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Faculty of Medicine

Human Development and Health

Investigation of Monitoring Technologies to Deliver 'Pill-in-the-Pocket' Oral Anticoagulation in Atrial Fibrillation

Thesis submitted for the degree of

Doctor of Philosophy

by

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Abstract

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and AF-related strokes account for approximately a quarter of all strokes. Current guidelines recommend continuous, lifelong oral anticoagulation (OAC) based on co-morbidities, irrespective of AF burden or pattern. Nevertheless, emerging evidence suggests that stroke risk is dynamic and modulated by AF episodes. A rhythm-guided 'pill-in-the-pocket' OAC, where anticoagulation is initiated only during and shortly after AF episodes, may be a safe and effective alternative. This approach requires accurate, reliable real-time AF detection with timely patient notification.

This thesis evaluates the diagnostic performance, adherence and participants' engagement across three closed-loop AF monitoring systems: implantable cardiac monitors (ICMs) integrated with the bespoke SMART-ALERT software, the Apple Watch and the CART Ring.

This thesis includes four complementary studies. A systematic review and meta-analysis of rhythm-guided OAC identified major limitations in detection and patient notifications, resulting in delays in OAC initiation, highlighting the need for better integrated solutions. The multicentre UK Confirm Rx study showed that the Confirm Rx ICM diagnostic accuracy improved with longer AF duration, from a positive predictive value of 74% for AF ≥6 minutes to 100% for episodes ≥24 hours. It identified sex-based differences in R-wave amplitude and AF detection.

The WEAR-TECH ECG study evaluated single-lead electrocardiograms from the Apple Watch and the CART Ring in three UK centres. Automated detection was suboptimal with the Apple Watch missing approximately one in three AF episodes and the CART Ring missing one in eight. However, physician interpretation for both sinus rhythm and AF was excellent, reinforcing the importance of a hybrid model for clinical decision-making. Finally, the SMART-ALERT study demonstrated feasibility of integrating the SMART-ALERT software with an ICM. The software sent automatic SMS following AF episode >30 minutes, with 74% of SMS sent within 24 hour of AF onset. Participant engagement was excellent (99.6%) with a median acknowledgement time of 4.5 minute. In contrast, both the Apple Watch and the CART Ring had poor AF detection and acknowledgement rates, and suboptimal adherence.

This thesis presents a comprehensive framework for using continuous AF monitoring and automated patient notification for rhythm-guided OAC. While some challenges remain, the SMART-ALERT platform represents an important step towards an alternative stroke prevention strategy based on 'pill-in-the-pocket' OAC guided by continuous rhythm monitoring.

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Briosa e Gala A, Pope MTP, Leo M, Lobban T, Betts TR. *"Patients' perspective on a 'pill-in-the-pocket' oral anticoagulation as an alternative stroke prevention strategy in atrial fibrillation."* **Poster presentation, European Heart Rhythm Association Congress 2022**

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Declaration of Authorship

Print name: Andre Briosa e Gala

Title of thesis: Investigation of Monitoring Technologies to Deliver 'Pill-in-the-Pocket' Oral Anticoagulation in Atrial Fibrillation

I declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research.

I confirm that:

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3. Where I have consulted the published work of others, this is always clearly attributed;
4. Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
5. I have acknowledged all main sources of help;
6. Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
7. Parts of this work have been published or presented as outlined in the following section entitled "Publications and presentations arising from this work".

Signature: …… Date: ……

Abbreviations

AF – Atrial Fibrillation

AHRE – Atrial High-Rate Episodes

AHA – American Heart Association

AV – Atrioventricular

CI – Confidence Interval

CIED – Cardiac Implantable Electronic Device

CRT – Cardiac Resynchronisation Therapy

DOAC – Direct Oral Anticoagulant

ECG – Electrocardiogram

EGM – Electrogram

EHRA – European Heart Rhythm Association

ESC – European Society of Cardiology

FN – False-Negative

FP – False-Positive

HR – Hazard Ratio

ICD – Implantable Cardioverter Defibrillator

ICM – Implantable Cardiac Monitor

LA – Left Atrium

LAA – Left Atrial Appendage

LAAO – Left Atrial Appendage Occlusion

NPV – Negative Predictive Value

OAC – Oral Anticoagulation

OR – Odds Ratio

PAF – Paroxysmal Atrial Fibrillation

PAC – Premature Atrial Contraction

PPG – Photoplethysmography

PPM – Pacemaker

PPV – Positive Predictive Value

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PsAF – Persistent Atrial Fibrillation

PVC – Premature Ventricular Contraction

RCT – Randomised Controlled Trial

SEC – Spontaneous Echo Contrast

SSE – Stroke and Systemic Embolism

TIA – Transient Ischaemic Attack

TOE – Transoesophageal Echocardiogram

TTR – Time in Therapeutic Range

VA – Veterans Affairs

VKA – Vitamin K Antagonist

1 Introduction

1.1 Publications and Abstracts

1.1.1 Publications

Briosa e Gala A, Pope MTB, Leo M, Lobban T, Betts TR. *"NICE 196 Atrial Fibrillation guideline snubs Wearable Technology: A missed opportunity?"* **Clin Med (Lond).** 2022 Jan;22(1):77–82

Clinical Medicine 2022 Vol 22, No 1: 77–82 OPINION

NICE atrial fibrillation guideline snubs wearable technology: a missed opportunity?

Authors: Andre Briosa e Gala,[A] Michael TB Pope,[A] Milena Leo,[B] Trudie Lobban[C] and Timothy R Betts[D]

ABSTRACT

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and a growing public health epidemic. In the UK, over 1.3 million people have a diagnosis of AF and an estimated 400,000 remain undiagnosed. AF-related strokes account for a quarter of all strokes and, as AF episodes are often asymptomatic, are still often the first manifestation of AF. Early diagnosis and initiation of oral anticoagulation, where appropriate, may prevent some of these thromboembolic strokes. Public Health England is committed to decrease the incidence of AF-related strokes and has sponsored initiatives aimed at improving AF detection by promoting the uptake of wearable technologies. However, the National Institute for Health and Care Excellence (NICE) has not recommended wearable technology in their recent AF diagnosis and management guidelines (NG196). Diagnostic accuracy of single-lead electrocardiography (ECG) generated by the latest iteration of wearable devices is excellent and, in many cases, superior to general practitioner interpretation of the 12-lead ECG. High-quality ECG from wearable devices that unequivocally shows AF can expedite AF detection. Otherwise, there is a real risk of delaying AF diagnosis with the potential of devastating consequences for patients and their families.

KEYWORDS: atrial fibrillation, stroke prevention, digital health technology, wearables, NICE

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Introduction

Atrial fibrillation (AF) is the most commonly encountered cardiac arrhythmia. In the UK, over 1.3 million people have an AF diagnosis with a further 400,000 remaining undiagnosed.[1]

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AF is associated with significant morbidity and mortality.[2] On average, there are 40 AF-related strokes in England each day which are known to be more severe and disabling than non-AF related strokes and, for many, prove fatal.[3] Public Health England's (PHE's) *The NHS Long Term Plan* is committed to decreasing the annual stroke rate by improving AF detection and optimising its management across the UK.[4]

Oral anticoagulation (OAC) is a highly effective prevention strategy for AF-related strokes, reducing the stroke risk by two-thirds.[5] However, up to a third of AF patients are asymptomatic and, unfortunately, an ischaemic stroke is still often the first presentation of AF.[6,7] Early diagnosis and initiation of OAC, where appropriate, may prevent some of these thromboembolic strokes. To this effect, PHE together with the Academic Health Science Networks have championed the deployment of innovative digital solutions, including a 6,338 mobile electrocardiography (ECG) device roll-out programme in 2018 aimed at improving AF detection.[8] It is therefore surprising that the National Institute for Health and Care Excellence (NICE) has not supported this technology in their recent AF diagnosis and management guidance (NG196).[9]

Digital health revolution

Technological advancements have led to a plethora of novel non-invasive devices, many commercially available, including patches, smartphones, wearables (watches, bands and rings) and handheld devices, which can detect and monitor arrhythmias and detect possible AF (Fig 1). Initially, volumetric variations in the peripheral microcirculation detected by photoplethysmography (PPG) was used to measure heart rate variability and peak-to-peak changes to detect AF (Fig 2).[10] PPG signals have several inherent limitations that increase the number of false-positive detections of AF, such as requiring good contact with the skin and, thus, are very susceptible to noise and artefacts from changes in pressure and motion.[11] The latest generation of wearables incorporate ECG sensor units. These have the advantage of generating high-quality limb-lead ECGs with the patient at rest, discriminating artefact noise from actionable arrhythmias, and are easily exported and reviewed by clinicians, improving diagnostic accuracy.[12–14]

Atrial fibrillation guidelines

The recently released (April 2021) NICE NG196 AF guidelines failed to incorporate wearable and handheld technology in their diagnostic pathway. Instead, NICE continues to advocate

1.1.2 Abstracts

Briosa e Gala A, Pope MTP, Leo M, Lobban T, Betts TR. *"Patients' perspective on a 'pill-in-the-pocket' oral anticoagulation as an alternative stroke prevention strategy in atrial fibrillation."*
Poster presentation, European Heart Rhythm Association Congress 2022

1.2 Introduction

Atrial fibrillation (AF) is the most commonly encountered sustained cardiac arrhythmia.[1,2] It is characterised by chaotic electrical activity in the atria, leading to uncoordinated atrial and ventricular contractions, often at rapid rates.[1] The prevalence of AF increases with age and it is projected to double in Europe reaching 17.9 million by 2060, occurring in one in three individuals over 55 years of age.[3-6] In the UK, an estimated 1.6 million people have an AF diagnosis, but hundreds of thousands more remain undiagnosed.[7]

AF is a leading cause of cardiovascular morbidity and mortality: up to three-fold increased risk of death and five-fold increased risk of stroke, even when accounting for other comorbidities.[8-10] On average, 40 AF-related strokes occur daily in England, and these strokes tend to be more severe, disabling, and recurrent than those unrelated to AF.[11-13] Oral anticoagulation (OAC) is effective in preventing AF-related strokes and it is the cornerstone of AF management.[1,9]

Other important detrimental consequences of AF are an increased risk of heart failure, poor quality of life, cognitive decline and worsening mental health.[14-17] In addition to the high societal cost from AF-related symptoms, as well as its complications, the economic burden is equally significant: AF management represents approximately 1% of the annual NHS budget, while in the USA, annual costs may be up to $26 billion.[18-20] In recognition of this, Public Health England has made the improvement of AF diagnosis and treatment a priority in its 10-year strategy, with the vision of decreasing the number of AF-related strokes and improving overall patient outcomes.[21]

1.3 AF Classification

Although an AF diagnosis may be suspected from presenting symptoms or an irregular pulse, formal diagnosis ultimately relies on electrocardiographic (ECG) evidence of an irregularly irregular rhythm with no distinct P-waves.[1,22] By convention, an arbitrary cut-off of 30 seconds on a rhythm strip or standard 12-lead ECG is required to establish the diagnosis of clinical AF.[1,2,23] Device-detected subclinical AF refers to asymptomatic AF episodes identified in patients on prolonged rhythm monitoring with cardiac implanted electronic devices (CIEDs), implantable cardiac monitors (ICMs) or consumer based wearable devices.[1,24] It requires confirmation by formal review of ECG recordings or electrograms to exclude false-positive (FP) detections.[25,26] Therefore, clinical AF detected incidentally on a 12-lead ECG often reflects a higher AF burden if it was documented in a single time point in contrast to continuous monitoring.[27]

AF is traditionally classified as paroxysmal (resolution within 7 days), persistent (lasting >7 days), or longstanding persistent (continuous for >1 year).[1,2] Permanent AF implies that both the patient and the physician have accepted that sinus rhythm cannot be restored. Physicians rely mainly on intermittent rhythm monitoring tools or patient reported symptoms to categorise AF, which are unreliable, especially in the elderly.[28,29] A large proportion of patients with AF are asymptomatic and, in many, reported symptoms of palpitations, chest pain or breathlessness may not be related to an arrhythmia.[30,31]

The clinical construct of paroxysmal, persistent, and permanent AF is widely used in research to create cohorts of patients with similar arrhythmia characteristics but oversimplifies a highly heterogeneous condition.[2,32] Charitos *et al.* found poor agreement between clinical AF classification and recorded AF patterns in 1,195 patients with CIEDs (Cohen's kappa: 0.12 [95% CI: 0.05 to 0.18]). Despite having a very high AF burden, most patients were still classified clinically as paroxysmal AF (PAF).[33]

New concepts derived from observed AF burden (proportion of time in AF) and AF density (temporal aggregation of AF) can be integrated to characterise different AF profiles.[32] For example, Sugihara *et al.* identified three PAF subtypes in 392 patients with pacemakers: non-progressive low burden (<1%), chronic progressive (>1% with sustained increase), and relapsing–remitting (fluctuating AF burden never reaching 100%).[34] The current clinical classification of AF is oversimplification and often fails to accurately represent complex AF patterns and true AF burden.[2]

1.4 AF Diagnosis

AF episodes are often intermittent, and many patients remain asymptomatic, making detection on a 12-lead ECG challenging.[30] In patients with brief symptoms or in those with a high index of suspicion, extended ambulatory monitoring using Holter monitors, patches, or ICM, is often warranted, particularly after a cryptogenic stroke.[35, 36] There is a strong correlation between the duration and intensity of ECG monitoring and the likelihood of AF detection during screening in asymptomatic patients.[37] For example, Lowres *et al.* reported a 1.4% new AF detection for a single time-point ECGs in patients over 65 years, whilst intermittent monitoring over a two-week period in the STROKESTOP study increased detection to 7% in adults aged 75 years old.[38, 39] Unsurprisingly, continuous rhythm monitoring in elderly patients with ICMs in the LOOP and ASSERT II studies yielded significantly higher rates of device-detected AF of 33.8% and 34.5%, respectively (Figure 1-1).[38-46]

