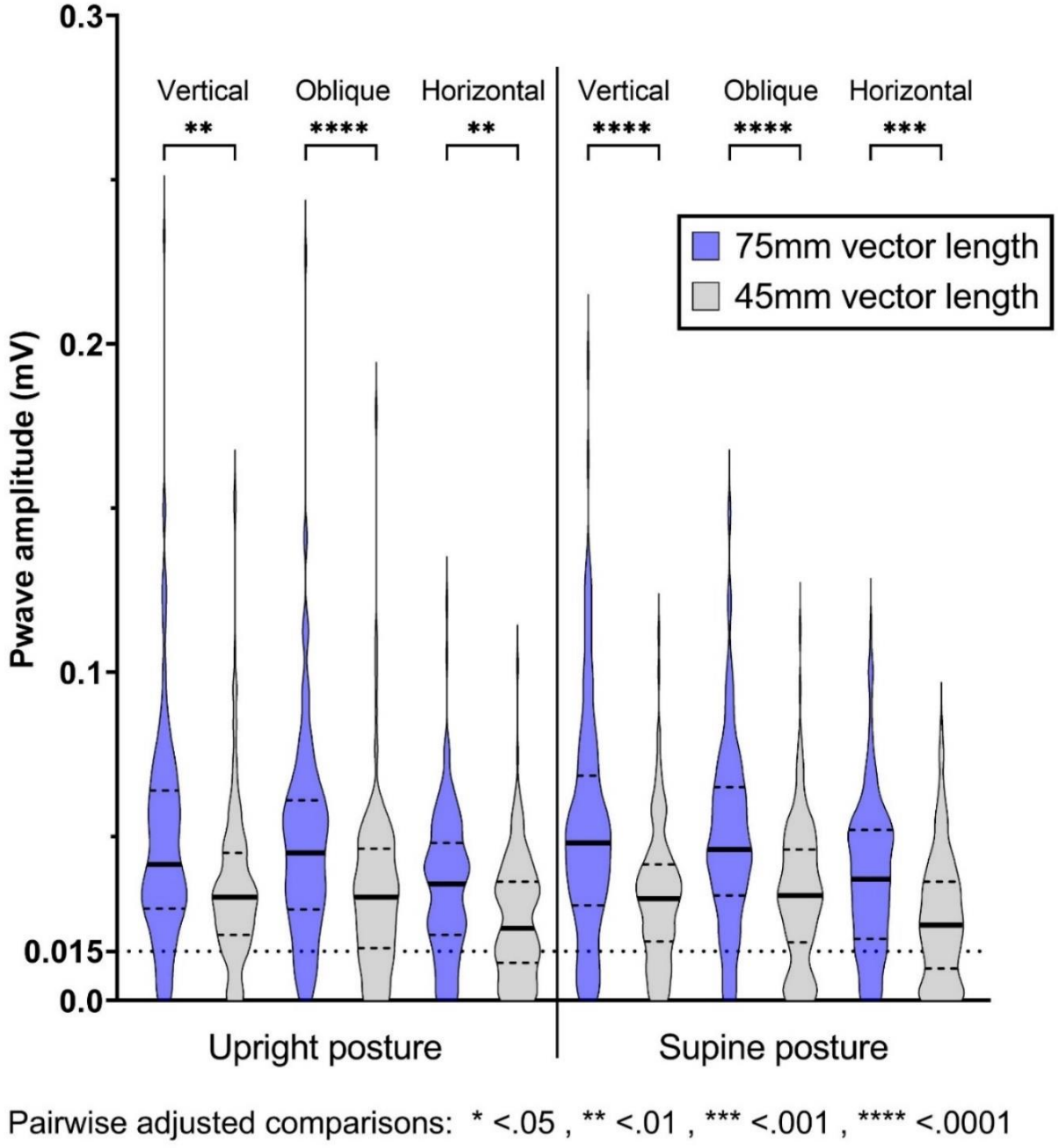


Figure 3: Violin plot comparison of P-wave amplitude by vector length, implant angle and posture



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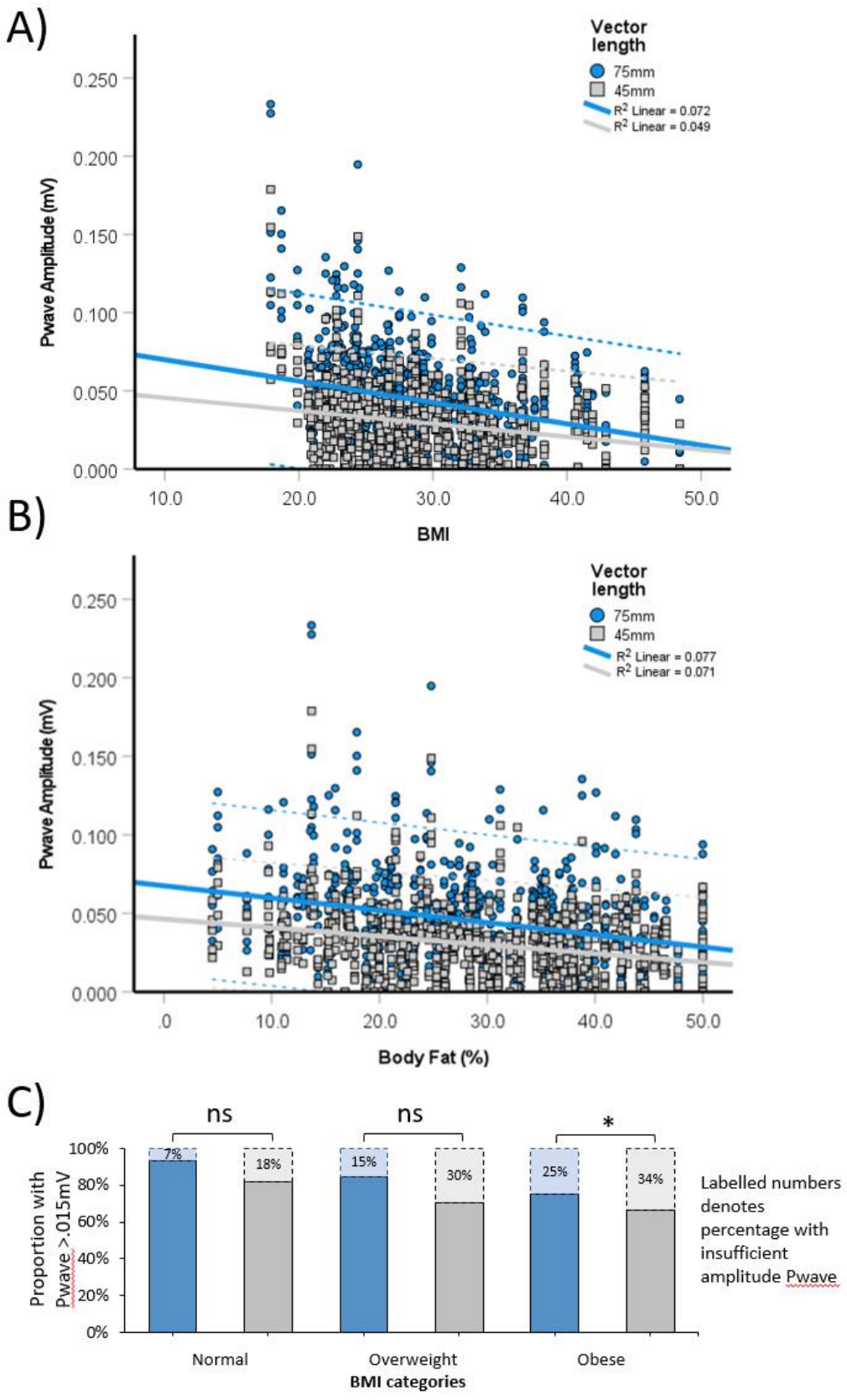
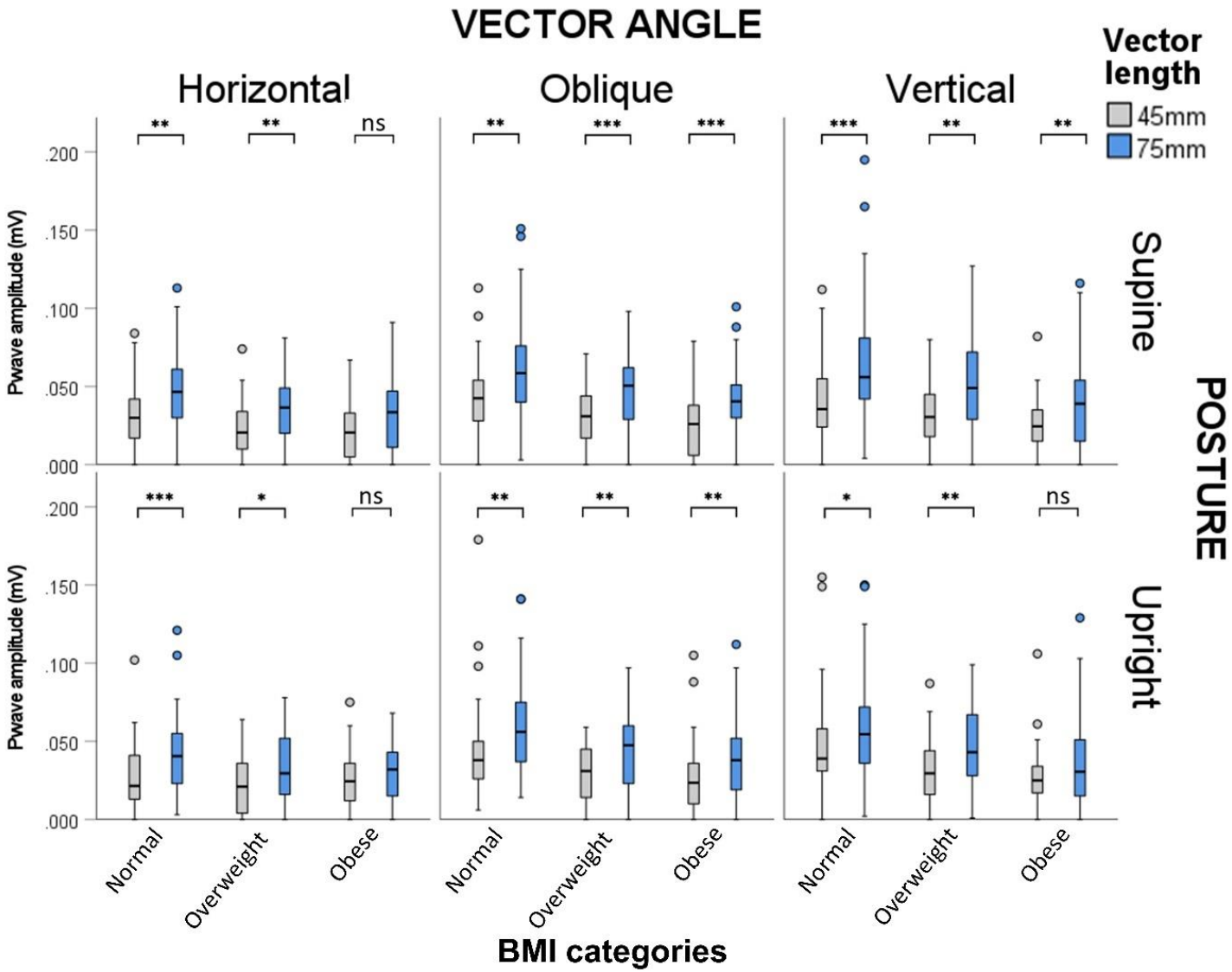


Figure 5: Box and whisker plots of P-wave amplitude by BMI category



CHAPTER SIX – TEFF-AF UTILITY STUDY

AUTHORSHIP STATEMENT

Statement of Authorship

Title of Paper	Performance of a Mobile Single-Lead Electrocardiogram Technology for Atrial Fibrillation Screening in a Semirural African Population: Insights From "The Heart of Ethiopia: Focus on Atrial Fibrillation" (TEFF-AF) Study
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Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Contribution to the Paper	Conception, Knowledge, Analysis, Drafting, Editing		
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Performance of a mobile single-lead electrocardiogram technology for atrial fibrillation screening in a semi-rural African population: Insights from the TEFF-AF Study

6 ABSTRACT

Background: Atrial fibrillation (AF) screening using mobile single-lead electrocardiogram (EKG) devices has demonstrated variable sensitivity and specificity. However, limited data exists on the usage of such devices in low resource countries.

Objective: To evaluate the utility of the KardiaMobile device's (KM, AliveCor Inc, CA, USA) automated algorithm for AF screening in a semi-rural Ethiopian population.

Methods: Thirty second single-lead EKG tracings obtained using the KM device from 1,500 TEFF-AF (**T**he h**E**art o**F** Ethiopia: **F**ocus on Atrial Fibrillation; ACTR Number: 12619001107112) study participants were analyzed. We evaluated the performance of KM automated algorithm against cardiologists' interpretation of 30-second single-lead ECG for AF screening.

Results: A total of 1,709 single-lead EKG tracings (including repeat tracing on 209 occasions) were analyzed from 1,500 Ethiopians (64% male, 35±13 years old) who presented for AF screening. Initial successful rhythm decision ("normal" or "possible AF") with one single-lead EKG tracing was lower with the KM automated algorithm versus manual verification by cardiologists (78% vs. 97%, *P*<.001). Repeat single-lead EKG tracings in 209 individuals improved overall rhythm decision, but the KM automated algorithm remained inferior (87% vs. 99%, *P*<.001). The key reasons underlying unsuccessful KM automated rhythm determination (n=408 traces) include poor quality/noisy tracings (52%), frequent ectopy (5%)

and tachycardia (>100bpm; 41%). The sensitivity and specificity of rhythm decision using KM automated algorithm was 80% and 82% respectively.

Conclusion: The performance of the KM automated algorithm was sub-optimal when used for AF screening. However, the KM single-lead EKG device remains an excellent AF screening tool with appropriate clinician input and repeat tracing.

Keywords: Atrial fibrillation; Screening; sub-Saharan Africa; single-lead EKG

6.1 INTRODUCTION

There has been a significant increase in consumer use of wearable technology capable of ambulatory assessment of heart rate and rhythm in recent years.(105) Large-scale population screening studies have demonstrated capability of wearable devices in detecting pulse irregularity utilizing photoplethysmography-based technology, with high positive predictive value of diagnosing atrial fibrillation (AF).(110, 114) However, the adoption of these smart wearable devices is much lower in low resource countries due to affordability and low internet penetration rate. Despite AF being recognized as a growing global epidemic, the 2010 Global Burden of Disease study has highlighted low availability of data on AF from several regions including Sub-Saharan Africa and the need for better estimates through targeted population surveillance studies.(2) Alternative active screening strategies for AF utilizing pulse palpation and electrocardiogram (EKG) are therefore more applicable in these low resource countries.(105, 166)

AF screening using single-lead EKG devices has been reported in hospital, primary care and community settings with variable sensitivity and specificity.(22) However, limited data exists on the usage of such devices for AF screening in low resource countries.(167) One such device

is the KardiaMobile (KM, AliveCor Inc, CA, USA) which is approved by the Food and Drug Administration of the United States Department of Health and Human Services for automatic classification of 30-second single-lead EKG tracing as “normal” or “possible AF”. However, the device also returns other results of “too short”, “tachycardia”, “bradycardia”, “unreadable” or “unclassified”. Notably, screening studies using the KM, including the Heart Rhythm Society/American College of Physicians AF screening and education initiative, have encountered between 5% and 28% of unclassified EKG recordings.(168-172) The high frequency of “unclassified” tracings may limit the effective utility of this device for AF screening. Here, we sought to determine the real-world feasibility and utility of the KM single-lead EKG device for AF screening in a semi-rural African population. Specifically, the present analysis evaluates the device’s accuracy for AF detection, factors underlying “unclassified” EKG tracings, and factors that may influence its screening performance from the first 1,500 subjects recruited in the ongoing TEFF-AF (**T**he h**E**art o**F** Ethiopia: **F**ocus on **A**trial **F**ibrillation study).

6.2 METHODS

TEFF-AF Study

The TEFF-AF study (ACTR Number: 12619001107112) is an AF screening study conducted at the Soddo Christian Hospital (SCH). The SCH is located in the semi-rural town of Soddo in south-central Ethiopia, with a population of around 200,000 individuals. AF screening was undertaken by a team of five nursing and research support staff from the SCH following specialized training on the use of the KM device, iPhone application (Version 5.7.4, KardiaAI: 1.1.7), and online REDCap (Research Electronic Data Capture, Vanderbilt University, TN, USA)

database. The training included an initial tutoring session followed by subsequent hands-on practice in acquiring best quality single-lead EKG tracing with the KM device. AF screening commenced at the SCH in August 2019 with inclusion criteria being any ambulant adult aged 18 years and above and able to provide informed consent. Signage in Amharic language was erected to advertise screening to aid recruitment (Figure 1A).

All participants provided informed consent and this study is approved by the SCH research ethics board. Baseline demographic and clinical parameters were obtained to characterize the cardiovascular risk profile of participating individuals. Measurements of height, weight and blood pressure (Omron Intellisense T5 automatic monitor, Omron Corporation, Kyoto, Japan) were obtained before single-lead EKG acquisition using the KM device. As per the study protocol (Figure 1B), the outcome of the automated algorithm assessment of rhythm dictated the need for repeat KM tracing and/or a 12-lead EKG. Participants with clinical abnormality detected were referred for follow-up by SCH physician.

KardiaMobile EKG Screening

The KM mobile single-lead EKG device records a bipolar lead I EKG tracing when two or three fingers from each hand of the user are placed in contact with the two electrodes (Figure 1A). Participants were instructed to relax arms and hands to reduce noise and artefacts. The KM device transmits a frequency modulated ultrasound signal that is detected by the smartphone (iPhone, Apple Inc, CA, USA) with installed Kardia application. A 30-second single-lead EKG recording can be viewed in real-time on the smartphone application and saved as a PDF file. The noise-filtered trace and computer-averaged complex on the KardiaMobile application is

then subjected to an automated algorithm for arrhythmia diagnosis using the two criteria of p-wave absence and R–R interval irregularity.(118)

EKG adjudication analysis

The KM EKG tracings obtained for the first consecutive 1,500 participants in the TEFF-AF study were included in this analysis. Each single-lead EKG tracing has a rhythm determination by the KM automated algorithm of “Normal”, “Possible AF”, “Bradycardia”, “Tachycardia”, “Unclassified”, “Unreadable”, or “Too Short”. Single-lead EKG traces were downloaded and analyzed independently by two cardiologists. The cardiologists also assessed diagnostic limitations for each tracing categorized as artefact, ectopy, bradycardia, tachycardia, or insufficient sample duration.

Data Availability

The dataset with de-identified information generated and analyzed during the current study is available from the corresponding author on reasonable request.

Statistical Analysis

The summary statistics were presented by number (percentage) or mean ± SD (standard deviation) as appropriate. Categorical data were analyzed using the chi-squared test. The sensitivity and specificity for the ability of the KM to produce a rhythm decision against the cardiologists’ EKG interpretation was calculated. Linear regression analysis was performed to assess the factors contributing to screening performance of the KM automated algorithm. All statistics were performed in SPSS (Version 26, IBM corp, Armonk, NY, USA) and statistical significance set at $P<.05$.

6.3 RESULTS

A total of 1,709 single-lead EKG tracings (including repeat tracing on 209 occasions) were analyzed from a cohort of 1,500 participants who presented for AF screening. The baseline clinical parameters of the participants are shown in Table 1. The mean age was 35 (13) years old and 64% were male. Of these 1500 participants 1,439 (96%) were from the regional state of Southern Nations, Nationalities, and People's Region (SNNPR) where the SCH is located and 87% (n=1,306) had secondary level education or above. The self-reported clinical history of the participants is shown in Table 1 with hypertension (6.9%, n=104) as the most prevalent co-morbidity.

Performance of KM automated algorithm

Of the initial single-lead EKG tracings from 1,500 participants, the KM algorithm was unable to provide a rhythm decision in 22% (n=324) due to 'unclassified' (8.7%, n=130), 'tachycardia' (8.5%, n=128), 'unreadable' (4.1%, n=62), 'too short (0.2%, n=3) and 'bradycardia' (0.1%, n=1). Representative examples of these tracings are shown in Figure 3. A repeat KM tracing was obtained in 65% (n=209 of 324) of the participants who did not have an initial rhythm decision. Of those participants (n=115) without repeat KM tracings, 96 had an initial result of 'tachycardia', which the screening team deemed as sinus tachycardia (>100bpm) and interpreted this as normal rhythm not requiring a repeat tracing. Twelve of the remaining 19 participants without repeat KM tracing proceeded directly to a 12-lead EKG and the remaining 7 participants declined repeat KM tracing or 12-lead EKG due to time constraint. On the repeat KM attempt, the KM algorithm again failed to achieve a rhythm decision in 40% (n=84 out of 209). Adjudications by cardiologists showed that the reasons underlying unsuccessful automated KM rhythm determination (n=408 traces; 324 from first attempt + 84 from repeat

attempt) were: poor quality/noisy tracings (52%, n=214), tachycardia (>100bpm; 41%, n=167), frequent ectopy (5%, n=22), inadequate recording duration (1%, n=3) and bradycardia (<50bpm; <1%, n=2).

KM automated algorithm versus cardiologists' adjudication

The KM automated algorithm successfully obtained a rhythm decision on the first attempt for 78% (n=1176 of 1500) of participants, which was considerably lower than manual assessment by cardiologists (97%, n=1455 of 1500; *P*<.001, Figure 4). The sensitivity and specificity of a rhythm decision by the KM automated algorithm from the initial single-lead EKG of each participant, when compared with manual assessment by cardiologists, was 80.3% (95% CI 78.1-82.3%) and 82.2% (95% CI 68.0-92.0%) respectively (Table 2A). The KM automated algorithm's success in rhythm decision improved to 87% (n=1301 of 1500) with the inclusion of repeat KM tracings achieving a rhythm decision for an additional 125 participants, although it remained lower than manual assessment by cardiologists (99%, n=1479 of 1500; *P*<.001, Figure 4). In total, 97% (n=1,657 of 1,709) of the single lead EKG tracings were of adequate quality for diagnostic purposes according to cardiologists' adjudication. Notably, all the KM algorithm determined "normal" single-lead EKG were confirmed to be normal sinus rhythm according to cardiologists' adjudication. However, three traces that failed to achieve a rhythm decision by KM (two 'unreadable' and one 'unclassified') were deemed as AF according to cardiologists' adjudication. The sensitivity and specificity of AF detection by the KM automated algorithm from n=1,709 single-lead EKG tracings, when compared with manual assessment by cardiologists, was 75.0% (95% CI 42.8-94.5%) and 96.4% (95% CI 95.4-97.2%) respectively (Table 2B).

12-lead EKG analysis

In total, there were 154 participants who met criteria for a 12-lead EKG but this was obtained in only 59% (n=91) due to the participants not wanting to wait for the 12-lead EKG to be performed in the SCH emergency room. However, upon review of the single-lead EKGs which met study criteria for a 12-lead EKG to be performed, the cardiologists adjudicated 90% of these single lead EKGs to be of adequate quality for a rhythm decision. In total, the diagnosis from the 12-lead EKGs were as follows: sinus rhythm (n=81), supraventricular tachycardia (n=1) and AF (n=9).

Utility of KM automated algorithm for AF screening

We analyzed the performance of the KM automated algorithm for providing an initial rhythm decision. There was a linear relationship between ongoing participant recruitment and the occurrence of 'no rhythm decision' from the initial KM tracing (Figure 5A). Linear regression analysis showed that there was a significant reduction in the cumulative incidence of 'no rhythm decision' compared to successful rhythm decision with ongoing patient recruitment (β=-14.4, 95% CI -26.6, -2.1; *P*=.02). As the KM results of 'tachycardia', 'unclassified' and 'unreadable' accounted for 98.7% of occasions without a rhythm decision on the first KM attempt, their contribution to 'no rhythm decision' was further analyzed. With ongoing patient recruitment, the occurrence of 'unreadable' tracing was significantly reduced when compared to 'unclassified' and 'tachycardia' tracings (β=-38.0, 95% CI -63.3, -12.6; *P*=.003, Figure 5B).