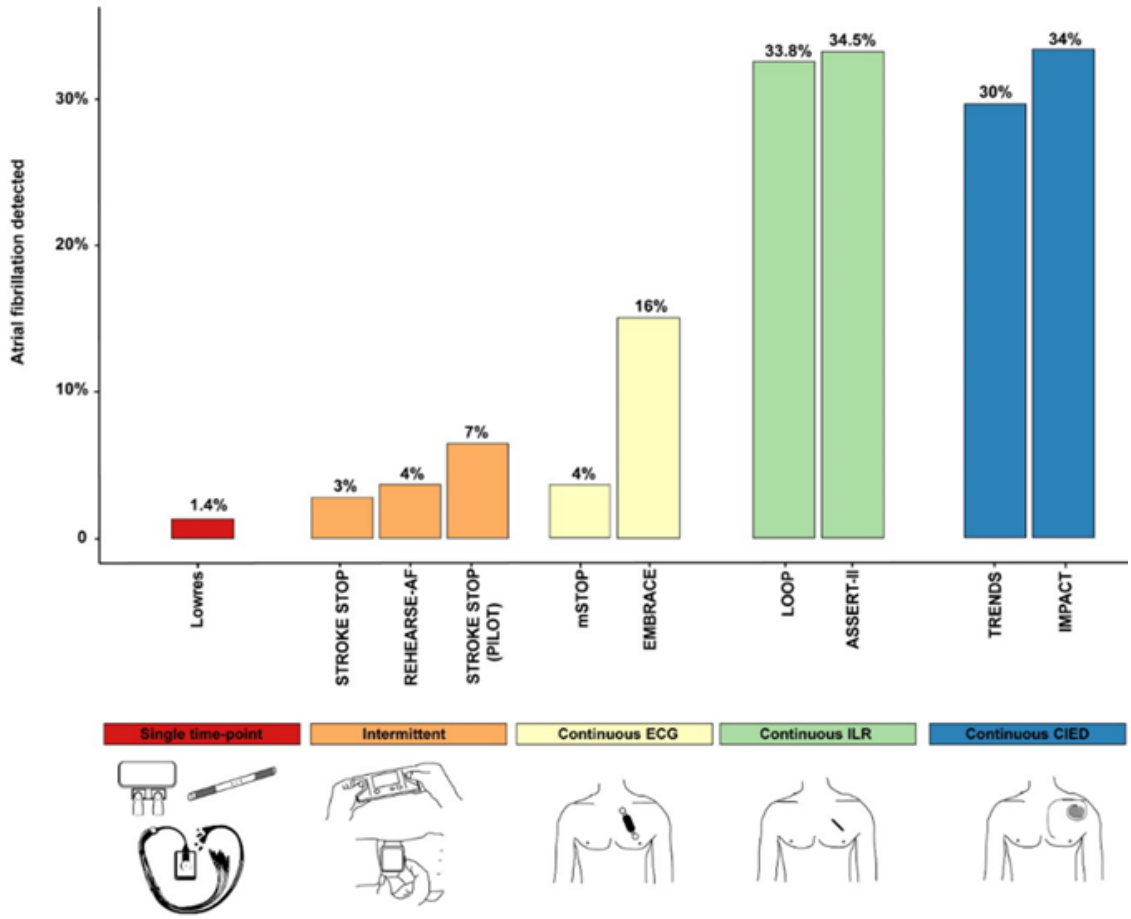


Figure 1-1. *Rates of AF detection with different screening modalities. Adapted with permission from Jones et al.*[37]

1.4.1 Implantable Cardiac Monitors

Modern ICMs are implanted subcutaneously using minimally invasive techniques and detect AF by relying on a variety of algorithms that primarily identify irregular R-R intervals.[47-49] ICMs demonstrate excellent sensitivity for AF detection, ranging between 88%-97% (Table 1-1).[47-52]

The main limitation of the earlier AF detection algorithms was the propensity for FP detections due to ectopy, myopotentials, undersensing, or motion artefacts.[47] Careful adjudication of all transmissions was required, which was extremely time-consuming given the large volume of data collected. Newer generations of ICMs, such as the Confirm Rx (Abbott, Lake County, IL, USA), Reveal LINQ (Medtronic, Minneapolis, MN, USA), and Biotronik III (Biotronik, Berlin, Germany), incorporate P-wave discriminators to their novel algorithms which search for evidence of P-waves before classifying the episodes as AF.[53,54] P-wave discriminators have

reduced FP detection by 97% and 46% in the Confirm Rx and Reveal LINQ, respectively, without compromising sensitivity.[55]

Beyond automatic AF detection, ICMs can help identify AF patterns, quantify AF burden and density, offering insights into an individual's arrhythmia. However, ICMs likely overestimate true AF burden as it is calculated from all episodes, including FP detections, and adjudication does not update the AF burden counters.[56] Moreover, ICM validation studies used Holter monitors for short periods of time, providing limited data on AF burden accuracy; hence, CIEDs which rely on atrial electrograms remain the gold standard.[34,57]

Table 1-1. *Summary of diagnostic performance of AF detection by ICMs compared to ambulatory electrocardiography.*

ICM	Sensitivity	Specificity	PPV	NPV
Reveal XT[58]	88.2%	Not reported	73.5%	Not reported
BioMonitor[59]	95.4%	Not reported	76.3%	Not reported
SJM Confirm[47]	94.0%	96.7%	59.1%	88.3%
Reveal LINQ[51]	97.4%	97.0%	92.5%	99.0%

ICM, Implantable cardiac monitor. **PPV**, positive predictive value. **NPV**, negative predictive value.

Remote monitoring with ICMs has historically used static home-based transmitters that perform nightly automatic transmissions of relevant arrhythmic episodes.[47-52] Patients had to remain within two metres of the transmitter for successful data transfer, leading to delays between an arrhythmic event, transmission and subsequent physician review. The latest generation of ICMs, such as the Confirm Rx (Abbott, Lake County, IL, USA) and LINQ II (Medtronic, Minneapolis, MN, USA) are equipped with low-energy Bluetooth® technology, which connects directly to patients' smartphones. In a multicentre study of 5,666 patients with a Confirm Rx implanted, 97% used the app, with patient-activated symptoms transmitted to the remote monitoring platform (Merlin.net) within 3 minutes and adjudicated by the clinical staff within 0.9 days.[60] This improved connectivity may enable 'real-time' alerts to prompt patients to take medications during AF episodes.

The combination of improved diagnostic performance and remote monitoring capabilities in ICMs has renewed interest in their use for AF diagnosis following cryptogenic stroke, monitoring of AF recurrence and total AF burden following catheter ablation, and cardiac surgery.[36,61-66]

Moreover, novel AF management strategies have been investigated, including three feasibility studies using ICMs to guide 'pill-in-the-pocket' OAC during and shortly after AF episodes.[67-69]

1.4.2 Mobile Health Technology

Technological advancements have led to a plethora of novel non-invasive mobile health (mHealth) technology devices for AF detection, including wearables (e.g., watches, bands, and rings) and handheld devices.[70] Many rely on photoplethysmography (PPG) to measure heart rate variability and detect AF through volumetric changes in peripheral microcirculation (Figure 1-2).[71] However, PPG is very susceptible to motion artefact, noise and poor skin contact, which can mimic an irregular pulse and result in frequent FP detections.[72,73] Some devices mitigate this by using accelerometers to identify motion and exclude PPG signals recorded during activity, but therefore can only offer semi-continuous monitoring, potentially missing AF episodes and providing unreliable AF burden data.[72,74,75] For example, Bashar *et al.* found that when 37 patients performed arm movement to simulate ambulatory activity, only 13% of their 30-second PPG recordings were of sufficient quality for analysis.[76]

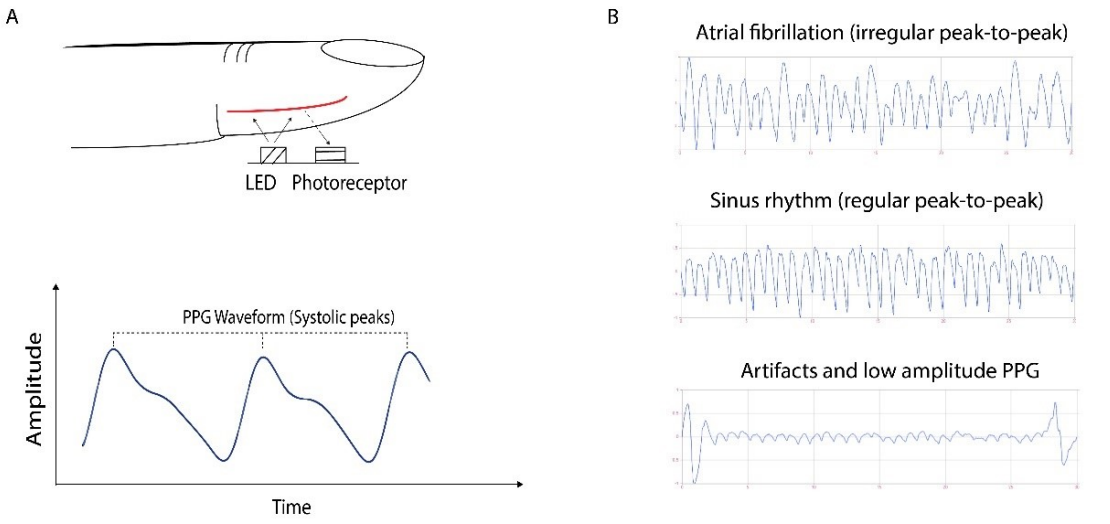


Figure 1-2. (A) *PPG relies on reflected light to measure blood volume changes in a microvasculature and the PPG waveform has a systolic and diastolic component and changes in both amplitude and period can identify heart rate irregularity.* ***(B)*** *Example of 30-sec PPG waveforms recorded by the CART Ring. Reproduced with permission from Briosa e Gala et al.*[75]

Many validation studies, often sponsored by the manufacturers, likely overestimate diagnostic performance by including only patients with either AF or sinus rhythm and thus excluding key sources of FP detection, such as ectopy, and performing measurements in optimal conditions at rest.[77,78] In contrast, the Digital AF II study, which screened over 60,000 patients, found that

12.3% of PPG traces were uninterpretable, which is a strong indication of the steep learning curve during the screening period.[79]

Some mHealth devices incorporate ECG sensor units capable of generating high-quality single-lead ECGs (SL-ECGs) with the patient at rest, which can help discriminate noise from actionable arrhythmias, improving diagnostic performance (Figure 1-3).[80-82] SL-ECGs, when reviewed by a physician, are now recognised by the European Society of Cardiology (ESC) as diagnostic of clinical AF.[1,22] However, this recommendation does not extend to automatic AF detection using PPG recordings, which cannot be easily reviewed by physicians and adjudicated.

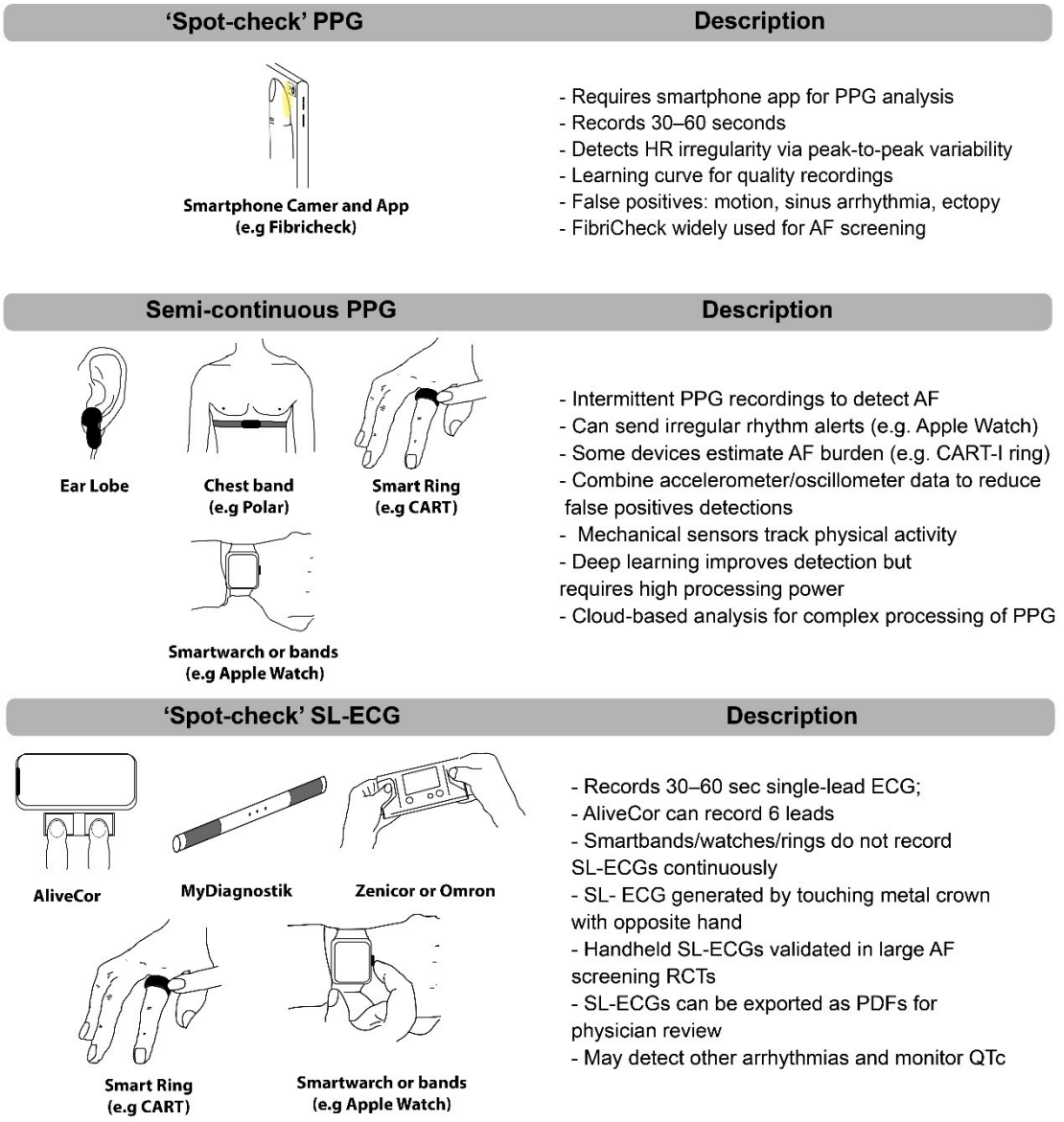


***Figure 1-3**. Example of different mHealth modalities used for AF screening or monitoring. Adapted with permission from Briosa e Gala et al.[75] **PPG**, photoplethysmography. **SL-ECG**, single-lead electrocardiogram.*

In contrast, NICE 196 AF guidelines continue to advocate pulse palpation followed by 12-lead ECGs as the gold standard for AF diagnosis. Whilst recognising that new generation mHealth devices are accurate and have great potential, NICE emphasises that a definitive test must have 'almost perfect' sensitivity and specificity.[75,83] Yet, several studies have reported that physician interpretation of SL-ECGs have high diagnostic performance (sensitivity 0.84–0.97; specificity 0.86–0.97), often outperforming general practitioners interpreting 12-lead ECGs, as shown in the SAFE study (Figure 1-4).[80-82,84-94] Acceptance of wearable devices within the cardiology community continues to steadily grow. A survey by Manninger *et al.* of over 500 cardiologists found that 83% would diagnose AF based on a SL-ECG from an mHealth device, and 72.8% would initiate OAC based on this finding. In contrast, only 27.1% would be confident enough to diagnose AF from a PPG trace.[95]

Despite mHealth devices having a great number of potential applications in healthcare, there are real concerns regarding the validation standards of commercially available mHealth devices, often funded by the manufacturers.[22,96] FP detections can result in overtreatment and unwarranted downstream investigations.