6.4 DISCUSSION

This study evaluated the utility of the KM single-lead EKG device for AF screening in a semi-rural Ethiopian population of 1,500 individuals from the TEFF-AF study. We found the KM device performance to be sub-optimal with successful automated rhythm decision following a single EKG trace of only 78%. This yield increased to 87% following a second KM EKG tracing. As experience increases with ongoing patient recruitment, we encountered significant reduction in 'unreadable' tracings. The ongoing occurrence of 'tachycardia' and 'unclassified' tracings contributed largely to the automated KM algorithm's inability to achieve successful rhythm decision. In contrast, manual cardiologist assessment was able to obtain a rhythm decision in almost all cases (97%) with a single EKG. Taken together, our findings suggest that manual physician input remains necessary when the KM device is utilized for AF screening.

The use of single-lead EKG devices is of increasing interest given the potential benefits of portability and scalability. Furthermore, automated rhythm analysis may allow for the use of such devices by individuals without formal medical training. However, there is limited data on the accuracy of these devices and their automated rhythm analysis algorithms in such settings despite the KM device been Federal Drug and Administration approved since 2012. In a small validation study, the KM's automated AF detection algorithm was reported to yield high sensitivity of 98% and specificity of 97% with overall accuracy of 97%.(118) In a single-center, adjudicator-blinded case series of 52 consecutive patients with AF admitted for antiarrhythmic drug initiation who had serial 12-lead EKG and nearly simultaneously acquired KM recordings, AF detection was reported at 96.6% sensitivity and 94.1% specificity.(119) However, 28% of the tracings obtained were deemed "unclassified" by the KM automated

algorithm and excluded from analysis. Similarly, others have reported the KM automated algorithm correctly detected AF with 93% sensitivity and 84% specificity in 100 participants with a history of AF who presented for a scheduled elective electrical cardioversion after excluding a substantial 34% of recordings with “unclassified” tracings.(171) Our study found that the KM automated algorithm failed to achieve rhythm decision in 22% of the tracings, which is comparable to previous studies. Consequently, this may limit the utility of mobile single-lead EKG device for mass AF screening and opportunity to offer oral anticoagulation for stroke prevention in those with newly detected AF. It remains unclear if other mobile single-lead EKG device which was found to have higher sensitivity and similar specificity when compared to the KM device will yield better AF screening performance.(117)

Recently, several studies have reported on the use of other smart wearable devices utilizing photoplethysmography-based technology for AF screening. The Apple Heart Study reported on the ability of a smartwatch photoplethysmography sensor and algorithm to screen individuals for an irregular pulse. Of 419,297 individuals, 2161 (0.52%) had a smartwatch-detected irregular pulse, with AF confirmed in 34% of those who returned an ECG patch. Of the 86 individuals who had a smart-watch detected irregular pulse while simultaneously wearing an ECG patch, 72 (84%) were in AF at the time.(110) The Huawei Heart Study similarly described the use of smartwatch or smartband photoplethysmography to screen 187,912 individuals. Of 227 with suspected AF who underwent complete history, examination, and ECG or 24-h Holter monitoring, 87% were confirmed to have AF.(114) Although these data highlight the utility of automated algorithms to flag possible AF, both studies still incorporated physician review of confirmatory traces and there remains paucity of data that compares photoplethysmography-based and single-lead EKG technology.

Clinical Implications

Our study has important clinical implications for AF screening and highlights opportunities for future research. Prior research has shown that automated device algorithms can achieve accurate rhythm analysis under ideal conditions. However, our real-world experience in a resource-limited setting demonstrates that single-lead EKG tracing artefact and other limiting factors frequently prohibits algorithm interpretation. Despite limitations with tracing quality, manual cardiologist adjudication can still provide a rhythm diagnosis in the vast majority of cases. Thus, our findings suggest that physician input remains necessary for AF screening until further improvements in automated algorithms occur. In the meantime, repeat EKG tracings and increasing familiarity with using single-lead EKG device are helpful to reduce 'unreadable' tracings to improve diagnostic yield. Future studies should be undertaken to validate other mobile device technology and automated algorithms in real-world settings.

Study Limitations

Our screening protocol required a repeat tracing for occasions without a rhythm decision. However, this was not performed in a proportion of the participants to result in incomplete data set. We acknowledge that the clinical value of AF screening in a young cohort with unknown risk factors for stroke is unclear. Nevertheless, given the knowns and unknowns of AF in sub-Saharan Africa and the higher prevalence of rheumatic heart disease, we did not restrict the AF screening to the typical target population of older individuals with higher stroke risk in developed countries.(137) As with all single time-point AF screening, paroxysmal AF may be missed, leading to false negatives. Although our liberal inclusion criteria did achieve a diverse sample of the local community, we acknowledge that our data may not

reflect the true prevalence of AF in this community due to the recruitment site being based at a local hospital.

6.5 CONCLUSION

The performance of the automated algorithm of the KM single-lead EKG device was sub-optimal when used for AF screening. However, the KM device remains an excellent and affordable tool when used in low-resource settings with appropriate clinician input.

6.6 TABLES & FIGURES

Table 1: Baseline clinical characteristics

Demographic and clinical information	Study Population (n=1,500)
Age (years), **mean ± SD**	35 ± 13
Gender, n (%)	
Male	960 (64)
Home region, n (%)	
SNNPR	1439 (96)
Omoria	30 (2)
Amhara	11 (1)
Other regions (including, Somalia, B-Gumuz, Addis Ababa, Harar)	19 (1)
Religion, n (%)	
Orthodox	416 (28)
Protestant	988 (66)
Muslim	70 (5)
Other religion or No religion	22 (1)
Education, n (%)	
Illiterate	55 (4)
Primary level school	137 (9)
Secondary level school	599 (40)
Certificate, Diploma or above	707 (47)
Occupation, n (%)	
Unemployed	175 (12)
Employed	682 (45)
Self employed	344 (23)
Others including student & retired	297 (20)
Clinical, mean ± SD, or n (%)	
Height (cm)	167.7 ± 8.6
Weight(kg)	67.1 ± 13.3
Systolic blood pressure (mmHg)	124.0 ± 17.7
Diastolic blood pressure (mmHg)	76.5 ± 11.7
Hypertension	104 (6.9)
Diabetes Mellitus	34 (2.3)
Congestive Cardiac Failure	20 (1.3)
Stroke	3 (0.2)
Coronary Artery Disease	2 (0.1)
Peripheral Arterial Disease	0 (0.0)
Chronic Lung Disease	16 (1.1)
Chronic Renal Disease	5 (0.3)
Valvular Heart Disease	11 (0.7)
Obstructive Sleep Apnea	2 (0.1)
Thyroid Disease	21 (1.4)
Smoker	5 (0.3)
Khat/Alcohol use	14 (0.9)
Infective Disease	288 (19.2)

Table 2:

(A) Rhythm decision from initial single-lead EKG in n=1,500 participants: KM automated algorithm vs. cardiologists' adjudication

		Cardiologists' Adjudication: Rhythm Decision of "Normal" or "Possible Atrial Fibrillation"	
		Y	**N**
KM Algorithm: Rhythm Decision of "Normal" or "Possible Atrial Fibrillation"	**Y**	1168	8
	N	287	37

Sensitivity = $\frac{1168}{1168+287}$ = 80.3% (95% CI 78.1-82.3%); Specificity = $\frac{37}{37+8}$ = 82.2% (68.0-92.0%)

(B) AF detection from n=1,709 single-lead EKG tracings: KM automated algorithm vs. cardiologists' adjudication

		Cardiologists' Adjudication: Atrial Fibrillation	
		Y	**N**
KM Algorithm: "Possible Atrial Fibrillation"	**Y**	9	61
	N	3	1636

Sensitivity = $\frac{9}{9+3}$ = 75.0% (95% CI 42.8-94.5%); Specificity = $\frac{1636}{1636+61}$ = 96.4% (95.4-97.2%)

FIGURE LEGENDS

Figure 1: AF Screening Advertising and KardiaMobile Single-lead EKG Recording

AF screening advertising & study information (in Amharic language) and single-lead EKG recording.

Figure 2: AF Screening Protocol

Figure 3: Examples of KM Single-lead EKG Tracings

Figure 4: Comparison of KM Algorithm versus Manual Assessment by Cardiologists

Results of rhythm decision outcome with KM algorithm (top row) and manual single-lead EKG assessment (bottom row).

Figure 5: Cumulative Occurrence and Contributors to 'No Rhythm Decision' from KM's Automated Algorithm on Initial EKG Tracing

(A) Cumulative occurrence of 'no rhythm decision' from participant's initial EKG tracing. (B) The occurrence of 'unreadable' tracing was significantly reduced when compared to 'unclassified' and 'tachycardia' tracings with increasing patient recruitment.