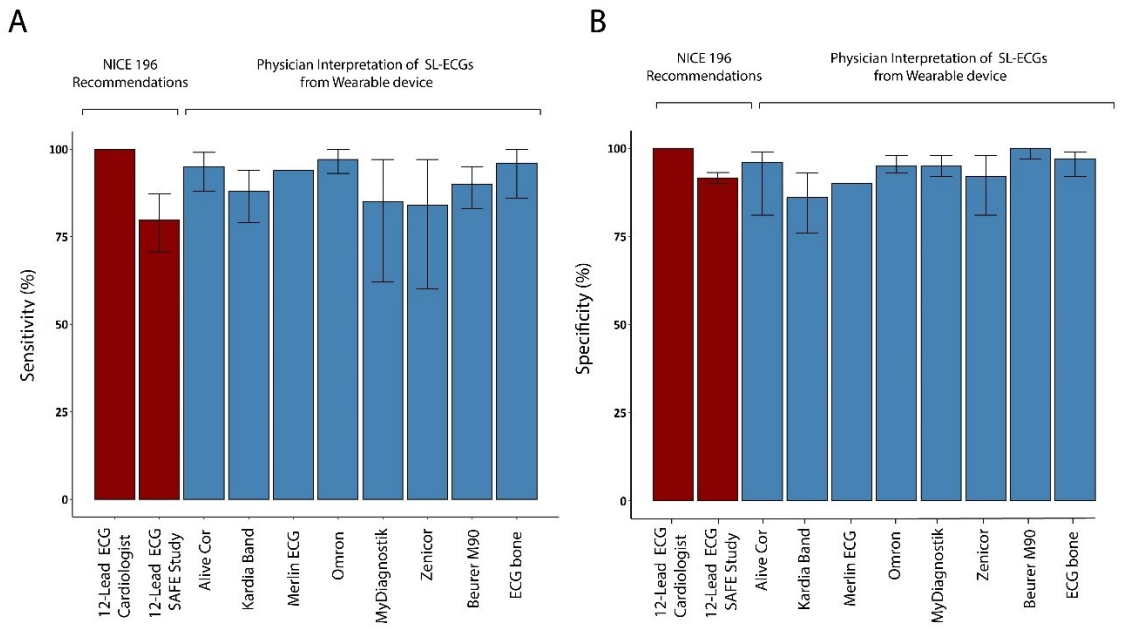


Figure 1-4. *Sensitivity and specificity of 12-lead ECGs interpreted by cardiologist and GPs and SL-ECGs from wearable devices interpreted by an expert physician included in NICE Expert Review B (CG 196). Reproduced with permission from Briosa e Gala et al.*[75]

For patients, an 'abnormal' heart rhythm detection may cause significant anxiety and lead to inappropriate medication use.[97] For physicians, this will likely result in a significant increase in clinical referrals and appointments, a higher number of further tests to confirm or refute the

findings, which will likely translate into additional healthcare cost. Robust independent validation studies are required to understand their true diagnostic performance, clinical utility and implementation into routine care.

1.5 Mechanisms of Thrombogenesis

The pathophysiology of thrombogenesis in AF is complex, multifactorial and not fully understood, but many of the factors that lead to intracardiac thrombus formation can be explained, in part, by the Virchow's triad: (1) abnormal blood flow and stasis; (2) abnormal blood constituents; and (3) abnormal endothelium.[98]

1.5.1 Abnormal Blood Flow

The left-atrial appendage (LAA) is a blind-pocket extension with marked trabeculations that connects to the atrium through a narrow ostium. The LAA is prone to blood stasis and is the primary site for thrombus formation in non-valvular AF.[99] Disorganised mechanical activity during AF impairs the flow of blood in the atria, sometimes visualised during echocardiography as spontaneous echo contrast (increased echogenicity) and correlates with an increased thromboembolic risk.[100-102] This impaired contractility can be formally measured in the LAA with transoesophageal echocardiography (TOE), which in sinus rhythm has a biphasic pattern with high amplitude (>50 cm/sec) but it is significantly reduced during AF.[103] A pulsed-wave Doppler with reduced LAA flow velocities (<25 cm/sec) is a marker of low contractility and has been associated with an increased stroke risk.[104]

Lastly, transient mechanical dysfunction of the left atria following cardioversion to sinus rhythm, often referred to as atrial 'stunning', can promote *de novo* thrombus formation, particularly if not appropriately anticoagulated, and it is associated with an increased stroke risk.[105] Notably, atrial stunning has been described irrespective of the mode of cardioversion: pharmacological, electrical and spontaneous.[106]

Conceptually, AF is considered a progressive condition with episodes of AF promoting structural and electrical remodelling within the atria which, in turn, help sustain the arrhythmia: "AF begets AF".[107-109] Atrial enlargement due to remodelling promotes sluggish blood flow and it is a maker for ischaemic stroke as well.[110]

1.5.2 Abnormal Blood Constituents

Hypercoagulability in AF is well recognised with several studies demonstrating increased levels of procoagulant blood constituents, platelet activation, and abnormal fibrinolysis.[98] Some of the

evidence is contradictory, particularly in studies assessing platelet function, which may be explained by differences in laboratory assays and techniques. Also, underlying co-morbidities may have an impact on background inflammation and haemostasis and are important confounders that must be taken into account.[111,112]

The final step in the coagulation cascade is the activation of prothrombin to thrombin, which cleaves fibrinogen, forming fibrin and stabilising the blood clot. Elevated levels of prothrombin fragments and D-dimer (by-product of fibrin), both markers of active coagulation, are higher in AF patients than in those in sinus rhythm.[113,114] Increased levels of plasminogen activators have also been reported in AF patients and in patients with sinus rhythm with previous stroke, suggesting fibrinolytic dysfunction from endothelial damage.[115,116] Finally, Von Willebrand factor, which is a key mediator of platelet adhesion and aggregation, is elevated in AF, and also shown to be an independent predictor of LAA thrombus and stroke.[117-119]

Interestingly, anticoagulation with warfarin has been shown to reduce prothrombotic markers whereas antiplatelet agents have minimal impact.[119] These findings corroborate clinical data showing that antiplatelets are inferior to OAC for stroke prevention and therefore are no longer recommended.[1,2,120]

1.5.3 Abnormal Endothelium

Evidence from abnormal endothelium mainly comes from necropsy studies in patients with a history of AF showing structural changes in endocardium, particularly hypertrophy, fibrosis and thrombosis on microscopy.[121] In addition to microscopic changes, other studies suggest that the endothelial is abnormal by reporting elevated levels of biomarkers, such as von Willebrand factor and circulating endothelial cells.[122-124]

1.5.4 Drivers of a Prothrombotic State

Other data suggest that inflammation and the release of growth factors actively contribute to the procoagulant state observed in AF.[98,125] Interleukin-6, a pro-inflammatory cytokine, reduces the anticoagulant proteins, such as antithrombin and protein S, and also stimulates the expression of fibrinogen and platelet aggregation leading to a prothrombotic milieu. Interleukin-6 has been shown to be raised in patients with AF and it is an independent stroke predictor.[126]

High levels of C-reactive protein found in patients with AF further suggest a background of inflammation. A study of 37 patients with long-term AF on warfarin found that the C-reactive protein concentration was associated with the appearance of SEC on TOE.[127] A later study by

Cianfrocca *et al.* showed that a raised CRP increases the odds three-fold of SEC and LAA thrombus.[128]

1.5.5 Changes in Paroxysmal AF

Sohara *et al.* reported that prothrombotic factor levels correlate with the duration of AF paroxysm, with elevated concentrations seen after an episode lasting longer than 12 hours.[129] In an elegant study in 33 patients, Lip *et al.* found that patients with PAF had intermediate levels of fibrinogen and D-dimer when compared to the lower levels in controls and higher levels individuals with persistent AF.[130] Cardioversion to sinus rhythm, whether pharmacological or electrical, reduces fibrin turnover in patients receiving heparin but without prior OAC regime.[131] Taken together, these small case series suggest that there is a stepwise increase in thrombogenesis as AF progresses PAF to persistent AF, which is reduced by restoring sinus rhythm.

However, a later study found no significant changes in prothrombotic factors at 30 days post-cardioversion in individuals with new-onset AF.[132] It is important to note that TOE was not used in this study and therefore it is possible that SEC or even LAA thrombus could explain the discrepancies in results.

1.6 Risk Stratification

Stroke prevention strategies require careful assessment of individual stroke and bleeding risks.[1,2,83] Risk assessment tools simplify and standardise decision-making but have inherent limitations.[133] First, many were developed using historical cohorts that differ from contemporary patients, whose cardiovascular risk profile may have improved with modern cardiovascular management.[134] Second, many risk factors are not binary and represent a continuum of risk which is not adequately captured in the conventional risk scores. Lastly, point systems do not account for the heterogeneity or unequal weight of individual risk factors.

1.6.1 Risk Scores for Stroke

Various stroke risk scores have been developed with varying degrees of complexity based on clinical parameters, biomarkers, and imaging findings, but all demonstrate an overall modest predictive ability (c-statistic 0.61-0.82).[133,135,136] The two most widely adopted in the last two decades are the $CHADS_2$ score, which was later refined into the CHA_2DS_2-VASc score.[135,136]

The $CHADS_2$ score (Congestive Heart Failure, Hypertension, Age ≥75 Years, Diabetes Mellitus [1 point] and Stroke/TIA [2 points]) was derived from risk factors of non-anticoagulated patients

from the AF investigators and Stroke Prevention in AF (SPAF) trials. The original validation study, which included 1,733 patients from the US National Registry of Atrial Fibrillation, demonstrated a c-statistic of 0.82.[136] $CHADS_2$ score of 0 was considered low risk, score of 1-2 moderate risk, and high-risk patients had a score ≥ 3 groups. Low-risk patients would either not have any antithrombotic therapy prescribed or only received aspirin. Conversely, patients who were deemed moderate risk could be treated with warfarin or aspirin. Despite its simplicity, this scoring tool had significant limitations.[137] A high proportion of patients fell into the intermediate-risk category, for which either aspirin or warfarin was appropriate; yet warfarin use remained low despite it being a more effective stroke prevention drug. Furthermore, 'low risk' patients had a high annual stroke rate of 1.5%, which questions the reliability of the $CHADS_2$ score as a risk stratification tool.

The CHA_2DS_2-VASc score, introduced into clinical practice by Lip *et al.*, added vascular disease, female sex, and age 65–74 years, refining the $CHADS_2$ score.[135] In the EuroHeart Survey (n=1,084), CHA_2DS_2-VASc outperformed other stroke risk tools and has since been externally validated across diverse populations.

In contrast to the $CHADS_2$ score, which was designed to identify high-risk individuals, CHA_2DS_2-VASc attempts to find low-risk patients who will not benefit from OAC.[138,139] A formal comparison of the two scores in a large Danish cohort of 73,538 non-anticoagulated AF patients yielded several important observations. At 1 year, patients with a score of 0 had far fewer thromboembolic events with CHA_2DS_2-VASc than $CHADS_2$ (0.78 vs 1.67 per 100 patient-years), suggesting that CHA_2DS_2-VASc of 0 reliably identifies low-risk patients. Intermediate-risk patients had more than double the event rate when the $CHADS_2$ score was used compared to CHA_2DS_2-VASc (4.75 vs 2.01 per 100 patient-years).[138] An analysis of the UK General Practice Database spanning almost 3 decades and containing 79,844 patients supported these findings: CHA_2DS_2-VASc score of 0 had an annual stroke rate of 0.5% with the authors concluding that it "truly identifies low-risk patients".[140]

The CHA_2DS_2-VASc score was the preferred risk stratification tool for guiding OAC decisions, previously endorsed by major international societies, such as the ESC and the American Heart Association (AHA).[1,222] An ESC update from 2024 now recommends the CHA_2DS_2-VA score which no longer uses sex (Table 1-2). Patients with a CHA_2DS_2-VA of 0 should not be offered OAC. The net clinical benefit of OAC is less clear in patients with a single-risk factor as available studies show contrasting event rates, ranging from 0.1% to 2.1%.[141] In all other patients with other CHA_2DS_2-VA score of 2 or above, continuous lifelong OAC is recommended.[1,2]

Other risk assessment tools offer marginal increase in predictive value over CHA_2DS_2-VASc score at the expense of greater complexity, which may negate their applicability

Table 1-2. *Updated CHA_2DS_2-VA score and HAS-BLED-score.*

CHA_2DS_2-VASc		**HAS-BLED**	
Risk factors	**Score**	**Risk factors**	**Score**
Congestive Heart Failure	1	**H**ypertension	1
Hypertension	1	**A**bnormal renal *or* liver function	1 or 2
Age ≥ 75 years	2	**S**troke	1
Diabetes Mellitus	1	**B**leeding history	1
Stroke /TIA/Thromboembolism	2	**L**abile INR	1
Vascular disease	1	**E**lderly *(Age >65 years)*	1
Age 65 to 74 years	1	**D**rug history *or* alcohol	1 or 2

TIA, transient ischaemic attack. **MI**, myocardial Infarction.