Figure 1: AF Screening Advertising and KardiaMobile Single-lead EKG Recording

Figure 2: AF Screening Protocol

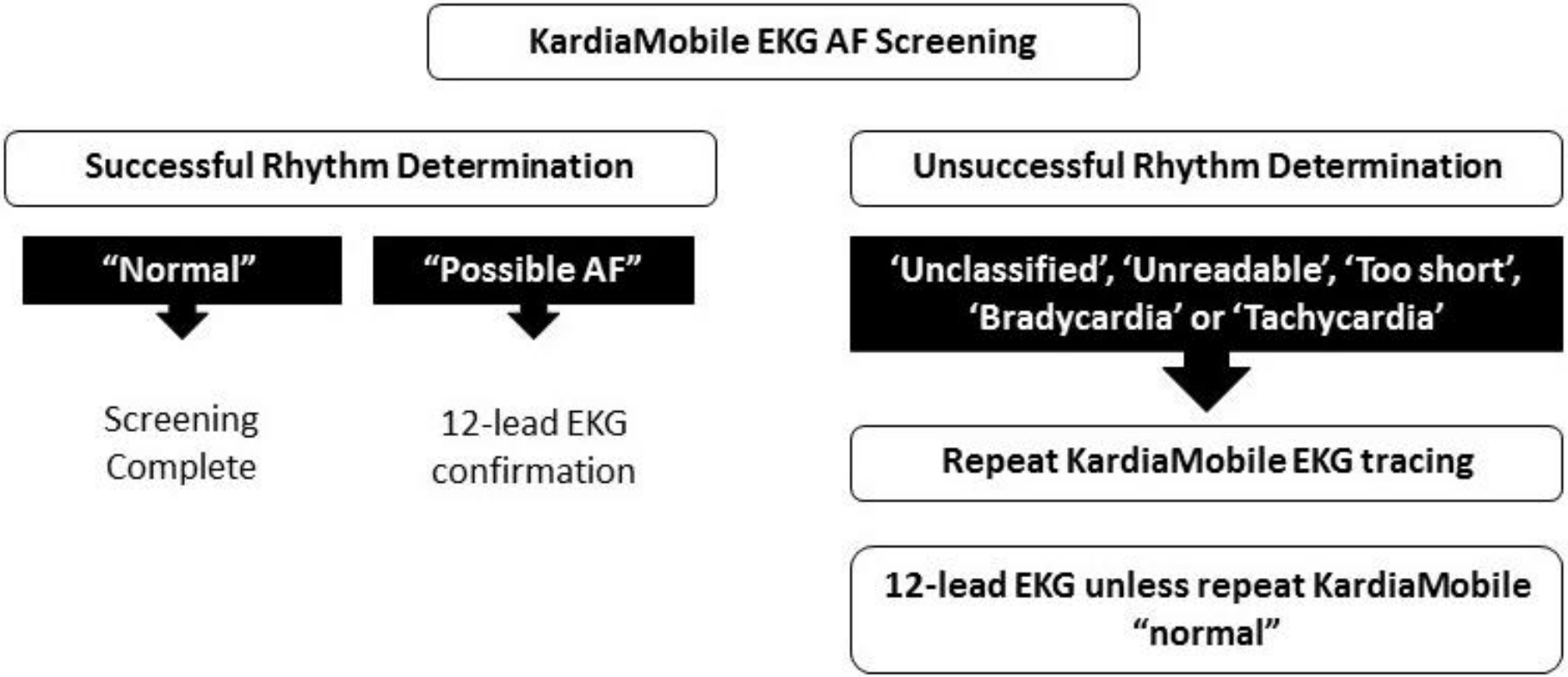


Figure 3: Examples of KM Single-lead EKG Tracings

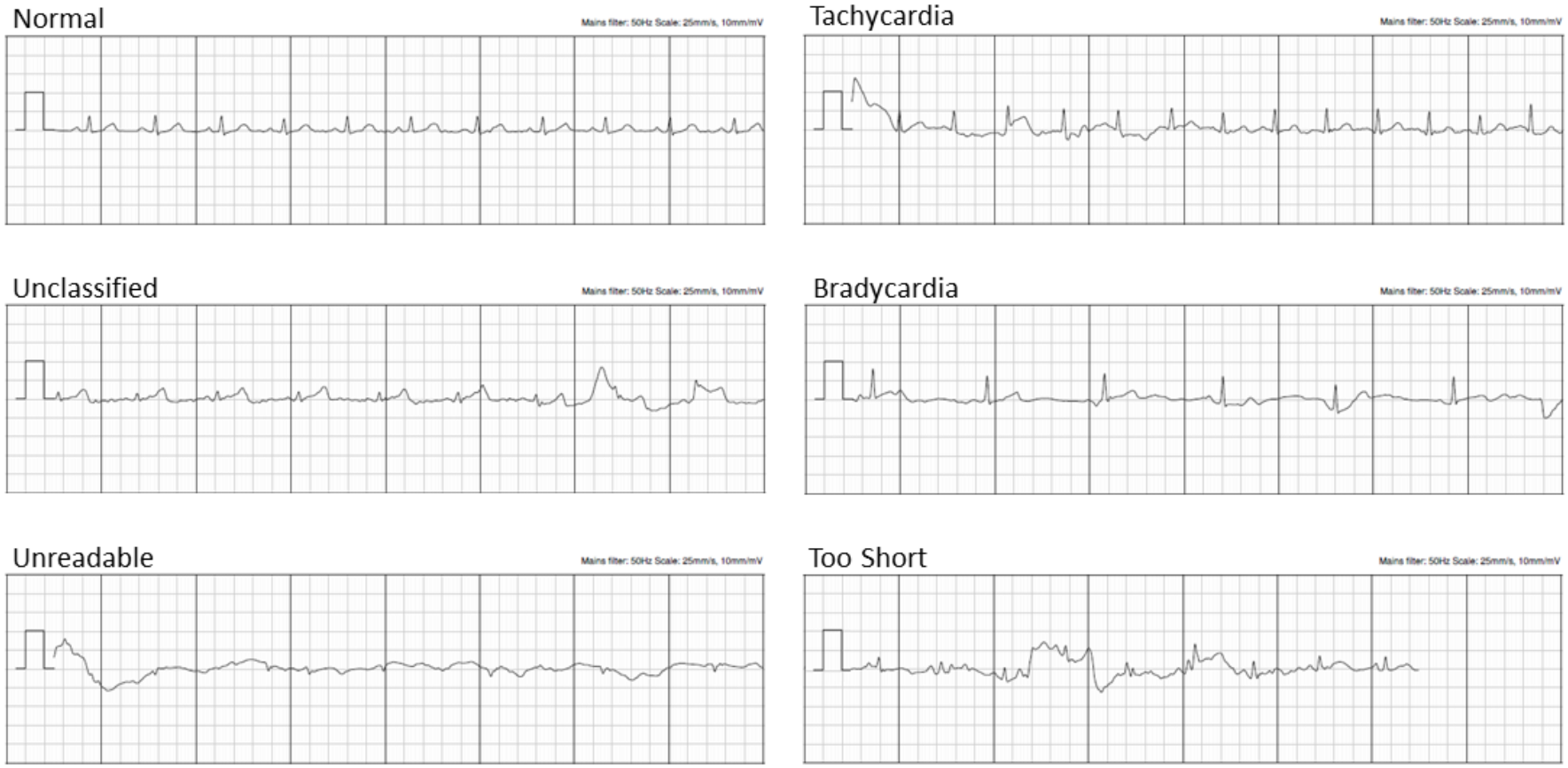


Figure 4: Comparison of KM Algorithm versus Manual Assessment by Cardiologists

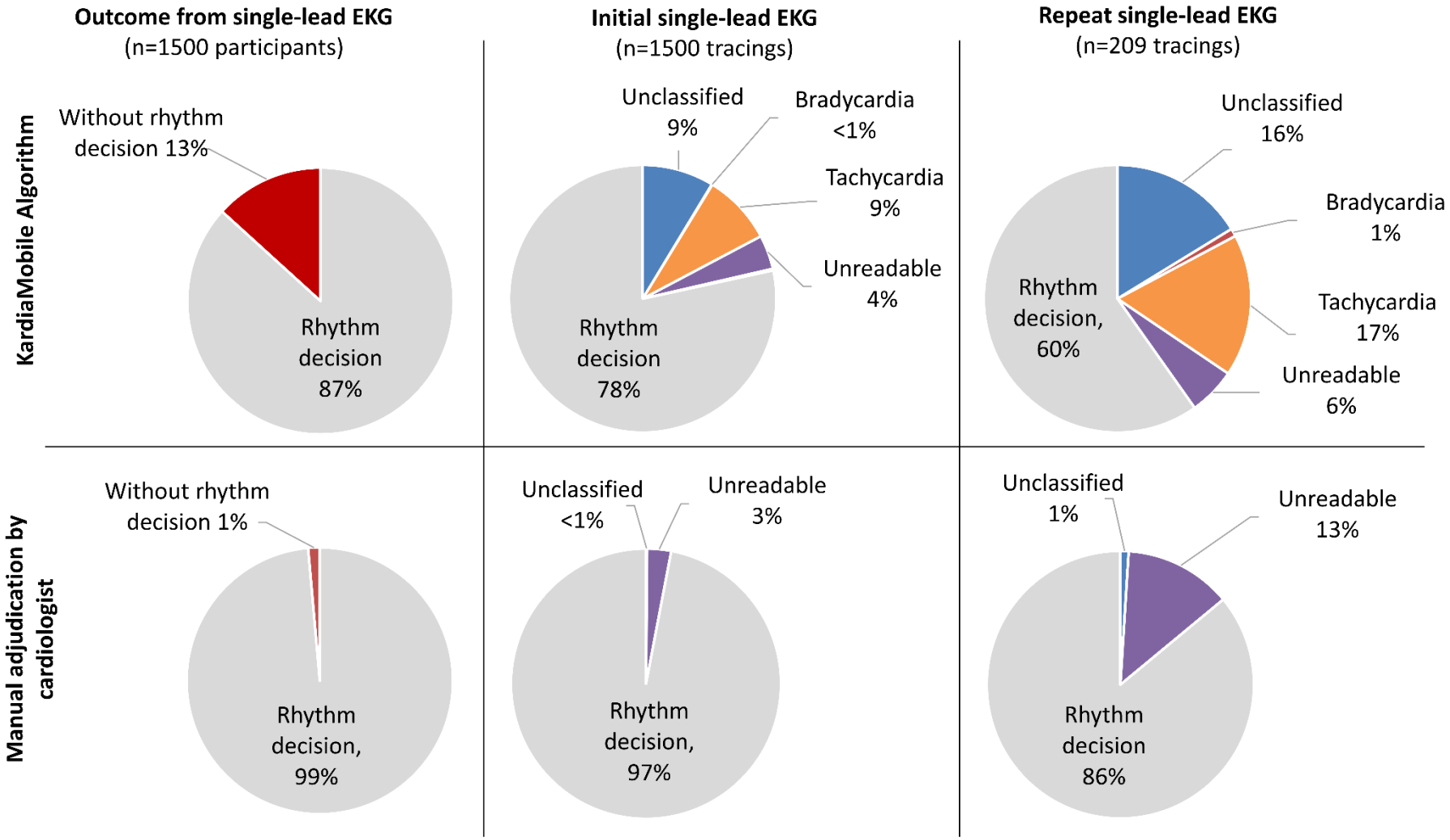
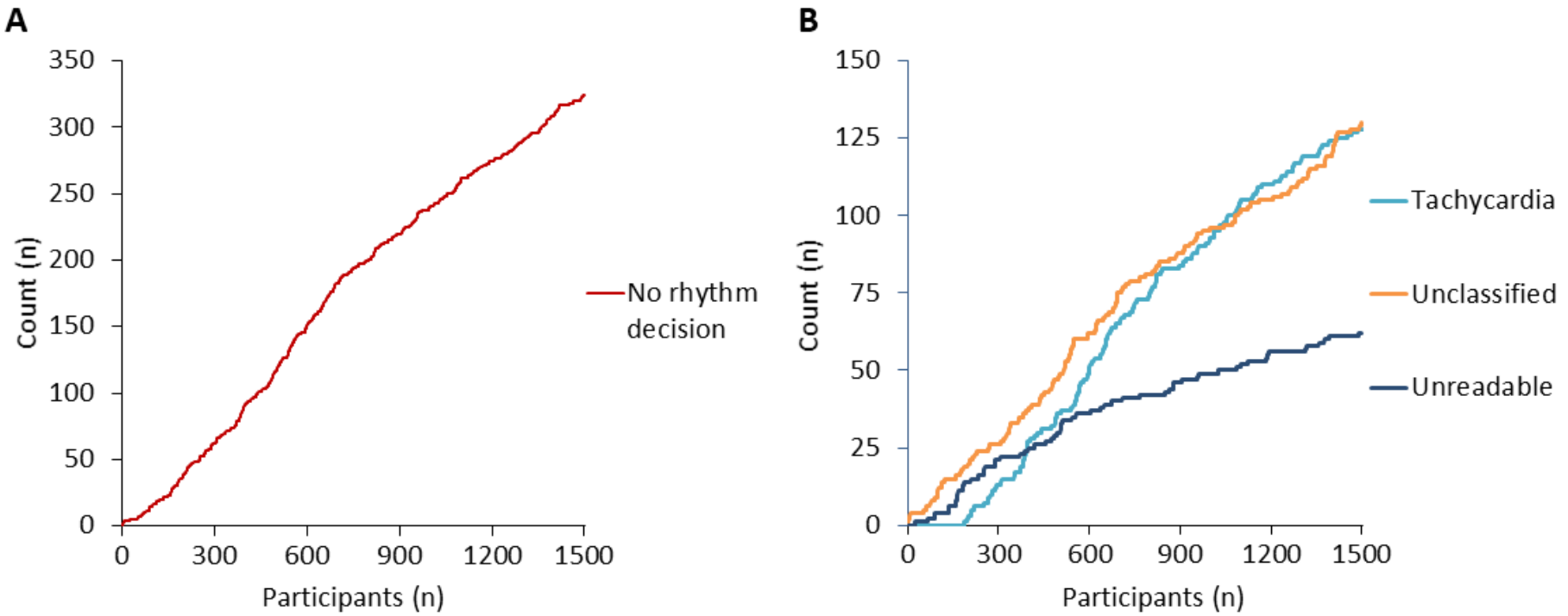


Figure 5: Cumulative Occurrence and Contributors to 'No Rhythm Decision' from KM's Automated Algorithm on Initial EKG Tracing



CHAPTER SEVEN – TEFF-AF PREVALENCE STUDY

AUTHORSHIP STATEMENT

Statement of Authorship

Title of Paper	The hEart oF ethiopia: Focus on Atrial Fibrillation assessing prevalence and risk factors in a semi-rural African population (TEFF-AF study)
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Prevalence and risk factors for atrial fibrillation in a semi-rural sub-Saharan African population - The hEart oF ethiopia: Focus on Atrial Fibrillation (TEFF-AF) Study

7 ABSTRACT

Background: There is a scarcity of reported data on the prevalence of atrial fibrillation (AF) in Sub-Saharan Africa.

Objective: To undertake AF screening in semi-rural Ethiopia.

Methods: The TEFF-AF (The hEart oF Ethiopia: Focus on Atrial Fibrillation) study conducted AF screening using single-lead electrocardiogram (EKG) device (KardiaMobile, KM) on willing community participants at the Soddo Christian Hospital, Ethiopia. Participants' clinical parameters and medical history were obtained to characterize their risk factor profile, including calculation of CHARGE-AF score.

Results: A total of 3,000 Ethiopians (median 31 (25-41) years old, 65% male) were screened. The participants were generally well-educated, from the local region and with low burden of cardiovascular risk factors. A total of 50 participants had CHARGE-AF score (five-year AF risk) of ≥2%. AF was detected in 13 (0.43%) individuals (median 50 (36-60) years old, n=7 male). The prevalence among participants over 40 years of age was 1% (9/930). AF prevalence was higher for older age groups, with ≥70 years of age reaching 6.67% (3/45). Population prevalence was estimated to be 234 persons (95%CI 7 - 460) per 10,000 for ≥60 years of age. Four (31%) of the 13 participants with AF had a CHA_2DS_2VASc score of ≥2, and others likely had rheumatic valvular AF, but only 2 of the 13 participants with AF were on oral anticoagulation therapy

Conclusion: In this semi-rural Ethiopian community of relatively younger participants, AF prevalence was found to be low but increased with increasing age. Mobile single-lead EKG technology can be used effectively for AF screening in low-resource settings.

Clinical Trial Registration: ANZCTRN12619001107112

Keywords: Atrial Fibrillation, Screening, Ethiopia, Prevalence, sub-Saharan Africa, risk factors.

7.1 INTRODUCTION

Atrial fibrillation (AF) is a growing public health problem worldwide. The Global Burden of Disease study estimated that the worldwide age-adjusted prevalence of AF in 2010 was approximately 0.5%, representing a total of 33.5 million individuals.(2) In Sub-Saharan Africa the leading cardiovascular cause of death and disability in 2010 was stroke, and the largest relative increases in cardiovascular disease burden between 1990 and 2010 were in AF and peripheral arterial disease(2). Furthermore, cardiovascular deaths occur at younger ages in sub-Saharan Africa as compared to the rest of the world. Individuals with AF in Africa have higher mortality rates,(11) although due largely to poor healthcare access and suboptimal therapy. The Global Burden of Disease study also highlighted the crucial need for more data from population surveillance studies in sub-Saharan Africa due to the paucity of data from this region.

Several factors may contribute to the changing prevalence of AF in developing nations. The burden of communicable disease persists and rheumatic heart disease is associated with higher AF prevalence in younger populations.(133) Additionally, the epidemiological transition in sub-Saharan African regions with gradual adoption of Western lifestyle is likely increasing the impact of modifiable risk factors on AF prevalence. There is significant variation

in the prevalence of AF reported across different countries in Africa and estimates may be skewed by poor health-seeking behaviors and limited access to diagnostic equipment.(138) Better understanding of the cardiovascular risk factor profile in these regions can help guide preventative and management strategies. Given the relative scarcity of AF epidemiology data from Sub-Saharan Africa regions, we undertook the TEFF-AF (**T**he h**E**art o**F** Ethiopia: **F**ocus on **A**trial **F**ibrillation) screening study to characterize the prevalence of AF and associated risk factor profile in semi-rural south-central Ethiopia.

7.2 METHODS

The TEFF-AF study (Australian Clinical Trials Registry Number: 12619001107112) was undertaken from August through December 2019, on the campus of the Soddo Christian Hospital (SCH) which provided institutional research ethics approval. This study complied with the ethical principles of the 2013 Declaration of Helsinki. SCH is a major trauma center situated in the town of Soddo, with a population of around 200,000 individuals in south-central Ethiopia. Eligibility was limited to ambulant adults aged 18 years and above who were able to provide informed consent. Signage in the Amharic language was erected at SCH to invite willing individuals from the community and visitors to the hospital to participate in the screening. Inpatients at SCH were not included in this study. A team of five nursing and research support staff from the SCH performed the screening following specialized training on the use of the KardiaMobile single-lead EKG device (KM, AliveCor Inc, USA) paired to an iPhone application (Version 5.7.4, KardiaAI: 1.1.7). Training included tutoring on acquiring the best quality single-lead EKG tracing with the KM device and subsequent hands-on practice.

An online customized REDCap (Research Electronic Data Capture, Vanderbilt University, TN, USA) database was utilized.(173) Baseline demographic and clinical parameters were obtained by a brief structured questionnaire to characterize the cardiovascular risk profile of participating individuals. The CHARGE-AF risk model adequately predicts five-year AF risk among Africans in the United States and Europe (using variables of age, race, height, weight, systolic and diastolic blood pressure, current smoking, use of antihypertensive medication, diabetes, and history of myocardial infarction and heart failure).(174) This score was calculated for each TEFF-AF participant. Stroke risk was calculated using CHA_2DS_2-VASc score for participants found to have AF. A multi-stage protocol for screening was undertaken which has previously been described.(175) Height and weight measurements were obtained to calculate body mass index (BMI, kg/m^2). Blood pressure measurements were undertaken in the seated position (Omron Intellisense T5 automatic monitor, Omron Corporation) which was repeated when the initial systolic reading exceeded 130mmHg. A 30-sec single-lead EKG acquisition using the KM device was then obtained from the participant.

EKG acquisition and AF determination

The KM device records a bipolar lead I EKG tracing when two or three fingers from each hand of the user is placed in contact with the two electrodes. Participants were instructed to relax their arms and hands to reduce noise and artefact. A 30-sec single-lead EKG recording can be viewed in real-time on the smartphone application and saved as a PDF file. The noise-filtered trace and computer-averaged complex on the smartphone application is then subjected to an automated algorithm for arrhythmia diagnosis using the two criteria of p-wave absence and R–R interval irregularity.(118) The outcome of the automated algorithm assessment of rhythm dictated the need for repeat KM tracing and/or a 12-lead EKG. The screening protocol

is deemed complete if the rhythm was assessed as 'normal' by the automated algorithm. A 12-lead EKG was indicated if the rhythm was assessed as 'possible AF'. A repeat KM tracing was required if the rhythm was assessed as "bradycardia", "tachycardia", "unclassified", "unreadable", or "too short". If the same results or 'possible AF' were obtained after repeat KM tracing, a 12-lead EKG will then be indicated.

The 30-sec KM traces obtained by participants were downloaded as PDFs for manual analysis by two cardiologists independently (investigators CXW and SI) to confirm rhythm diagnosis. The cardiologists also assessed diagnostic limitations for traces categorized automatically as "bradycardia", "tachycardia", "unclassified", "unreadable", or "too short" into the following: artefact, ectopy, bradycardia, tachycardia, or insufficient sample duration. All 12-lead EKGs were standardized with scale of 1mV:10mm and paper speed of 25mm/s. They were independently adjudicated by two physicians (investigators SC and DHL). Participants in AF were offered transthoracic echocardiogram at SCH to evaluate the presence of any structural heart disease and referred for follow-up by SCH physician.

Statistical Analysis

Continuous data are expressed as mean and standard deviation or median and interquartile range appropriate to data distribution assessed by Shapiro-Wilk test. Binary data are presented as percentage (with numerator/denominator in brackets). Categorical data were analyzed using the chi-squared or Fisher's exact test. The sensitivity and specificity for the ability of the KM to produce a rhythm decision against the cardiologists' interpretation was calculated. All statistics were performed in SPSS (Version 26), with statistical significance set at $p<0.05$.

7.3 RESULTS

A total of 3,000 participants were recruited. The baseline clinical parameters of the participants are shown in Table 1. The median age was 31 (25-41) years old (35% female, median BMI 23.0 (20.5-26.4) kg/m^2) with 31% being 40 years of age or older. The vast majority (94%) of the participants were from the regional state of Southern Nations, Nationalities, and People's Region (SNNPR) where the SCH is located. Seventy-eight percent (n=2,352) had at least secondary level education and 44% (n=1,320) reported salaried employment.

Prevalence of AF

There was a total of 13 participants (n=7 were male) determined to have AF, equating to an overall prevalence of 0.43% (Figure 1A). The prevalence of AF increased exponentially with increasing age from 0.18% in those under 30 years old to 2.3% for those aged above 60 years of age. The AF prevalence for participants aged ≥70 years was 6.67% (3/45). The estimation of AF prevalence for each age group is shown in Figure 1B, with 234 persons (95%CI 7 - 460) per 10,000 population among those aged 60 and above. The clinical parameters of the participants with AF are shown in Table 2. History of known structural heart disease were reported by 6 of these participants and 4 participants had a systolic blood pressure above 130mmHg during screening. The median heart rate of those in AF was 94bpm (IQR 85-100), including one individual at 148bpm. Transthoracic echocardiogram was obtained for 7 of these participants demonstrating presence of underlying valvular pathology in all of them.

Associated comorbidities in those with and without AF

Participants with AF were more likely to be older with higher proportion with known heart failure, valvular heart disease and on regular medications (Table 3). The most prevalent reported risk factor was hypertension (5.2%) although 17.8% (533/3000) of subjects had systolic blood pressure greater than 140mmHg during screening. Malaria and typhoid (10% and 14% respectively) were common amongst participants, but not for those with AF. A total of 50 participants had CHARGE-AF score (five-year AF risk) of ≥2%. The CHARGE-AF score was on average higher for those with AF than those without (0.84% vs. 0.22%, p=0.029), although only 3 participants with AF (23%) had a CHARGE-AF score of ≥2% five-year risk of AF (Figure 2A). Four (31%) of the 13 participants with AF had a CHA_2DS_2-VASc score of 2 or greater (Figure 2B) consisting of 3 females with CHA_2DS_2-VASc score ≥3 and 1 male with CHA_2DS_2-VASc score ≥2, while none of these participants were on oral anticoagulation therapy. Only 2 other participants with AF were on oral anticoagulation therapy who were both males with congestive heart failure associated with mitral and/or aortic regurgitation (Table 2).

Outcomes from KM automated algorithm

Of the initial single-lead KM tracings performed on the 3,000 participants (Figure 3A), the KM algorithm was unable to provide a rhythm decision in 18% (n=549) due to 'unclassified' (8.6%, n=258), 'tachycardia' (7.2%, n=215), 'unreadable' for (2.1%, n=63), 'too short (0.1%, n=3) and 'bradycardia' (0.3%, n=10). A repeat KM tracing was obtained in 70% (n=383 of 549) of the participants who did not have an initial rhythm decision, which achieved a rhythm decision in 207 additional subjects, with an overall rhythm decision in 89% (n=2658; Figure 3B & C). The remaining repeat KM tracings showed 'tachycardia' (n=79), 'unclassified' (n=75), 'unreadable' (n=12), and 'bradycardia' (n=10). Manual assessment of the KM tracings by cardiologists provided a greater rhythm decision yield than the KM algorithm. Only 2% of KM traces were

considered non-diagnostic by manual adjudication. Overall, the KM AliveCor had a sensitivity of 81.3% and specificity of 96.5%, and although the negative predictive value of 99.9% was high, the positive predictive value was only 12.4%.

12-lead EKG analysis

In total, there were 456 (15%) participants who met protocol criteria for a 12-lead EKG but only 181 EKGs were obtained (Figure 4). This was largely due to participants not wanting to wait for the 12-lead EKG to be performed in the SCH emergency room, or a KM outcome of "tachycardia" which the screening team assessed as sinus tachycardia not requiring a 12-lead EKG. The majority (n=160/181) of 12-lead EKGs showed sinus rhythm. Twelve-lead EKG was performed in 65% (n=74) of the 114 "possible AF". However, manual cardiologists' assessment of the remaining n=40 "possible AF" KM traces without 12-lead EKGs only found 2 AF tracings. There were no 12-lead EKG diagnosis of AF not having a KM outcome of "possible AF". A repeat KM attempt without a rhythm decision indicated the need for a 12-lead EKG for 342 participants. However, 12-lead EKG was obtained for only 74% (17/23) of "unreadable", 64% (67/104) of "unclassified", 33% (4/12) of "bradycardia" and 9% (19/203) of "tachycardia". Of these 107 EKGs, the majority were adjudicated as sinus rhythm or sinus arrhythmia and the remainder were found to have intraventricular conduction delay, pre-excitation, multiple ectopics, supraventricular tachycardia, complete heart block or junctional rhythm (Figure 4).

Participant experience and protocol compliance

During the screening protocol, the majority of participants (84%; n=2,531) only performed one KM EKG trace without a repeat or a 12-lead EKG. There were additionally 10% (n=288)

who completed two KM attempts but did not have a 12-lead EKG. A 12-lead EKG was performed in addition to the KM screening for the remaining 6% (n=181). Overall, 90% (n=2694) of participants completed the screening protocol as defined. Non-compliancy was due to not having performed a required repeat KM in 5.6% (n=168), and not having performed a required 12-lead EKG in 3.6% (n=107). Additionally, there was 31 participants who did not undergo repeat KM EKG acquisition but had a 12-lead EKG performed instead. There were 21 participants who provided an additional KM trace beyond the protocol requirement who did not have a 12-lead EKG performed as required after a KM algorithm result of "possible AF". There were only 2 occasions when this repeat KM attempt again returned a result of "possible AF".