For example, the Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF) score incorporates 16 parameters, including, pulse rate, blood pressure and carotid artery imaging, whilst the ABC (Age, Biomarkers, and Clinical History) score includes high-sensitivity troponin and NT-pro-BNP.[142, 143]

AF burden and temporal patterns are notably absent from current risk scores, likely due to challenges in accurate characterisation without continuous rhythm monitoring. Nonetheless, there is growing interest in understanding how AF temporal patterns and thromboembolic risk are linked and whether this information could refine future OAC strategies.[32]

1.6.2 Risk Scores for Bleeding

The major trade-off of OAC is increased risk of bleeding, particularly major bleeding events.[9,144,145] Indeed, studies of real-world cohorts show that the yearly major bleeding rate is close to 4% in those taking OAC.[144] In the seminal RCTs, apixaban demonstrated the lowest annual major bleeding rate at 2.13%, while rivaroxaban showed the highest rate at 3.6%.[146,147] The most feared complication is intracranial haemorrhage (ICH) resulting in significant disability and mortality. ICH rates are 0.3%–0.6% annually in patients on vitamin-K antagonists (VKAs), but significantly lower with direct oral anticoagulants (DOACs), at 0.1%–0.2%.[9,148,149]

Several bleeding risk assessment tools exist, but no absolute threshold exists for withholding OAC.[150-152] Instead, these tools help identify and manage modifiable risk factors, enabling safer initiation of OAC.[1,2,22] Nonetheless, the perceived high bleeding risk remains a major barrier to OAC use. In the Get With The Guidelines-AFIB registry of 33,235 patients, only 80.3% eligible individuals were discharged on appropriate OAC, with high bleeding risk and patient or physician preference cited as key reasons for non-adherence.[153] However, this study showed a consistent increase in the uptake of OAC over time.

The HAS-BLED score, derived from the EuroHeart AF Survey, is the most widely adopted scoring system (Table 1-2).[150] Alternative scores, such as the ABC (incorporate biomarkers) and HEMORR$_2$HAGES scores, offer marginally improved predictive value but are less frequently used due to their complexity.[135,151,154]

1.7 Temporal AF Patterns and Thromboembolic Risk

1.7.1 Paroxysmal Versus Non-Paroxysmal AF

The simplest way to assess thromboembolic risk in different AF patterns is to dichotomise AF into two groups: PAF and non-PAF (persistent, longstanding persistent, and permanent). Whilst historical studies suggested a comparable stroke rate across different AF patterns, these findings have been rebutted by contemporaneous evidence, particularly from post-hoc analyses of the landmark DOACs trials (Table 1-3).[155-162]

Hart *et al.* analysed 1,990 patients treated with aspirin in the SPAF trials, which included 1,550 patients with sustained AF and 440 with intermittent AF.[155] Over a mean follow-up of two years, the annualised ischaemic stroke rate was similar in both groups (3.3% [95% CI; 2.2 to 4.6] vs 3.2% [95% CI: 2.2 to 4.6]). It is important to highlight that the intermittent AF cohort may have predominantly selected patients with a high AF burden, who were likely to be classified as persistent AF with modern definitions, as it primarily included patients admitted to hospital and excluded those with 'lone AF' or a single 12-lead ECG showing AF.

Similarly, the ACTIVE-W trial, which randomised patients to either dual-antiplatelet or warfarin, reported comparable thromboembolic event rates between PAF (2.0%) and sustained AF (2.2%).[158] Yet, the higher use of antiplatelets in the PAF group, now recognised as inferior to OAC for stroke prevention, significantly limits any strong conclusions.

Two registries, EuroHeart Survey and the Stockholm Cohort of Atrial Fibrillation, contributed to this narrative of risk equivalence between PAF and non-PAF patients; however, lower rates of OAC in PAF cohorts may have biased the results.[163,164]

In contrast, a larger cohort of 6,573 aspirin-treated patients from the AVERROES and ACTIVE-A trials demonstrated a significantly higher stroke risk in persistent AF (adjusted HR 1.83, p<0.001).[156] The main strengths of this analysis are the inclusion of a broad range of CHA_2DS_2-VASc scores, classification of AF patterns consistent with current guidelines (paroxysmal, persistent, and permanent), and over 500 adjudicated thromboembolic events.

Earlier studies using antiplatelet therapy and VKA yielded conflicting results regarding stroke risk for different AF patterns. Despite inherent limitations — variations in OAC use, patient selection, and AF classification — these studies reinforced the prevailing notion of equivalent stroke risk in PAF and non-PAF patients. The introduction of DOACs revolutionised OAC practice with four landmark RCTs: RE-LY (dabigatran), ARISTOTLE (apixaban), ROCKET-AF (rivaroxaban) and ENGAGE-AF (edoxaban).[146,147,165,188] The high rates of adherence to guideline-recommended therapy and standardised AF definitions allowed further exploration of thromboembolic risk across different AF patterns.

A limited post-hoc analysis of RE-LY reported that dabigatran 150 mg was superior to warfarin in stroke prevention across all types of AF, while dabigatran 110 mg showed superiority only in PAF.[160] The authors did not report a difference in stroke rates, but there was no comparison between different AF patterns. Three other post-hoc analyses performed formal comparisons of event rates between PAF and non-PAF patients, making them more informative.

In ROCKET-AF, a significantly lower thromboembolic event rate was observed in PAF patients (1.73%) compared to persistent AF (2.18%; adjusted HR 0.79, p = 0.048).[159] Similar trends were reported in the ENGAGE-AF and ARISTOTLE post-hoc analyses (HR 0.79, p = 0.015, and HR 0.79, p = 0.04, respectively).[161,162]

More recently, a meta-analysis of approximately 100,000 patients across 12 studies (10 RCTs and 2 prospective cohort studies) demonstrated higher rates of stroke and systemic thromboembolism (SSE) in non-PAF patients (2.17% [95% CI: 1.81–2.53%]; p<0.001) and also greater risk of all-cause mortality (HR 1.27 [95% CI: 1.085–1.365]; p<0.001).[166]

Taken together, these findings suggest a lower stroke risk in PAF patients. A recent AHA position paper challenged the assumption of risk equivalence in current guidelines, arguing that non-PAF carries a higher stroke risk.[167] The statement advocated moving “beyond atrial fibrillation as a binary entity” and highlighted that continuous rhythm monitoring could further help characterise the relationship between AF burden and clinical outcomes.

Table 1-3. *Summary of RCTs comparing thromboembolic risk between PAF and non-PAF patients.*

Studies	Anti-thrombotic drugs	PAF (n)	PsAF (n)	PmAF	Yearly SSE PAF	Yearly SSE PsAF	Yearly SSE PmAF	P-value	PAF vs non-PAF Adjusted HR (95% CI)
SPAF studies[155]	Aspirin	440	1550	—	3.2%	3.3%		NS	NR
AVERROES & ACTIVE AF[156]	Aspirin	1576	1136	3854	2.1% (77)	3.0% (74)	4.2% (385)	<0.01	NR
SPORTIF III & V[157]	Warfarin Ximelagatran	836	6493	—	0.93%	1.73%	—	0.037	—
ACTIVE-W[158]	Aspirin Clopidogrel	1202	5495	—	2.4% (18)	3%	—	NS	0.79 (0.48-1.30)
ROCKET-AF[159]	Rivaroxiban Warfarin	1245	5786	—	1.73%	2.18%	—	0.048	0.79 (0.63-1.00)
RE-LY[160]	Dabigatran Warfarin	5943	5789	—	1.32%	1.55%	—	0.04	NR
ARISTOTLES[161]	Dabigatran Warfarin	2786	15412	—	0.98%	1.52%	—	0.004	0.70 (0.51-0.93)
ENGAGE-AF[162]	Edoxaban Warfarin	5366	4868	10865	1.49%	1.83%	1.95%	0.015	0.79 (0.66-0.96)

HR*, Hazard ratio.* ***CI****, Confidence interval.* ***NS****, non-significant.* ***PAF****, Paroxysmal AF.* ***PmAF,*** *Permanent AF.* ***PsAF,*** *persistent AF.* ***SSE,*** *Stroke and Systemic embolism.*

Studies: SPAF*, Stroke Prevention in Atrial Fibrillation.* ***AVERROES****, Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment.* ***ACTIVE-A****, Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events.* ***SPORTIF III & V****, Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation.* ***ACTIVE-W,*** *Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events.* ***ROCKET-AF,*** *Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation****. RE-LY,*** *Randomized Evaluation of Long-Term Anticoagulation Therapy.* ***ARISTOTLE****, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation.* ***ENGAGE-AF****, Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation.*

1.7.2 AF Burden and Thromboembolic Risk

It is biologically implausible that a universal cut-off of AF burden exists or that there is a linear relationship between AF burden and stroke risk. However, a high AF burden may promote a prothrombotic milieu through reduced atrial contractility, particularly in the LAA, and blood stasis.

Continuous rhythm monitoring offers valuable insights into how AF burden may modulate thromboembolic risk.[24,32]

1.7.2.1 Device-Detect AF

CIEDs detect atrial arrhythmias via atrial leads, commonly referred to as atrial high-rate events (AHRE). The AHRE cut-off commonly employed ranges from 170 to 220 beats per minute for longer than 5 minutes, to improve PPV.[168,169] Several studies have investigated the FP rate of AHRE detection by CIEDs. These include the Impact of Detection of Atrial High-Rate Episodes on Stroke Risk (IMPACT) trial and the Non-vitamin K antagonist Oral anticoagulants in patients with Atrial High-rate episodes (NOAH-AFNET 6).[45,170] Modern algorithms have reduced the FP rate from 9.3% in IMPACT to 3% in NOAH-AFNET 6. AHRE adjudicated as AF are termed device-detected subclinical AF, and they often capture short asymptomatic episodes that would otherwise be missed without continuous monitoring.

Growing evidence suggests that device-detected AF is associated with increased thromboembolic risk, albeit lower than clinical AF.[24,32,169] However, defining an AF burden threshold for elevated risk is difficult, with studies reporting values as low as 5 minutes and as high as over 24 hours (Table 1-4).[171-184] Inconsistencies in AF burden definitions, varying measures of burden (e.g., total AF time vs longest episode), heterogeneous baseline characteristics and OAC, complicate direct comparisons.

Glotzer *et al.* were the first to explore the relationship between device-detected AF and thromboembolic events in a secondary analysis of the MOST study.[171] Among 312 patients with sinus node disease and pacemaker implants, 10 (3.2%) patients had a stroke over a median follow-up of 27 months. AHRE >5 minutes had a two-fold risk of death or non-fatal strokes (adjusted hazard ratio [HR] 2.79, 95% CI: 1.51-5.15; p=0.001). Subsequent smaller studies confirmed that AHRE >5 minutes predict cardiovascular death and fatal stroke, and are associated with ischaemic brain lesions.[177,181]

Table 1-4. *Summary of studies investigating device-detected AF in patients with CIEDs and ICMs and associated thromboembolic risk.*

Study	Design	Patients (n)	AF detection	Clinical AF	AF/AHRE Definition	Patient with AF/AHRE	SSE	Comments
MOST[171] (2003)	Secondary analysis of RCT	312	PPM	6.4%	AF > 5 min	160 (51.3%)	10 (3.2%)	• AF >5min: adjusted HR=2.79 (95% CI 1.51-5.15) death or nonfatal stroke
Capucci *et al.*[172] (2005)	Prospective registry	725	PPM	87.2%	AF 5min to 24h AF >24 h	552 (76.2%)	14 (1.9%)	• AF>24 h: adjusted of HR=3.1 (95% CI 1.1-10.5) for thromboembolism
Botto *et al.*[173] (2009)	Prospective observational	568	PPM	100%	AF >5min to <24h AF >24h	179 (31.5%) 223 (39.2%)	14 (2.5%)	• AF >24 h: had a RR=5.0 (p=0.035) irrespective of $CHADS_2$ score for thromboembolism
TRENDS[174] (2009)	Prospective observational	2,486	PPM	20%	AF ≥5.5h/24h	1389 (55.9%)	NR	• AF ≥5.5h: adjusted HR=2.2 (95% CI 0.96-5.05) for thromboembolism
ASSERT[175] (2012)	RCT	2,580	PPM ICD	0	AT/AF > 6 min	261 (10.1%)	51 (0.56%)	• AT/AF >6 min: HR=1.76 (95% CI 1.28-4385) for thromboembolism
Shanmugam[176] (2012)	Prospective observational	560	CRT ICD	31%	AHRE≥ 3.8h/24 h	223 (39.8%)	11 (2.0%)	• AHRE ≥3.8h: HR=9.4, p=0.006) for thromboembolism
Gonzalez *et al.*[177] (2014)	Retrospective observational	224	PPM	0	AF ≥6 min	39 (17%)	5 (2.2%) †	• AHRE ≥6 min HR=2.8 (95% CI 1.24-6.31) cardiovascular mortality and HR=9.65 (95%CI 1.56-59.9) for stroke mortality
SOS AF [178] (2014)	Pooled 3 prospective	10,016	PPM ICD	23%	AF ≥ 5 min AF ≥ 1h	4287 (43%)	99 (0.98%)	• AF≥1h (HR=2.11, p=0.008) for thromboembolism
VA study[179] (2015)	Case-crossover	9,850	PPM ICD		AF ≥5.5h (daily)	NR	360(3.6%)	• AF >5.5 h: HR= 4.33 (95% CI 1.19–23.7)

Study	Design	Patients (n)	AF detection	Clinical AF	AF/AHRE Definition	Patient with AF/AHRE	SSE	Comments
Witt[180] (2015)	Retrospective registry	394	CRT	0	AHRE ≥6 min AHRE ≥24 h	79 (20%)	30 (7.7%)	• AHRE ≥6 min: HR=2.30 (95% CI 1.19–23.7 for thromboembolism • AHRE ≥24 h: HR 3.13 (95%CI1.16–8.39) for thromboembolism
Benezet-Mazuecos *et al.*[181]	Prospective observational	109	PPM ICD CRT	22 (20.2%)	AHRE >5 min	28 (25.7%)	NR	• AHRE >5 min: HR=3.05 (95%CI 1.06-8.81) for ischaemic brain lesions
RATE registry[182] (2016)	Prospective registry	5,379	PPM ICD	NR	AHRE≈20-30 sec	NR	41 (0.76%)	• AHRE ≈ 20-30 sec: HR=0.87 (95% CI) for stroke/TIA
Van Gelder *et al.*[183] (2017)	Secondary Analysis of RCT	2,455	PPM ICD	0	AF 6 min- 6 hours AF 6h-24 h AF >24 h	462 (18.8%) 169 (6.9%) 262 (10.7%)	51 (0.56%)	• AF >24 h: HR 3.24 (95% CI 1.51-6.95) for thromboembolism
Uittenbogaart *et al.*[184] **(2018)**	Meta-analysis	18,943	PPM ICD CRT	NR	AF ≥6 min AF ≥24 h	255 (1.1%)		• AF ≥6 min: HR 1.82 (95% CI 1.32-2.51) for thromboembolism • AF ≥24 h: HR 3.20 (95% CI 1.75-5.86) for thromboembolism

***AF**, atrial fibrillation. **RCT**, randomised controlled trials. **HR**, hazard ratio. **RR**, relative risk. **AHRE**, atrial high-rate episodes. **PPM**, pacemaker. **ICD**, implantable cardiac defibrillator. **CRT**, cardiac resynchronisation therapy. **NR** not reported. **TIA**, transient ischaemic attack. Study acronyms: **MOST**, MOde Selection Trial. **TRENDS**, The Relationship Between Daily Atrial Tachyarrhythmia Burden From Implantable Device Diagnostics and Stroke Risk. **ASSERT**, Atrial Fibrillation Reduction Atrial Pacing Tria. **RATE**, Registry of Atrial Tachycardia and Atrial Fibrillation Episode. **SOS AF**, Screening and Optimising Prevention in Atrial Fibrillation. **VA study**, Veterans Affairs Study.*

†Fatal strokes

In the ASSERT study, a 6-minute cut-off was used to investigate thromboembolic risk in 2580 patients aged ≥65 years and without prior AF.[175] Individuals in whom an episode of AF>6 minutes was captured in the first 3 months had an annualised SSE rate of 1.69% compared to 0.69% in those with AF <6 minutes (adjusted HR 2.58; 95% CI: 1.28 to 4.89; p = 0.008).