7.4 DISCUSSION

This study is the largest AF screening study from semi-rural Ethiopia. First, we found overall AF prevalence of 0.43% in 3,000 generally younger (median 31 years old) and well-educated participants. Second, AF prevalence was higher with increasing age and in the presence of known structural heart disease. Third, hypertension was the most common risk factor for AF followed by diabetes and valvular heart disease. Fourth, the KM single-lead EKG technology was suitable for AF screening with the automated algorithm able to detect 85% as normal sinus rhythm. Additional 12-lead EKG and manual assessment was needed for rhythm assessment in the remainder. Last, 31% of the participants screened with AF in this study had CHA_2DS_2-VASc score of more than two and were not on oral anticoagulation therapy. Our findings have important public health and implications given the scarcity of such reported data from this community.(125) In a prospective global registry of >15,000 AF patients, it was observed that annual AF mortality in Africa was twice that as compared to North America,

Western Europe, and Australia, and the rate of strokes was highest in African patients with AF.(11) Furthermore, as life expectancy in Ethiopia has increased by approximately 22 additional years over the last two decades (47 years in 1990 to 69 years by 2019),(139) the impact of aging and chronic diseases such as AF will become more significant.

Ascertaining AF prevalence from screening

It is known that the incidence of detecting previously undiagnosed AF is dependent on the underlying population risk of AF, the intensity or duration of screening, and the method used to detect AF.(125) In a nearby Southwest town from our screening venue, a community-based cross-sectional study with 12-lead EKG in 634 adults (mean 63 years old) reported an AF prevalence of 4.3%.(145) Consistent with the results of our screening, the prevalence of AF rose steeply with advancing age. They reported a prevalence of 6.9% (4/58) in those above 80 years of age, which is comparable to the 6.67% prevalence in those above 70 years old in this current study. Although our 30-sec single-lead EKG screening found an overall low prevalence of AF in a relatively young cohort, it remains in the ballpark of the estimated worldwide age-adjusted prevalence of ~0.5% and the 2010 Global Burden of Disease study estimation of 0.44-0.66% in the sub-Saharan African region.(2) However, these estimates may be skewed by the effects of sampling, with known variability in healthcare infrastructure and services among sub-Saharan African countries and poor health-seeking behavior.(138) Notably, AF patients in sub-Saharan Africa tend to be younger and with higher mortality rates due to poor healthcare access and suboptimal therapy,(133) and screening may help to identify individuals who can benefit from risk factor modification and medical therapy to reduce the burden of disease and associated morbidities.

Impact of digital technology for AF screening in the low-resource settings

AF screening by palpation is a simple technique that is useful in low-resource settings, but portable digital technology, such as handheld single-lead EKGs or plethysmography devices are becoming more readily available and have shown greater yield.(22) We used the KM device which has previously been shown to have high sensitivity and specificity for AF detection in validation study.(118) The utility of this technology for mass screening in low-resource communities has previously been demonstrated.(112) However, we reported a limitation of this technology with the inability of the device algorithm to provide a rhythm decision for ~13% of participants even with repeat tracing.(175) This limitation can be minimized through increased user familiarity and careful execution of the acquisition technique to obtain better quality EKG signals. One advantage of EKG tracing over plethysmography in low-resource settings is the option of remote manual adjudication by a clinician to enhance diagnostic yield and reduced dependence on automated algorithm performance.(171, 176) Our study protocol included repeated tracing attempts, along with select use of 12-lead EKG, to optimize yield from this single occasion screening strategy. Although mobile digital technology provides the opportunity for continuous monitoring of large cohorts as seen in the Apple heart and Huawei studies, the affordability of such in low-resource settings and the low sensitivity of AF detection would reduce its utility.(114, 115)

Risk factors for AF in sub-Saharan Africa

The risk factors for AF in sub-Saharan Africa are likely to be altered by the high prevalence of rheumatic heart disease, which is also known to be the most common acquired cardiovascular disease in young individuals under 25 years of age.(136, 177) Unfortunately, not much is known about the burden of AF related to rheumatic heart disease in this region.(137) A recent

meta-analysis has shown the global prevalence of AF in rheumatic heart disease to be 32.8% (range: 4.3%–79.9%).(135) In the Ethiopian capital of Addis Ababa, a retrospective chart review of 500 adult cardiology patients with rheumatic heart disease found that 46.8% had AF.(140) Indeed, valvular heart disease was more common in those with AF in our study, as confirmed with echocardiographic imaging, including the two on warfarin, and one on monthly Benzylpenicillin. It is likely that the burden of valvular heart disease was higher given that 6 of the participants with AF did not undertake an echocardiogram. However, many parts of sub-Saharan Africa are undergoing epidemiological transitions with gradual adoption of Western lifestyle leading to development of new AF risk factors including hypertension, dyslipidaemia, diabetes and obesity.(130) Others have recently reported smoking, hypertension and increased BMI as main risk factors associated with AF in Southwest Ethiopia.(145) Our data shows that hypertension was the most common risk factor for AF followed by diabetes and valvular heart disease in a younger cohort in semi-rural Ethiopia. Although no studies have demonstrated that AF screening reduces mortality or incidence of thromboembolic complications,(178) we are able to characterize the risk factor profile of this semi-rural Ethiopian cohort and detect high-risk individuals with AF who are not on anticoagulants and may benefit from long-term oral anticoagulant therapy. More work is necessary to characterize the burden of AF and the associated risk factor profile including rheumatic heart disease in sub-Saharan Africa where healthcare resources are scarce and more targeted public health and lifestyle measures would be valuable to curtail the expected significant increase in AF over the coming decades.(133, 136, 137, 179)

Clinical Implications

Our study has important clinical implications for AF screening and highlights opportunities for future research especially in the younger population with underlying structural heart disease as well as more urbanized communities that are undergoing epidemiological transition in sub-Saharan Africa. We have shown that portable digital technology can be utilized for AF screening programs in low-resource settings. Employing a strategic protocol when utilizing such technology for AF screening will ensure optimized diagnostic yield and reduce dependence on physician input to achieve screening accuracy.

Study Limitations

Our screened sample had a low number of participants in the older age group. However, it reflects the demographic of this semi-rural regional hub with higher education institutions and professional employment opportunities. We did not specifically collect data on why a participant had attended the hospital precinct for screening. We cannot rule out inclusion of participants who were screened whilst they were awaiting treatment. The participant medical history was self-reported and not able to be verified against medical records with potential underestimation of the cardiovascular risk factor profile. AF detection rate would be higher with longer monitoring period. Low health literacy could have contributed to the inability to distinguish incident new AF from prevalent AF, and explained the relatively low proportion of participants on oral anticoagulation therapy. Echocardiogram examination was mostly qualitative due to the non-availability of fully trained imaging expertise and we could not confidently ascertain the true proportion of valvular disease due to rheumatic versus degenerative changes. Valvular disease may also have been present in the 6 participants who had AF but did not undertake an echocardiogram.

7.5 CONCLUSION

The prevalence of AF from the TEFF-AF AF screening study in a relatively young semi-rural Ethiopian cohort was less than one percent. The AF prevalence was higher with increasing age and in those with structural heart disease. Mobile single-lead EKG technology can be used effectively for AF screening in low-resource settings.

7.6 TABLES & FIGURES

Table 1: Baseline clinical characteristics

Demographic and clinical information (n=3,000)	Participants, n (%)
Age; median 31 (IQR 25-41) years	
<30	1224 (41)
30 - 39	846 (28)
40 - 49	472 (16)
50 - 59	287 (10)
60 - 69	126 (4)
70+	45 (2)
Gender	
Male	1975 (65)
Female	1025 (35)
Home region	
SNNPR	2810 (94)
Oromia	61 (2)
Amhara	17 (1)
Other regions (including, Somalia, B-Gumuz, Addis Ababa, Harar)	47 (2)
Unspecified	65 (2)
Religion	
Orthodox	786 (26)
Protestant	2015 (67)
Muslim	129 (4)
Other religion or No religion	70 (2)
Education	
Illiterate	160 (5)
Primary level school	462 (15)
Secondary level school	1028 (34)
Certificate, Diploma or above	1324 (44)
Unspecified	26 (1)
Occupation	
Unemployed	84 (3)
Employed (worker)	484 (16)
Employed (professional)	836 (28)
Self employed	737 (25)
Householder/housewife	251 (8)
Retired	22 (1)
Student	472 (16)
Other	114 (4)
Clinical	
BMI; 23.0 (IQR 20.5-26.4) kg/m2	
Underweight (BMI <18.5)	223 (7)
Normal (BMI 18.5 – 24.9)	1749 (58)
Overweight (BMI 25 – 29.9)	770 (26)
Obese (BMI ≥30)	258 (9)
Blood Pressure; 124 (IQR 114 – 135) mmHg systolic	
Hypertensive (Systolic BP >140mmHg)	533 (18)

Table 2: Participants with atrial fibrillation

Age (years)**; gender**	**BMI** (kg/m^2)	**Medical history**	**Medications**	**BP** (mmHg)**; heart rate** (bpm)	**CHA_2DS_2-VASC**	**Echocardiogram**
20; M	20.2	CHF, Heart disease	Enalapril, warfarin	100/80; 128	1	Dilated LV with systolic dysfunction, dilated LA, MR & TR
20; M	16.3	CHF, Heart disease(valvular)	Enalapril, metoprolol, warfarin, Frusemide	120/70; 100	1	Dilated LV with systolic dysfunction, dilated LA, AR/MR/TR
30; M	23.9	Heart disease(valvular)	Monthly Benzylpenicillin	122/90; 88	0	N/A
36; F	23.8	HTN, DM	Nil	117/86; 99	3	Normal size LV and low-normal systolic function; dilated LA; MR/TR; pulmonary hypertension; RV dilated with poor systolic function.
40; F	26.3	Malaria	Nil	132/92; 94	1	N/A
48; F	19.4	Nil reported	Nil	127/86; 83	1	N/A
50; M	18.8	CHF, Heart disease(valvular)	Enalapril, Phenytoin, statin, aspirin	120/70; 100	1	Normal size LV, grossly dilated LA, severe MS, severe MR & severe TR
50; F	24.6	Thyroid disease	Nil	145/85; 80	1	N/A
58; M	19.8	Nil reported	Nil	100/64; 85	0	N/A
60; M	17.0	Nil reported	Nil	116/83; 69	0	N/A
70; F	21.3	HTN, DM, CHF	Frusemide, aspirin, enalapril, digoxin, spironolactone	145/83; 108	5	Normal size LV, dilated LA, MR & TR
75; M	19.1	CHF, Heart disease(valvular)	Enalapril, Frusemide, spironolactone	116/88; 148	3	Valvular regurgitation (AR/MR/TR)
80; F	18.2	HTN, currently has Pneumonia	Nil	150/80; 65	4	Normal biventricular size and function. Moderate AR/AS & mild MS.

F - female; M - male; BMI - body mass index ; BP - blood pressure; CHF - congestive heart failure; HTN - hypertension; DM - diabetes mellitus; LV - left venticle; LA - left atrium; AR - aortic regurgitation; MR - mitral regurgitation TR - tricuspid regurgitation; RV - right ventricle; MS - mitral stenosis; AS - aortic stenosis

Table 3. Participant clinical parameters, self-reported medical history and risk factors

	Participants without AF (n=2987)		Participants with AF (n=13)		p-value
Age (years)	31	(25-41)	50	(36-60)	0.005
Age ≥65 years	76	3%	3	23%	0.18
BMI (kg/m^2)	23	(21-26)	20	(19-24)	0.007
Measured systolic blood pressure ≥140mmHg	530	18%	3	23%	0.71
Hypertension	153	5%	3	23%	0.27
Diabetes mellitus	66	2%	2	15%	0.41
Heart failure	19	1%	7	54%	<0.001
Stroke	3	<1%	0	-	-
Valvular heart disease	7	<1%	4	31%	0.046
Renal failure	5	<1%	0	-	-
Chronic lung disease	16	1%	0	-	-
Obstructive sleep apnoea	2	<1%	0	-	-
Thyroid disease	21	1%	1	8%	0.79
Smoker					
- Current	7	<1%	0	-	-
- Previous	19	1%	1	8%	0.78
Khat chewing					
- Current	11	<1%	0	-	-
- Previous	21	1%	0	-	-
Alcohol					
- Current	7	<1%	0	-	-
- Previous	17	1%	0	-	-
Malaria	409	14%	0	-	-
Typhoid	308	10%	0	-	-
Any infective disease					
- Current	50	2%	2	15%	0.38
- Previous	233	8%	2	15%	0.80
Currently taking any medication	128	4%	7	54%	0.001

FIGURE LEGENDS

Figure 1: AF prevalence

A) Frequency of AF detected by screening for males and females by age group, and B) estimated AF prevalence per age group.

Figure 2: CHARGE-AF and CHADSVASc scores

A) Calculated CHARGE-AF score for five-year risk of AF, and B) calculated CHA_2DS_2VASc score for AF participants.

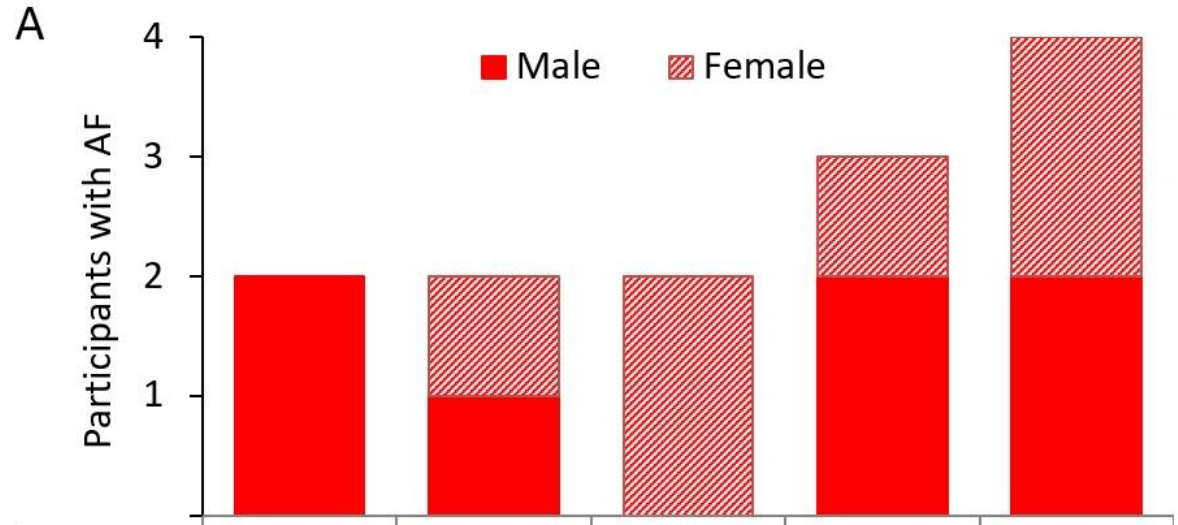
Figure 3: Participants' rhythm assessment by KM Algorithm

A) KM algorithm outcomes on first attempt, and B) KM algorithm outcome on second attempt, and C) overall KM algorithm outcome.

Figure 4: Diagnosis by 12-lead EKG

Diagnostic yield of 12-lead EKGs performed for each final KM outcome. SR; Sinus rhythm. AF; Atrial fibrillation. CHB; Complete heart block. IVCD; Intraventricular conduction delay. SVT; Supraventricular tachycardia.

Figure 1: AF prevalence



Age group	<30	30-39	40-49	50-59	60+
AF detected	2	2	2	3	4
Screened	1224	846	472	287	171