The authors concluded that an AF episode >6 minutes increased the risk of SSE events by a factor of 2.5. However, a subsequent analysis by Van Gelder *et al.*, stratified subclinical AF into three duration groups (<6 min, 6 min-24 h, >24 h) and found significant thromboembolic risk only for those with AF >24 hours (adjusted HR 3.24; 95% CI: 1.51–6.95; p = 0.003).[183] Similarly, Capucci *et al.* identified AF >24 hours as the sole predictor of thromboembolism in a registry of 727 patients, while Witt *et al.* reported a stronger association for AF >24 hours than AF >6 minutes in a Danish cohort of patients with cardiac resynchronisation therapy (CRT).[172,180]

Contradictory data emerged from the SOS AF project, which pooled data from over 10,000 patients with CIEDs from three studies and found that only AF ≥1 hour was associated with highest SSE risks, but this was not observed with longer thresholds of AF ≥23 hours.[178] The sample size of individuals with AF ≥23 hours was almost a third of those with AF ≥ 1hour (4,314 versus 11,428 patient-years of follow-up). However, when AF burden was modelled as a continuous variable, each additional hour of AF within a 24h-period resulted in 3% increase in relative risk.

TRENDS enrolled 2,486 patients with pacemakers or defibrillators and a $CHADS_2$ score >1.[174] A high AF burden, defined as AF/AT ≥5.5 hours, nearly doubled the thromboembolic risk (HR 2.20; 95% CI: 0.96–5.05; p = 0.06), but the absolute event rate was still lower than clinical AF. A Veterans Affairs (VA) study of 9,850 patients mirrored these findings: daily AF burden ≥5.5 hours was strongly associated with an increased SSE risk (HR 4.33; 95% CI: 1.19–23.7).[179]

1.7.2.2 Oral Anticoagulation in Device-Detected AF

The NOAH-AFNET 6 and ARTESiA trials have furthered our understanding of AF burden and stroke risk in device-detected AF.[170,185] NOAH-AFNET 6 evaluated the efficacy of stroke prevention of edoxaban versus aspirin (or placebo) in patients with AHRE ≥6 minutes and at least one stroke risk factor, whilst ARTESiA tested apixaban versus aspirin.[172] NOAH-AFNET 6 was terminated early as edoxaban did not lead to a reduction in thromboembolic events (1.1% vs 0.9%) and significantly increased major bleeding rates. Interestingly, thromboembolic risk remained unchanged across different AHRE durations and stroke risk profiles, challenging the assumption that longer AHREs episodes confer a greater thromboembolic risk.[186] In contrast, ARTESiA showed a modest reduction in thromboembolism with apixaban (0.6% vs 1%), but this

was offset by a higher major bleeding rate, albeit without an increase in fatal bleeding.[173] A subgroup analysis reaffirmed previous findings: patients with CHA_2DS_2-VASc <4 had an annual stroke risk <1%, reinforcing the argument against routine OAC in this group.[187] Both trials once again demonstrated a lower-than-expected ischaemic stroke rate (<1%), notably lower than that what is observed in clinical AF.[188]

Patient-level meta-analysis of both RCTs found that OAC reduced thromboembolic risk by 32%, but at the cost of a 62% increase in major bleeding. In other words, for every 100 patients with device-detected AF treated with DOAC, it would take 2.67 years to prevent a single stroke, compared to just 1.67 years to cause one major bleeding event.[189] Therefore, a critical unanswered question remains: at what burden threshold does the balance between stroke prevention and bleeding risk shift in favour of OAC in device-detected AF?[188]

1.7.2.3 Clinical AF

Evidence linking AF burden to thromboembolism risk is sparse due to the limitation of non-invasive monitoring tools, which typically provide rhythm data for only days to weeks.

Two studies demonstrate that having a high AF burden is associated with higher rates of thromboembolic complications in patients with PAF who are not anticoagulated. The KP-rhythm is a retrospective study that analysed 1,965 patients undergoing rhythm monitoring with a 14-day ZioPatch.[190] Patients in the highest tertile of AF burden (>11.4%) had a three-fold increased thromboembolic risk (2.9 per 100 patient-years) compared to the lower tertiles.

Similarly, a sub-analysis of the FinCV study examined the impact of AF burden on thromboembolism in PAF patients. The high burden group was defined as those requiring more than one cardioversion per year.[191] Among 2,074 patients not receiving long-term OAC, 107 SSEs occurred during a median follow-up of 5.4 years. The high AF burden group had a significantly higher event rate (1.82 vs 0.62 per 100 patient-years), and cardioversion frequency independently predicted both thromboembolism (HR 2.87; 95% CI 1.47–5.64; $p = 0.002$) and mortality (HR 2.54; 95% CI 1.73–3.74; $p < 0.001$).

1.7.2.4 Future Directions

Overall, most of the evidence supports a gradient in thromboembolic risk with increasing AF burden (Figure 1-5).[171,172,175,178,180,182-184] The absolute risk is likely modulated by a complex interplay between AF burden and the underlying risk profile. Contrasting with historical cohorts such as the AFFIRM study, recent rhythm control RCTs have demonstrated improvement in cardiovascular outcomes with strategies aimed at reducing AF burden.[192-195] In EAST-AFNET 4,

this benefit was primarily driven by the presence of sinus rhythm at one year.[196] Ongoing studies, including EAST^{high}-AFNET 11 (NCT06324188) and CABA-HFPEF (NCT05508256), are investigating whether AF burden reduction with catheter ablation translate into a reduction of cardiovascular events.[197]

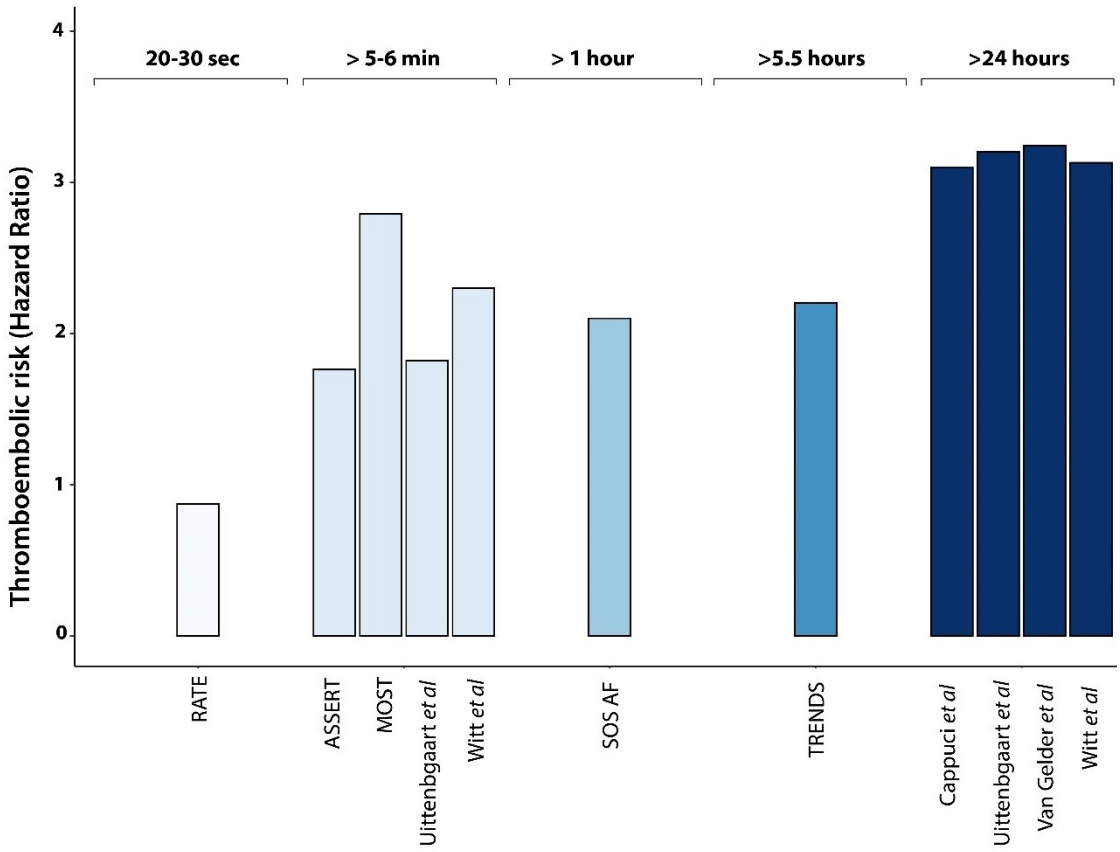


Figure 1-5*. Stepwise increase in thromboembolic risk in studies with device-detected AF and progressively longer AF burden or episode duration.*

Efforts to refine risk stratification continue. Tiver *et al.* proposed a new CHA_2DS_2-VASc-AFBurden score, combining AF burden with conventional risk factors.[198] Others have explored a novel tailored or 'pill-in-the-pocket' OAC in small feasibility studies for patients with infrequent AF episodes and low AF burden.[68,199]

As continuous rhythm monitoring becomes more widely adopted, it may offer a means to personalise stroke prevention and refine OAC decisions beyond current binary models.

1.8 Stroke Prevention

In the last decade, available therapies have broadened with the introduction of DOACs and refinement of percutaneous minimally invasive left atrial appendage occlusion device techniques.[146,147,165,200-204]

The efficacy of warfarin and other VKAs in preventing thromboembolic complications is well established, particularly when the time in therapeutic range (TTR) exceeds 70%.[8,205] However, achieving optimal TTR in clinical practice is challenging driven, in part, by warfarin's pharmacokinetic properties — narrow therapeutic range, slow onset of action and a high susceptibility for food and drug interactions.[206]

DOACs exert their anticoagulant effect either by inhibiting thrombin directly (dabigatran) or by inhibiting factor X (rivaroxaban, apixaban and edoxaban). Real-world data and the landmark RCTs support the efficacy and safety of DOACs in stroke prevention in patients with AF.[146,147,165,200] A large meta-analysis showed an additional 10% reduction in all-cause mortality and 19% in SSE with DOACs when compared to VKA, driven largely by a lower rate of haemorrhagic strokes.[9] Notably, only apixaban and high-dose dabigatran were superior to VKA, while all other DOACs met only non-inferiority.[146,147,165,200]

Bleeding complications are a well-recognised trade-off of OAC therapy and remain an important barrier to its use. In the Get With the Guidelines registry, 16.2% of 32,806 patients had a contraindication for OAC with a third being an absolute contraindication, such as previous intracranial haemorrhage. Annual major bleeding rates with DOACs ranged from 2.1% with apixaban in ARISTOTLE to 3.6 % with rivaroxaban in ROCKET-AF.[146,147] Real-world evidence shows even higher rates of major bleeding, at 1 in 25 of patients taking a DOAC experiencing a major bleeding event every year and higher event rates that previously thought.[207] Moreover, even minor bleeding is independently associated with higher risk of death and subsequent major bleeding.[208]

Several studies in various settings have shown that adherence and persistence with DOACs and warfarin remain suboptimal.[209,210] A meta-analysis of 48 observational studies involving over half a million DOAC users found that 1 in 3 patients had poor adherence (<80% of the time), with an overall persistence rate of 69%.[211] Suboptimal adherence and OAC discontinuation are strongly associated with an increased risk of stroke.[211]

DOACs are attractive drugs due to a rapid onset of action, predictable anticoagulant effect, and limited drug interactions, which obviates the need for routine monitoring and dose adjustment. Both ESC and AHA recommend DOACs over warfarin as first line treatment for stroke

prevention.[1, 2] However, VKAs still have a large role in the management of AF in patients with mechanical heart valves or in developing countries where the cost of DOACs is prohibitive.

1.9 'Pill-in-the-pocket' Oral Anticoagulation

A 'pill-in-the-pocket' OAC strategy challenges the dichotomous approach to anticoagulation. It is based upon the concept that the thromboembolic risk is dynamic, increasing during and shortly after an AF episode before decreasing in sinus rhythm.[212] With the advent of DOACs, therapeutic OAC is established within hours and dose adjustments and monitoring are no longer required.