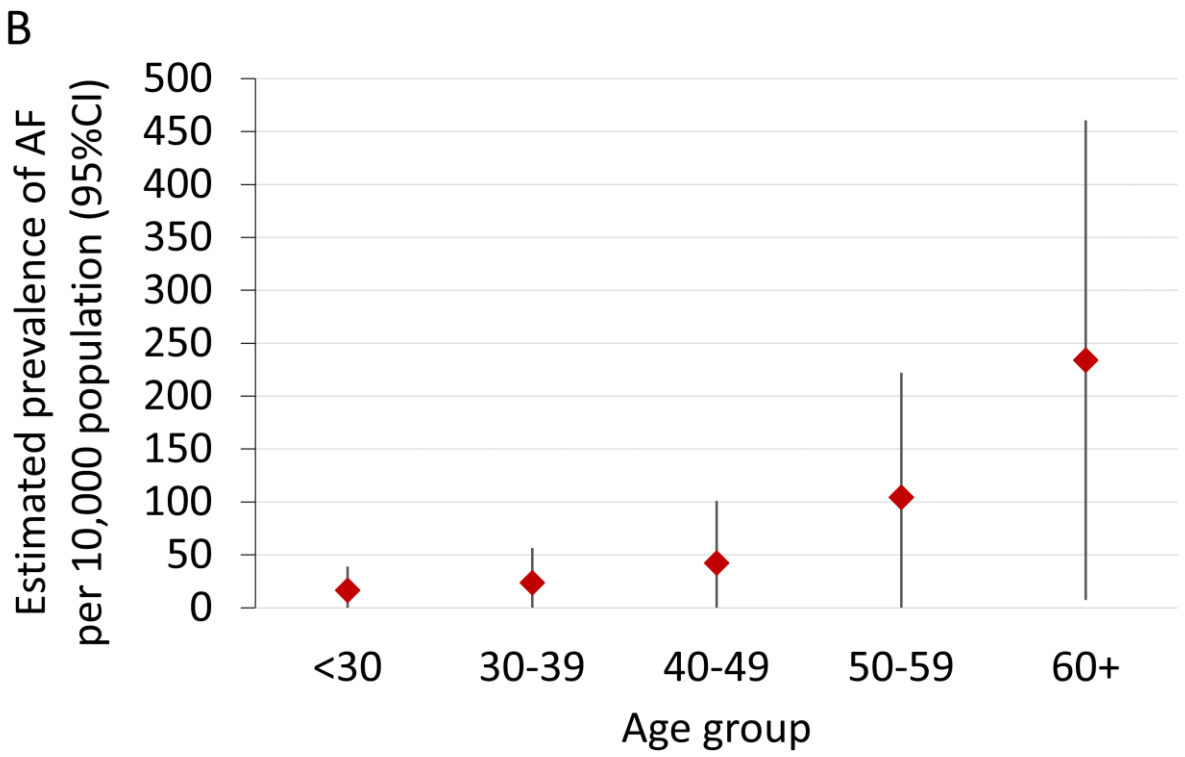


Figure 2: CHARGE-AF and CHADSVASc scores

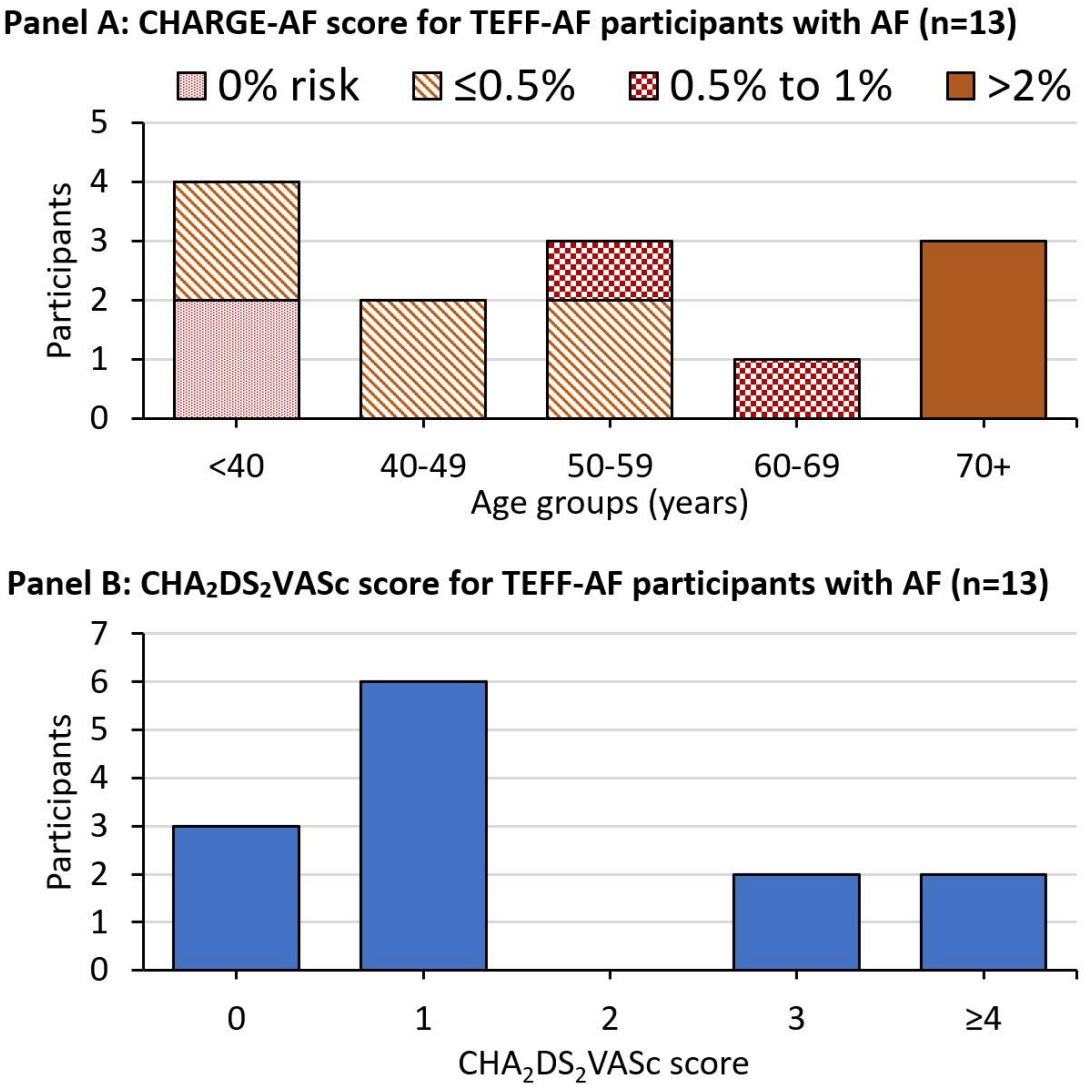


Figure 3: Rhythm assessment by KardiaMobile automated algorithm

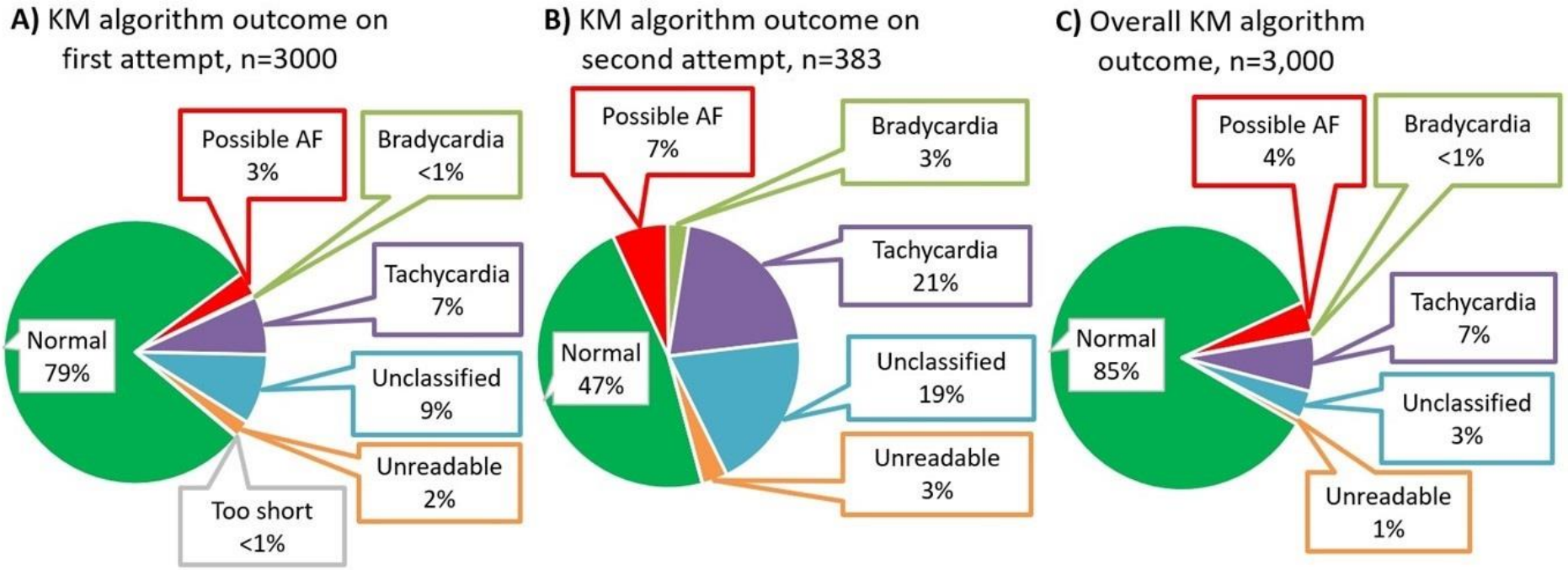
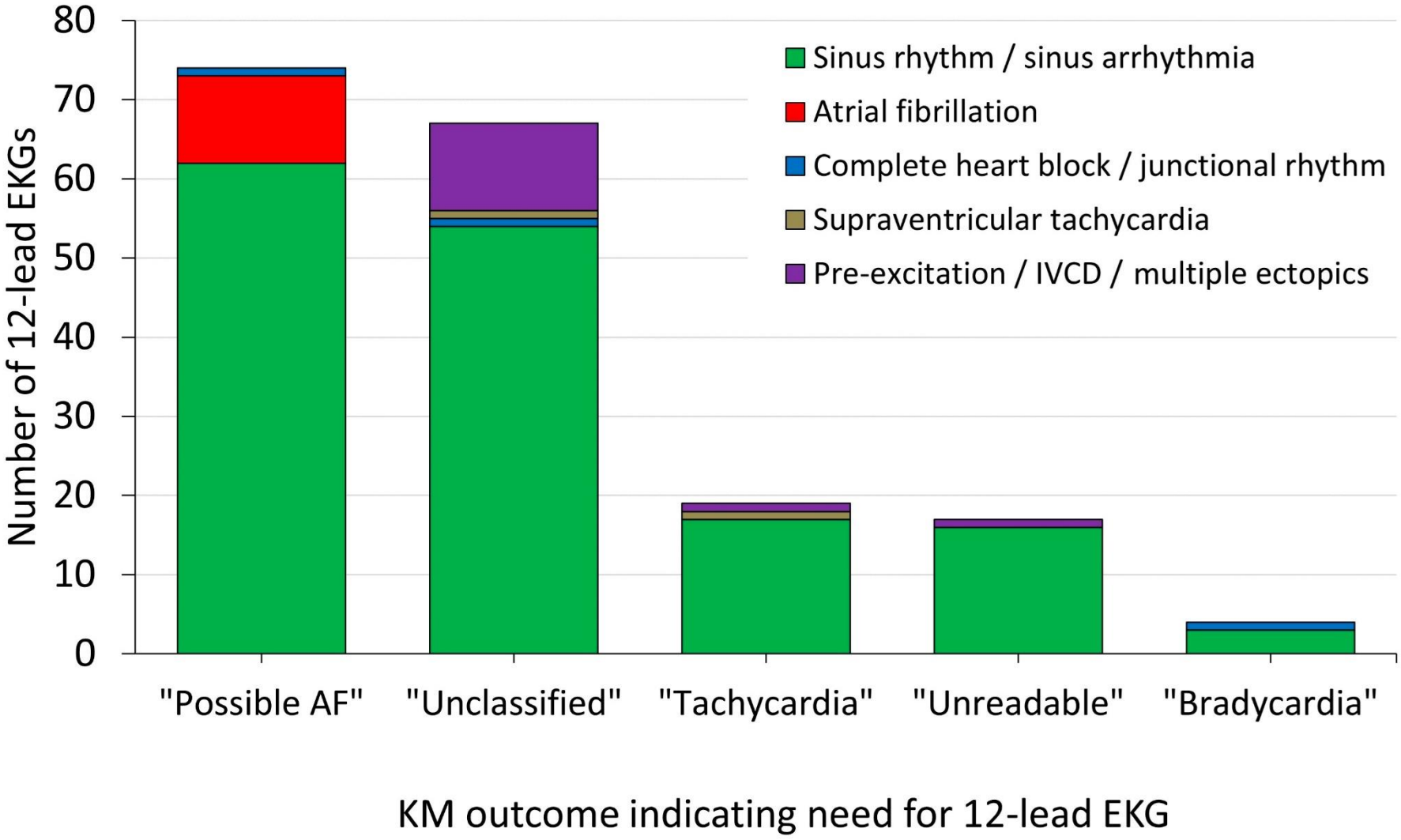


Figure 4: Diagnosis by 12-lead EKGs



CHAPTER EIGHT – FINAL DISCUSSIONS

8 FINAL DISCUSSIONS

This thesis presents an evaluation of the current state of play in the care and management of heart rhythm disorders, with a focus on identifying opportunities where utilising technology may help to improve outcomes. It was hypothesized that there are clinical workflow inefficiencies and challenges that could benefit from the application of emerging technologies in the field of heart rhythm disorders. This has been confirmed by the research presented, with three major areas of need for improved service provision in heart rhythm disorders care having been identified.

Firstly, the need for improved service delivery in follow-up of patients with CIEDs has been shown for ED presentations and MRI scan requirements, with opportunities identified for new technology integration into the services. Chapter 2 and chapter 3 have provided real-world insight into the clinical challenges and demand for such CIED services. Provision of these services occupies a considerable allocation of clinical resources which will continue to worsen with CIEDs becoming more common. Evidently there exists opportunities for workflow optimisation and the use of new technology to improve efficiency in the setting of a growing need.

Secondly, the importance of having optimal CIED technology has been demonstrated regarding the utility of a longer sensing vector for ICM design, which can obtain superior EGM

recordings that may improve diagnostic performance. Chapter 4 provided an investigator-initiated evaluation of tracings obtained from two ICM types in real-world clinical use, including a new generation ICM with a longer sensing vector. The importance of this particular design feature was investigated in the novel clinical study of chapter 5, which showed that a longer sensing vector consistently provides superior P-wave amplitude on surface ECG rhythm strip tracings in comparison to a shorter sensing vector across various implant orientations and patient posture. This has particular significance given the need for optimal EGM tracings to minimise false arrhythmia detections as well as the growing use of P-waves in arrhythmia detection algorithms and artificial intelligence software for enhanced arrhythmia discrimination.

Thirdly, the utility of digital technology with algorithms for arrhythmia detection has also been shown, with single-lead ECG tracings being particularly useful when able to be captured by personal digital devices that are commonly available even in low-resource communities. The KM AliveCor device paired to Apple iPhone application used in the TEFF-AF study was evaluated in Chapter 6 to determine the utility of such technology for AF screening. Personal digital devices are becoming increasingly common worldwide and present an opportunity for utilisation in arrhythmia detection with the incorporation of heart rhythm identification algorithms. The ability of this particular technology to obtain single-lead ECG tracings was found to be particularly valuable by allowing manual adjudication of rhythm by clinicians to improve the AF detection sensitivity and specificity above what was capable of the automated algorithm alone. As described in Chapter 7, there are challenges for AF screening a semi-rural community in a developing region that is burdened by resource scarcity but for which the

population AF prevalence is unknown. The application of digital technology in a structured screening protocol allowed identification of individuals with AF, so that informed healthcare decision-making could be made to improve their outcomes. The demonstrated effectiveness of digital technology for care delivery in heart rhythm disorders highlights one of the roles it can play in future healthcare service.

It is evident that opportunities exist for further technology integration into arrhythmia care. However, as various options of novel technology become available, it is important to first understand the current clinical landscape so that appropriate options can be identified for implementation. Some of the gaps in our knowledge regarding the needs of clinical services and how newer technology can best be utilised have been addressed within this thesis. Resource scarcity is often a barrier limiting availability of healthcare services, but ingenuity of technology utilisation provides solutions that can improve efficiency. Identifying opportunities for integration of emerging technologies can allow strategic investment of expenditure and resource allocation to provide optimal future healthcare service and patient outcomes.

CHAPTER NINE – FUTURE DIRECTIONS

9 FUTURE DIRECTIONS

Understanding the clinical context of service provision for heart rhythm disorders is crucial in our effort to improve patient outcomes and ensure sustainability of healthcare. It has been identified that there are specific opportunities for new technology to assist services for follow-up care of patients with CIEDs as well as improve methods of arrhythmia detection in implanted devices and personal digital devices. However, the outcomes from integrating such technology into service delivery remains unknown.

Recently, the COVID-19 global pandemic has broadly altered clinical services and arrhythmia care has been impacted. Compared to the pre-pandemic period, there has been a significant increase in the use of remote monitoring in patients with CIEDs, with the frequency of in-office visits significantly lower during the pandemic.(79) The subsequent change in service delivery for CIED follow-up has led to more home monitoring of devices with periodically scheduled transmissions and ad-hoc device alerts able to be sent for issues regarding clinical status or CIED function. For example, heart failure patients with CIED in-situ who are at risk of worsening heart failure episodes with subsequent hospital presentations can be evaluated remotely through home monitoring of device multisensory algorithms to better triage resources for these patients.(34) Consequently, home monitoring has allowed more early detection of device or clinical abnormalities that can be managed without unscheduled hospital presentations to the ED. However, there will continue to be many ED presentations for patients with CIEDs and the potential utility of read-only systems in this setting may be beneficial for service delivery and should be explored. Future research should look to assess

the specific need for CIED check request to be performed in-person compared to by remote evaluation within a convenience timeframe and the outcomes of each. It may be that timely CIED check could facilitate faster patient discharge from various clinical settings, but promoting indiscriminate low-value checks is likely undesirable from an optimal resource allocation perspective, making appropriate triage even more critical.

Recently, remote interrogation of CIEDs has been used to overcome the logistical issues identified in the peri-MRI scan setting. Remote access software imbedded in a CIED programmer allowed a remote operator to perform CIED reprogramming to MRI mode for patients receiving MRI scan.(69) Such technology could also be useful in other clinical settings such as peri-radiotherapy and peri-operative management of CIEDs, warranting future research in these areas. This novel approach has only been enabled for one CIED manufacturer limiting its utility for application into clinical workflow.(70) This particular limitation means that clinical support services by on-site CIED specialists remain necessary with the associated cost burden. In the absence of a singular solution to the logistical challenges of the peri-MRI scan setting, further evaluation of each CIED manufacturer's technology solutions in this field are required as well as examination of alternate workflows.

The utility of a longer sensing vector on ICM for obtaining optimal amplitude P-waves on rhythm strips has now been shown. However, the importance of a larger amplitude P-wave on ICM strips for arrhythmia adjudication and discrimination remains less well established. A recent paper reported P-wave amplitudes were higher in patients with Biomonitor III, but that

did not lead to higher P-wave visibility compared to other ICM, namely the Confirm RX or the Reveal LINQ.(21) Additionally, it remains unknown if higher P-wave amplitude is sustained over the course of an ICM lifetime.(162) Given that P-wave has been incorporated into some device arrhythmia detection algorithms and also into artificial intelligence software, it is likely that larger P-wave on tracing can be beneficial for such applications, but this requires further investigation. Similarly, the utility of personal digital devices to obtained ECG strips and accurately identify arrhythmia presents opportunities for their implementation into standard clinical workflow. It has been proposed that such devices could be utilised to monitor post ablation arrythmia recurrence episodes or provide a simple cost-effective alternative for ambulatory Holter monitoring for infrequent occasions of symptomatic palpitations. In particular, one recent single-centre study evaluated the use and cost of a smartphone ambulatory ECG clinic for ED patients with palpitations.(180) More similar investigations are necessary to elucidate the utility of such technology in clinical practice.

The remaining unknowns present additional opportunities for investigation to further improve arrhythmia service delivery. In particular, the outcomes of integrating new technology in CIED workflow, the potential gain of improved electrogram sensing in ICM with longer sensing vector, and the use of varying digital devices for targeted arrhythmia screening should be explored. Furthermore, there are likely other branches of clinical services within the field of heart rhythm disorders that could also benefit similarly from technology integration to improve service provision. Indeed, thorough service evaluation is crucial in identifying the appropriate opportunities for technology implementation to achieve service optimisation and potential cost-savings.

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10 REFERENCES

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