Current stroke risk scores, such as the CHA_2DS_2-VASc score, rely solely on clinical risk factors.[135] Decisions are binary: if the annual predicted stroke rate is above 1%, there is a net clinical benefit in initiating lifelong OAC, regardless of AF temporal patterns or burden.[1,22,213] This assumes that a 65-year-old hypertensive man (CHA_2DS_2-VASc score of 2) with a single 24-hour AF episode per year has the same stroke risk, and benefits equally from OAC, as 65-year-old hypertensive man with longstanding persistent AF, despite vastly different AF burdens (Figure 1-6).

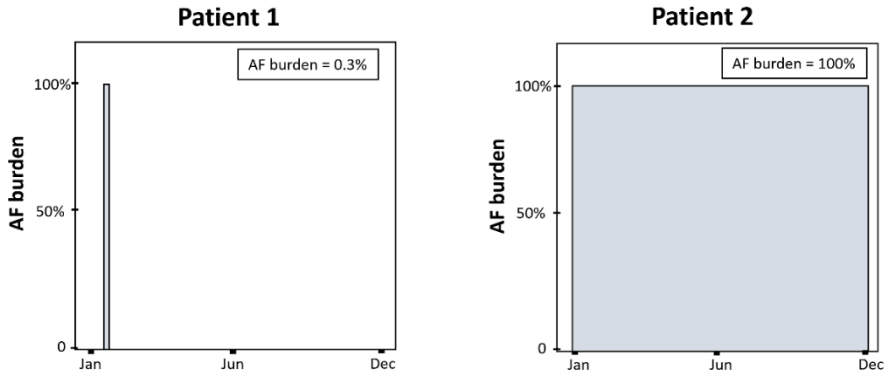


Figure 1-6. *Example of different AF burden with 'assumed' similar stroke risk based on current models, such as CHA_2DS_2-VASc, which ignore AF temporal patterns.*

1.9.1 Is There a Causal Relationship Between AF and Stroke?

The main premise of this strategy is a causal link between AF and ischaemic stroke: AF promotes blood stasis and thrombus formation which can embolise to the cerebral arteries. However, evidence for this direct relationship remains a matter of debate, particularly due to the temporal disconnect between AF and stroke observed in some continuous rhythm monitoring studies.[185,45,162]

The association between AF and thromboembolism is well established in longitudinal studies and large trials.[8-10] Thrombi predominantly form in the LAA, and its closure, surgically or percutaneously, has been shown to reduce ischaemic strokes, suggesting that in many patients, but not all, the mechanism is indeed thromboembolic.[202,214,215] Similarly, OAC in the peri-cardioversion period is effective in reducing thromboembolic events.[191,216-219]

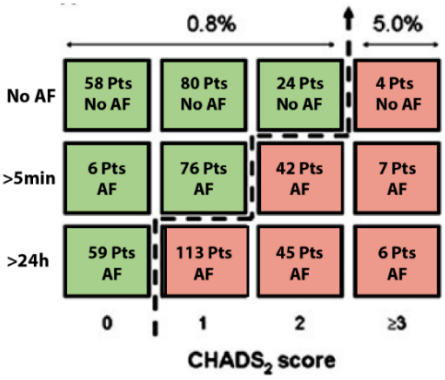
The argument that AF is merely a marker of atrial myopathy rather than a direct cause of stroke stems from observations that atrial size, function and fibrosis are associated with stroke even in the absence of AF.[220-224] Moreover, temporal dissociation between arrhythmic episodes and thromboembolic events has also been widely reported. Only 4 (7.8%) out of 51 ischaemic strokes in ASSERT and 6 (13%) out of 69 thromboembolic events in IMPACT were preceded by AF.[45,175] However, a much larger retrospective study of nearly half a million patients with CIEDs found that only a third of 891 strokes had AF in the preceding 120 days.[225] Similarly, other studies have found that approximately a quarter of individuals with ischaemic stroke have AF within 30-day window.[226-228]

Our current understanding is incomplete; arrhythmia alone is not responsible for all ischaemic strokes and there is likely a complex interplay of several factors.[224,229,230] Temporal disconnect may be explained by competing stroke mechanisms, such as large-artery atherosclerosis or hypertension-induced small vessel disease. Many AF patients have vascular comorbidities, and a CHA_2DS_2-VASc ≥5 independently predicts stroke risk even in the absence of AF.[231-233] Stroke adjudication is mostly based on clinical assessment without routine brain imaging, limiting insights into their aetiology.

In lower-risk patients, AF may play a more dominant role in modulating stroke risk (Figure 1-6).[173,231] Botto *et al.* found that patients with a $CHADS_2$ score of 1 had low thromboembolic events rates when AF was <24 hours.[173] Risk increased in those with $CHADS_2$ score of 2 with shorter AF episodes, while patients with $CHADS_2$ score of 3 had high event rates regardless of AF duration. Similarly, Kaplan *et al.* showed that in those with CHA_2DS_2-Vasc scores of 2 to 4, the thromboembolic risk increased with longer AF episodes, but those with a CHA_2DS_2-Vasc score ≥5 had a high event rate even without AF (Figure 1-7).[231] Similarly, in an ARTESiA sub-analysis, it was shown that among patients with a CHA_2DS_2-VASc score <4, thromboembolic risk was <1% regardless of therapy. The benefits of OAC were only observed in those with a CHA_2DS_2-VASc score ≥5.[186] These findings support a time-threshold effect, whereby stroke risk in intermediate-risk patients is modulated by AF burden.

Perhaps more crucial to the concept of 'pill-in-the-pocket' OAC is demonstrating a dynamic increase in thromboembolic risk following an AF episode, which could be mitigated by timely OAC initiation.

A



B

Maximum Daily AF Duration	CHA_2DS_2-VASc Score 0 n=2922 (13.4%)	1 n=2151 (9.9%)	2 n=4554 (20.9%)	3-4 n=7164 (32.9%)	≥5 n=4977 (22.9%)
No AF n=16815 (77.2%)	0.33% 40 events	0.62% 46 events	0.70% 95 events	0.83% 139 events	1.79% 157 events
AF 6 min–23.5 h n=3381 (15.5%)	0.52% 11 events	0.32% 4 events	0.62% 17 events	1.28% 42 events	2.21% 36 events
AF >23.5h n=1572 (7.2%)	0.86% 4 events	0.50% 3 events	1.52% 19 events	1.77% 28 events	1.68% 13 events

***Figure 1-7**. Stroke risk as a function of atrial fibrillation duration and **(A)** $CHADs_2$ score and **(B)** CHA_2DS_2-VASc score. Net clinic benefit for OAC as seen if annual thromboembolic event rate is over 1% (red boxes). Adapted with permission from Botto et al.[173] and Kaplan et al.[231]*

Cardioversion data suggest that conversion to sinus rhythm is associated with a transient increase in thromboembolic risk.[234] In electrical cardioversions without appropriate OAC, most thromboembolic events occur within 10 days, with rates as high as 7% in historical cohorts.[219,235] OAC dramatically reduces this to <1% in the post-cardioversion period and it is currently recommended for four weeks following a cardioversion irrespective of CHA_2DS_2-Vasc score.[191,216-219]

The primary mechanism for thrombus formation post-cardioversion is transient mechanical dysfunction (atrial stunning) following sinus rhythm restoration, a process independent of cardioversion mode (spontaneous, pharmacological, or electrical) or AF recurrence. Recovery of atrial function depends on AF episode duration: brief episodes have a swift return to baseline function within days, whereas longer episodes may take up to a month.[105,236]

Further evidence of dynamic risk following AF episodes comes from two elegant case-crossover studies by Turakhia *et al.* and Singer *et al.*, which used similar methodology.[179,225]

Case-crossover studies isolate AF as the variable of interest by using patients as their own controls and therefore ensure that the other baseline clinical risks factors are unchanged. Turakhia *et al.* screened 9,850 patients with CIEDs in the VA Health Care System, identifying 187 with an acute ischaemic stroke.[179] The 30-day period prior to the stroke was the case period,

while a distant window (91–120 days) served as the control. AF burden was considered significant if it was over 5.5 hours on any day. Thirteen patients had a discordant AF burden, with high burden in the case period but none in the control period. For these patients, the odds ratio (OR) for stroke with a daily AF burden greater than 5.5 hours was 4.21 (95% CI: 1.53–13.44). The highest risk occurred within 10 days and returned to baseline after 30 days.

Singer *et al.*, who co-authored the VA study, analysed a larger dataset of 466,635 patients, again demonstrating a temporal increase in stroke risk with daily AF burden ≥5.5 hours (OR 3.7, 95% CI: 2.06–6.70).[225] The highest risk was within 5 days, returning to baseline within one month (Figure 1.7). Mirroring previous studies, the highest risk was seen in AF >23.5 hours which conferred the greatest risk, increasing the stroke likelihood fivefold.

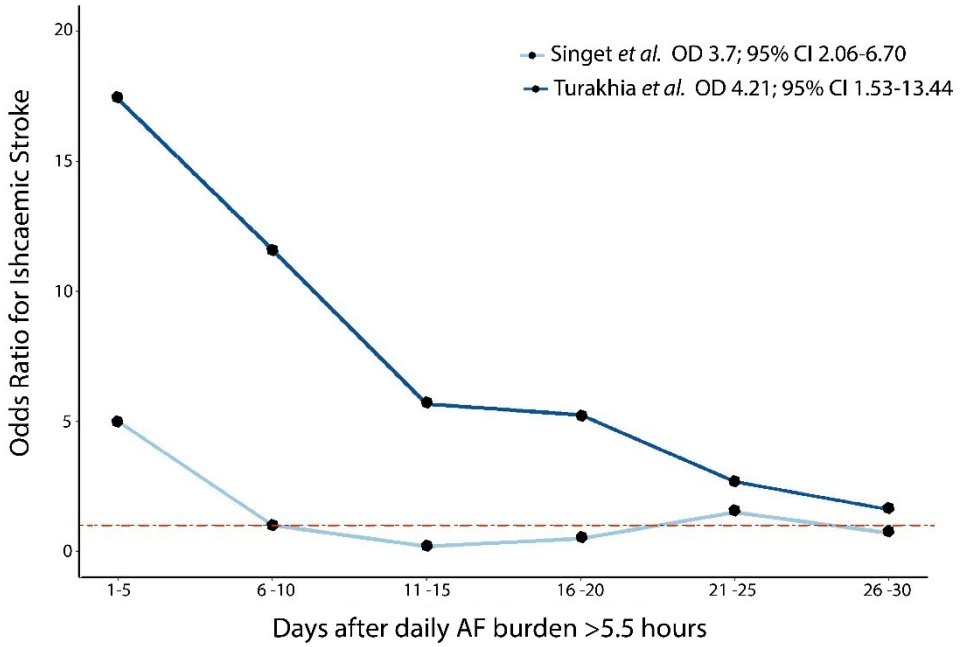


***Figure 1-8**. Odds ratios for ischaemic strokes for sequential 5-day intervals in patients with AF burden >5.5 hours observed Turakhia et al. and Singer et al.[179, 225]*

Both studies strengthen the case for a causal link and suggest a transient increase in stroke risk following AF episodes, independent of baseline risk factors (Figure 1-8). Kaplan *et al.* further demonstrated that non-anticoagulated patients with AF paroxysms lasting less than 23.5 hours and a CHA_2DS_2-VASc score of 1–2 had an annual stroke rate below 1%.[231] These findings challenge the rationale for continuous, long-term OAC in this group, where the risk-benefit balance may not justify indefinite OAC. Indeed, indefinite OAC may therefore expose patients with short or infrequent AF episodes to high bleeding risk relative to the more limited benefit in stroke reduction.

1.9.2 Remote Monitoring and 'Pill-in-the-Pocket' OAC

Limiting OAC to periods of AF in low-risk patients with infrequent AF episodes may offer similar thromboembolic protection as continuous OAC whilst reducing costs, bleeding risk, and improving adherence.[237]

Small feasibility studies have explored 'pill-in-the-pocket' OAC using continuous monitoring via CIEDs or ICMs.[67-69,199,238,239] REACT.COM enrolled 59 patients with an ICM implanted and with PAF and a $CHADS_2$ score of 1 to 2.[68] Over a mean follow-up of 15 months, 98.7% adhered to the study protocol and performed daily transmissions. Limiting OAC to one month after AF ≥1 hour resulted in a 94% reduction in OAC time compared to indefinite OAC.

1.9.3 AF Progression

The natural history of AF is often viewed as a progression from PAF to persistent AF: "AF begets AF".[107-109] Studies suggest that up to one third of patients develop persistent AF within 5 years of the diagnosis of AF.[107, 240-242] However, progression is not inevitable; many patients remain in PAF for years, particularly those without significant cardiovascular comorbidities, with almost half remaining with PAF at 25 years.[243,244] Risk factor modification and early rhythm control strategies may further reduce AF progression and burden.[245-249]

A meta-analysis of 4 RCTs found that catheter ablation significantly reduced progression to persistent AF to 2% compared to 13.6% for antiarrhythmic drugs at 3 years.[250] The EAST-AFNET 4 trial showed that early rhythm control with catheter ablation reduces AF burden and progression risk.[196] Similarly, LINQ usability data reported that 72% of post-ablation patients had no clinically significant AF and a yearly burden of <0.1%.[53]

Sughiara *et al.,* found that 69% of patients with PAF and CIEDs have an extremely low yearly burden (< 0.1%), with no increase in burden over a 3-year follow-up.[34] Similarly, in the LOOP study, 55% of patients with device-detected AF exhibited a declining AF burden over time, and 22% had no recorded episodes in the final six months of follow-up.[251]

1.9.4 Candidates for 'Pill-in-the-Pocket' OAC

A significant subset of AF patients with low AF burden may be eligible for 'pill-in-the-pocket' OAC if proven safe and effective. This strategy is particularly suited to patients with PAF. Patients appear receptive. I conducted an online survey in collaboration with the AF Association which included 320 patients (Figure 1-9).[252] Just over two-thirds of patients worried about bleeding from taking OAC and one-quarter had experienced a bleeding event. While most adhered well

to OAC, 23.5% missed at least one dose per month. Encouragingly, 54% of patients would choose a 'pill-in-the-pocket' OAC strategy guided by continuous rhythm monitoring with an ICM and 48% preferred wearable device guidance over indefinite OAC.[253]

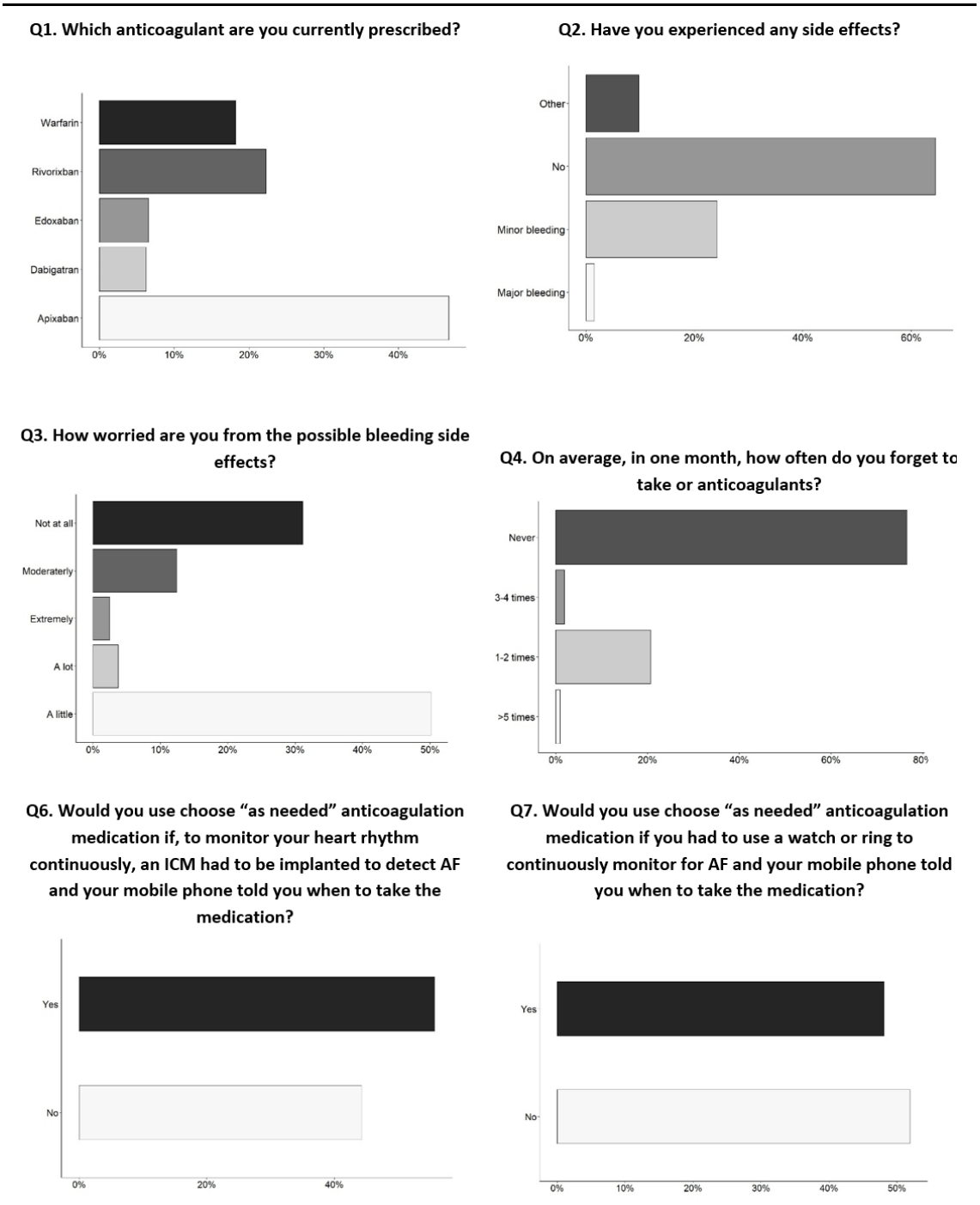


Figure 1-9. *Summary of main results of 'pill-in-the-pocket' OAC questionnaire. Adapted with permission from Briosa e Gala et al.*[253]

1.10 Research Aims

This research work investigated whether minimally invasive monitoring technologies — ICMs and wearable devices CART Ring and Apple Watch — can accurately detect AF episodes of varying durations. Additionally, it assessed the feasibility of AF detection and delivering 'real-time' alerts to patients, whilst evaluating adherence and engagement with AF notifications.

The overarching aim of this research was to develop a robust platform for guiding 'pill-in-the-pocket' OAC hereby enabling the development of an optimal monitoring and notification system to be used in a future RCT.

I explored following research questions in detail:

1. **What is the feasibility, safety and efficacy of 'pill-in-the-pocket' OAC?**
   A systematic review and meta-analysis were conducted to synthesise existing evidence, as detailed in **Chapter 3**: *'Pill-in-the-Pocket' OAC Guided by Daily Rhythm Monitoring: A Systematic Review and Meta-analysis*.
2. **What is the diagnostic performance of the Confirm Rx ICM with SharpSense technology for AF episodes of different duration and what are the sources of false positive detection?** This question was investigated through a retrospective research study, as detailed in **Chapter 4**: *UK Confirm Rx study.*
3. **What is the diagnostic accuracy of the automatic AF detection algorithm and physician interpretation of a SL-ECGs generated by the CART Ring and Apple Watch compared to the gold-standard 12-lead ECG?**
   This question was examined in a prospective, multicentre, randomised study, as detailed in **Chapter 5**: *WEAR-TECH ECG study.*
4. **Can ICMs (LINQ II™) and wearable devices (Apple Watch and SkyLabs CART Ring) accurately detect AF episodes, send real-time alerts to participants' smartphones, and ensure patient compliance with notifications?**
   This question was explored through a prospective, single-centre, randomised study, as detailed in **Chapter 6**: *SMART-ALERT study*.

2 Methodology

2.1 Overview of Research Design

This chapter outlines the general framework of my research and study devices. Study-specific methodology is discussed in detail in Chapter 3 to 6. This thesis includes three studies investigating the performance of wearable devices and ICMs in detecting AF, identifying strengths and limitations and exploring the implications for delivering 'pill-in-the-pocket' OAC.

A range of different study designs was employed to address specific research questions (Chapter 1), including:

- **Systematic review and meta-analysis of 'pill-in-the-pocket' OAC guided by continuous rhythm monitoring** (Chapter 3): This study systematically summarised the available evidence pertaining to the feasibility, safety and efficacy of 'pill-in-the-pocket' OAC. This systematic review provided a foundational understanding of prior studies, highlighting important knowledge gaps which guided subsequent investigations. The in-depth discussion of the methodology, including search strategy and statistical analysis used, can be found in Chapter 3 and Appendix B.[254]

- **Retrospective study** (Chapter 4): The UK Confirm Rx study was a multicentre study of investigating the diagnostic performance of the Confirm Rx ICM in detecting AF episodes of different duration.[255]

- **Prospective validation study** (Chapter 5): The WEAR-TECH ECG study was a multicentre study investigating the diagnostic performance of two consumer-grade wearable devices (Apple Watch and CART Ring) in detecting AF with a spot-check SL-ECGs. This study explored the potential role of these devices in a 'pill-in-the-pocket' OAC as a second step to validate an AF episode before taking OAC.[256]

- **Feasibility study** (Chapter 6): The SMART-ALERT study was a single-centre feasibility study investigating the performance of real-time AF detection and notification for episodes >30 minutes of three different devices: (1) ICM integrated with a bespoke software; (2) Apple Watch; and (3) CART Ring. This study evaluated the feasibility of patient-centred alert systems and their applications in targeted OAC strategies.[257]

2.2 Ethical Approval and Funding

2.2.1 Systematic Review and Meta-analysis (Chapter 3)

The systematic review and meta-analysis followed the framework set out in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, and it was prospectively registered in PROSPERO (CRD42020209564), an international systematic review registry.

2.2.2 UK Confirm Rx Study (Chapter 4)

The UK Confirm Rx study was exempt from Research Ethics Committee (REC) review as this was a retrospective analysis of de-identified data collected as part of routine clinical care. Patients provided informed consent for their de-identified data to be used for research purposes at the time of the ICM implant. The study was approved by the Health Research Authority (HRA; ID 297175).

2.2.3 WEAR-TECH ECG Study (Chapter 5)

The WEAR-TECH ECG study received approval from the London-Stanmore REC (22/LO/0029) and had HRA (ID 291671) approval. The study consumables (CART Rings) were supported by a Skylabs (Gyeonggi-do, South Korea) grant.

2.2.4 SMART-ALERT Study (Chapter 6)

The SMART-ALERT study (Chapter 6) was funded by the Heart Research UK Novel and Emerging Technologies Grant and Oxford Hospitals Charity (2020/1352). Ethics approval was given by the West Midlands Research Ethics Committee (21/WM/0217) and had HRA (ID 294367) approval.

2.3 Study Populations

Study populations were different for each study and are described in detail in individuals Chapters 3 to 6.

2.4 Study Devices

2.4.1 Confirm Rx ICM

The Confirm Rx with SharpSense is an ICM manufactured by Abbott. It is a small (49 mm x 9.4 mm) monitor that is injected under the skin and continuously monitors heart rate and rhythm for cardiac arrhythmias for up to three years (Figure 2-1A).

2.4.1.1 Implant Procedure

The ICM implant is perform in aseptic conditions under local anaesthetic with the recommended position in the 4th intercostal space at a 45-degree angle (Figure 2-1B). The device is injected via a small incision (1-2 cm) made by a triangular blade and using the manufacturer's tools to create a tight pocket. The small wound is usually closed with either steri-strip to approximate the wound edges or surgical glue. Potential adverse events include bruising, haematoma (<1%), superficial infection (<1%), keloid formation, migration and extrusion. All participants provided signed informed consent.

2.4.1.2 AF Detection Algorithm

Confirm Rx ICM has four new discriminators (three discriminators for bradycardia and pauses and one AF discriminator) designed to improve arrhythmia detection. The original AF algorithm (SJM Confirm) was validated against a 48-hour monitor in 79 patients in the DETECT-AF study.[47] The SJM Confirm ICM showed both high episode and patient sensitivity of 94% and 100%, respectively. However, it had only a moderate PPV of 64% for AF episodes ≥ 2 minutes.[47]

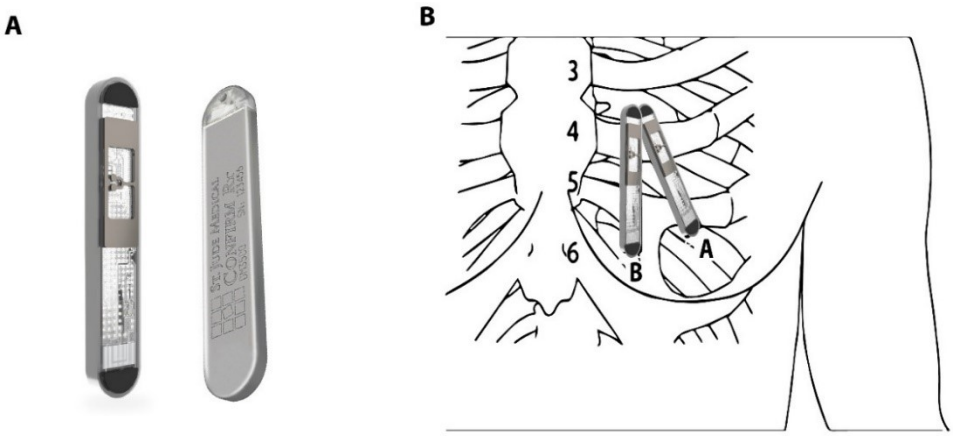


Figure 2-1 (A) *Image showing the LINQ II ICM (on the left) and the Confirm Rx ICM (on the right)* ***(B)*** *Illustration of recommended ICM insertion positions in the chest wall. The conventional ICM device placement in the 4th intercostal space at a 45-degree angle (A) and an alternative position which is vertical along the left sternal edge (B). Adapted with permission from Sakhi et al.[258]*

The SJM Confirm algorithm relied on monitoring R-R intervals during a 64-beat rolling window for three criteria to be met: sudden onset, irregularity and large variance. A Markov chain model was used to assess for irregularly irregular R-R intervals by comparing observed intervals in the rolling window with known patterns of both of AF and non-AF rhythms. To distinguish AF from other irregular rhythms, such as bigeminy, variance models were subsequently used to detect a truly irregularly irregular rhythm.

Table 2-1. *Confirm Rx ICM nominal settings used in the UK Confirm Rx study.*

Reason for monitoring	AF duration	AF	Pause	Tachycardia	Bradycardia	Sudden onset
Syncope	6 min	Low	High	High	High	On
AF management	6 min	High	Low	High	Low	On
Suspected AF	6 min	High	Low	Low	Low	On
Palpitations	6 min	High	Low	Low	Low	On
Others	2 min	High	High	Low	Low	Off

The Confirm Rx ICM includes an optimised algorithm called SharpSense. In addition to the steps described above, it improves AF detection by adding a P-wave discriminator, which reduces FP detection by 97% without compromising sensitivity.[259] The nominal settings of the Confirm Rx ICM are depicted below in Table 2-1.

This discriminator analyses P-waves segments from the preceding 30 seconds for morphology and amplitude and stacks them together. This is the final step in the rhythm analysis and an AF episode is detected if no consistent pattern is found in the sampled P-wave sampled. In other words, there were no obvious P-waves seen in that segment that had met all the other conditions of sudden onset, irregularly irregular and a large variance between R-R intervals. By selecting the reason for monitoring, the Confirm Rx automatically sets episode parameters including AF duration cut-off, ECG trigger priority and alert notification settings (Table 2-1). With the newer generation of the Confirm Rx ICM, the nominal R-wave sensitivity was increased from 0.150 to 0.125 mV.

Confirm Rx ICM uses low-energy Bluetooth® for secure wireless communication with the myMerlin mobile app. This app act as a conduit for episode transmission to the Merlin.net Patient Care Network for remote monitoring when there is an active internet connection.[260] For each episode there is a rhythm diagnosis, date and time of onset, and duration. Some episodes, depending on device settings and available memory, will have a 120-second heart rate scatter plot and ECG which can be used for adjudication. An example of a report generated by the Confirm Rx from the UK Confirm Rx study can be found in Figure 2-2.

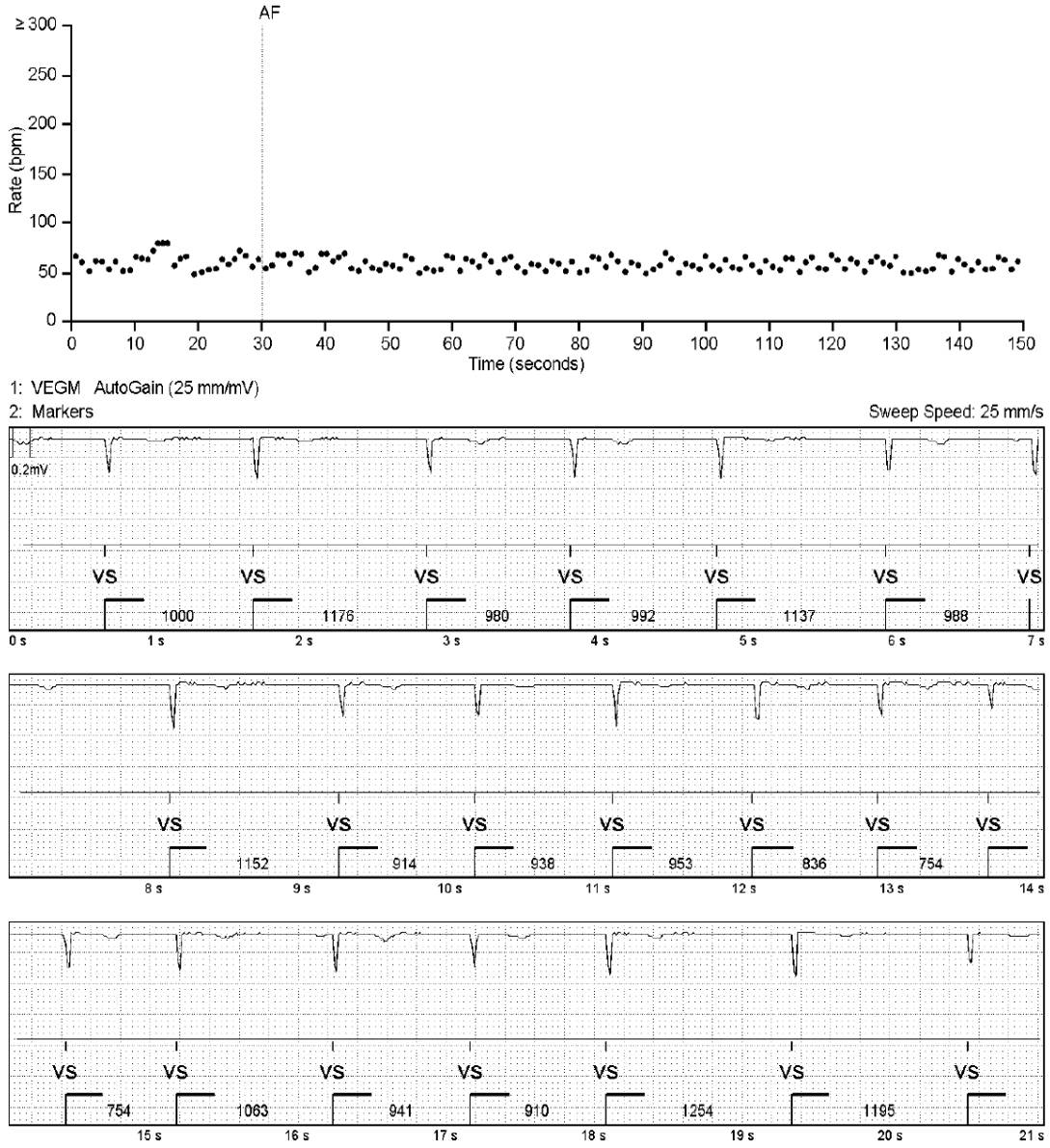


***Figure 2-2**. Example of an episode of AF from a report generated by Confirm Rx ICM. The top panel has a heart rate scatter plot with time in (seconds) on the x-axis and heart rate (bpm) on the y-axis. This plot shows an irregularly irregular rhythm characteristic of AF. Below there is a SL-ECG. The rhythm is annotated with ventricular sense (VS) markers, each corresponding to a QRS complex. The varying cycle lengths between QRS complexes without a consistent pattern further confirms the presence of AF. There are no obvious P-waves.*

2.4.2 LINQ II ICM

The LINQ II ICM with AcuRhythm is manufactured by Medtronic. It is also a compact (44 mm x 7 mm) minimally invasive device used long term heart rhythm monitoring. Implant technique is similar to the Confirm Rx ICM, but with the insertion tools supplied by its manufacturer.

2.4.2.1 AF Detection Algorithm

The LINQ II ICM AF detection algorithm analyses R-wave variability using a Lorenz plot, which maps consecutive R-R intervals to distinguish AF patterns.[258] AF is characterised by irregularly irregular ventricular activation, whilst sinus rhythm and atrial tachycardia (AT) are regular rhythms (Figure 2-3).[261]

In the Reveal LINQ usability study, which compared 151 patients with a Reveal LINQ ICM and a Holter monitor, the sensitivity for AF episodes longer than 2 minutes was 97.3%, and PPV was 74.8%.[53] The PPV improved progressively for longer AF episodes (≥6 minutes, 1 hour, or 6 hours) to 83.8%, 97.1%, and 100%, respectively.[262] The LINQ II ICM is the new iterations of the Reveal LINQ ICM.

To classify and store an episode as AF, the TruRhythm algorithm analyses the Lorenz plot every 2 minutes and calculates an AF evidence score.[258, 262] This is followed by searching for consistent P-waves to assign a P-wave evidence score, which is then subtracted from the AF evidence score. If the final score is above the detection threshold, AF is detected, and that episode is stored on the device.[55]

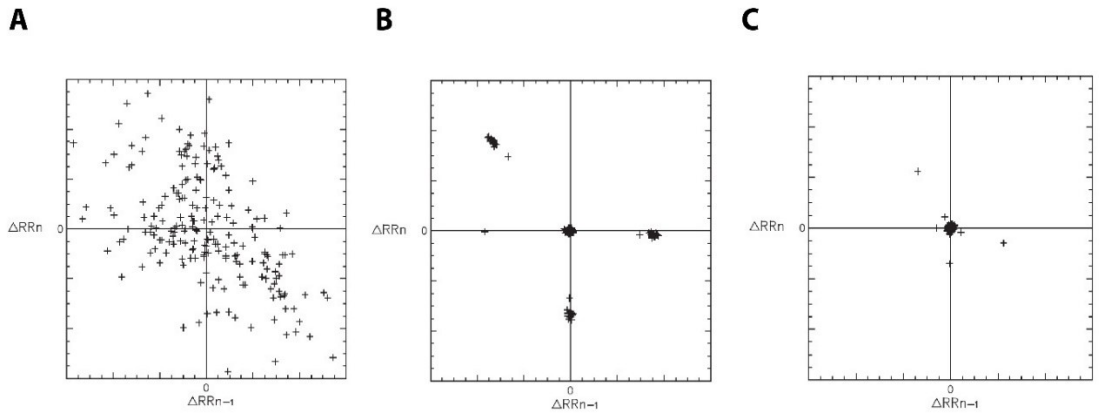


Figure 2-3. *Examples of Lorenz plots of different cardiac rhythms based on R-R interval variability. The x-axis (ΔRRn) shows the current R-R interval, whilst the y-axis (ΔRRn-1) depicts the previous R-R interval.* ***(A)*** *Points are widely scattered, indicating a very irregular R-R intervals, characteristic of AF.* ***(B)*** *Points are scattered in an "island pattern" with four distinct clusters, typically seen in AT.* ***(C)*** *Points cluster around a central diagonal line, reflecting consistent R-R intervals in keeping with sinus rhythm. Adapted from Medtronic LINQ II ICM manual.*

The AccuRhythm is a post-transmission cloud-based algorithm that employs deep learning techniques to compare detected AF episodes against a large dataset of stored arrhythmia patterns. It provides the final step before an episode is categorised as AF. Therefore, all AF episodes initially classified by the LINQ II ICM as AF are analysed a second time once they are

uploaded to the CareLink remote monitoring platform. In validation studies, the second-pass analyses of AccuRhythm reduced FP AF alerts by 88.2% but maintained a very high rate of true-AF detection (99%), resulting in an overall improvement in detection accuracy.[263]

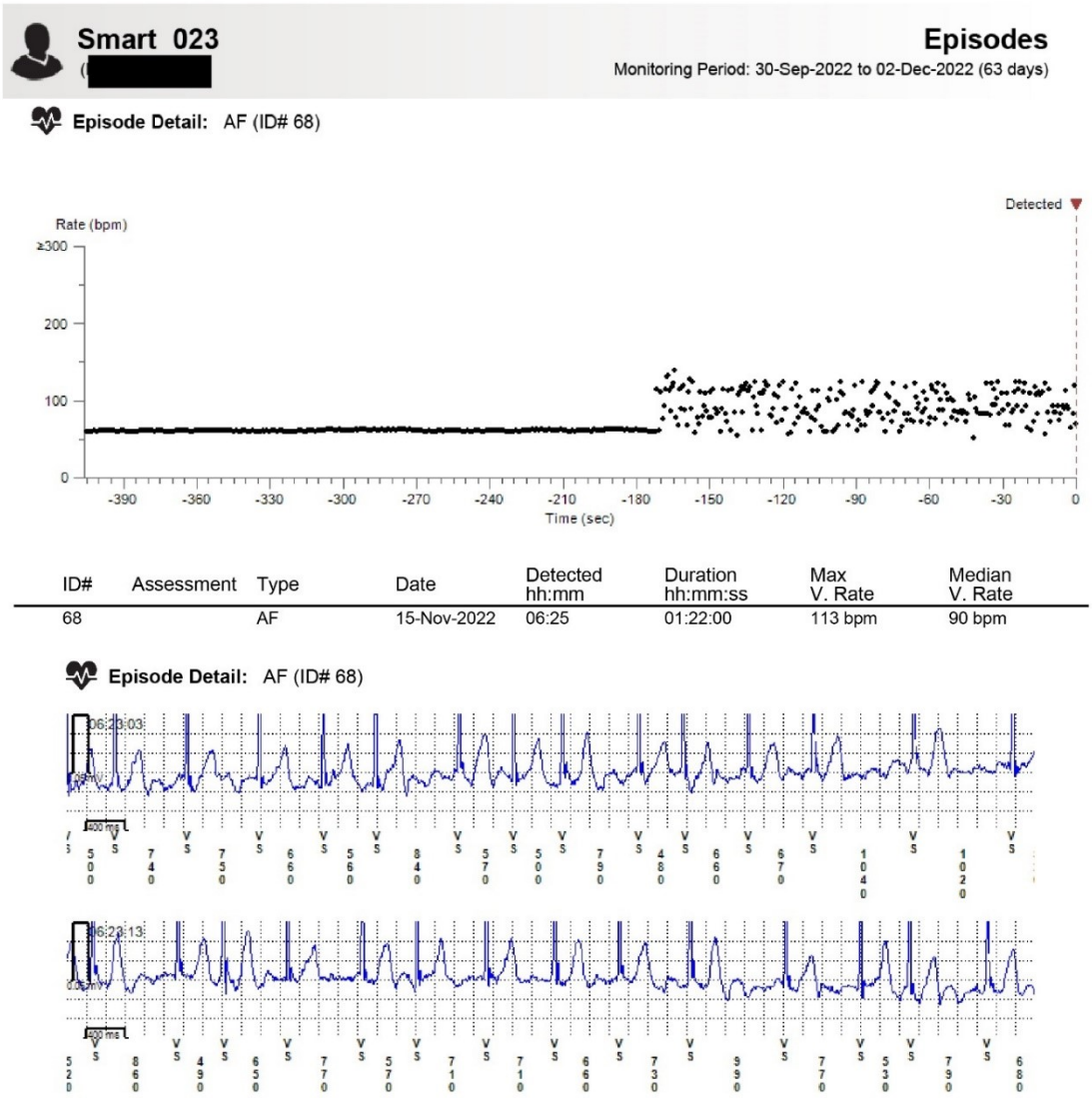


Figure 2-4. *Example of a LINQ II report from patient SMART023 (SMART-ALERT study; Chapter 6). This report shows Episode 68, classified as AF. The top panel shows a heart rate scatter plot, with time (seconds) on the x-axis and heart rate (bpm) on the y-axis. There is a clear abrupt transition from a regular heart rate of approximately 60 beats per minute to chaotic and irregular heart rate, in keeping with AF. Below, the summary table contains episode details including date and time, episode onset and total duration. The lower panel is the rhythm strip showing a SL-ECG for this episode. Each QRS has a ventricular sense (VS) marker below with the cycle length duration annotated between VS markers. The variable cycle lengths of the QRS confirm that this is AF.*

For each AF episode, the LINQ stores an ECG of the first 2 minutes with a corresponding heart rate scatter plot (Figure 2-5).[260] The device's memory is capable of storing a total of 27 minutes of ECG storage from automatic detections. It provides episode data on all AF detection (date of

onset, duration and mean heart rate); however, ECG tracings are stored for only up to three episodes. If more than three AF episodes occur in a single day, the device retains the ECGs for the longest episodes, overwriting the most recent ones. [262] The LINQ II ICM also records patient-activated episodes, which include three segments of 10 minutes each.

An example of a report generated by the LINQ II ICM from the SMART-ALERT study can be found in Figure 2-4.

2.4.2.2 Data Transmissions and Remote Monitoring

Data transmissions occur via low-energy Bluetooth® to either a stationary home monitor or the MyCareLink Heart mobile app. If an active internet connection is available, data is uploaded to the CareLink remote monitoring platform. The mobile app is currently compatible only with the iOS operating system and a limited number of Android devices, primarily Samsung. To connect with the LINQ II ICM, the MyCareLink Heart app must be open and running in the background. A pop-up notification is sent to patients if the app is closed for four consecutive days and no transmissions are received on CareLink.

2.4.3 SMART-ALERT Software

Although episodes detected by the LINQ II ICM are transmitted by the MyCareLink Heart app to its remote monitoring platform (CareLink), the app serves purely as a conduit for data transfer and does not provide direct feedback to participants. Whilst data from AF episodes is continuously transmitted when the MyCareLink Heart app and LINQ ICM are in communications, participants receive no real-time notifications of detected AF episodes. Indeed, they do not have access to any episode data.

To address this limitation, I collaborated with BrainLogic Inc. to develop a bespoke software solution: the SMART-ALERT software (see Chapter 6).[257]

2.4.3.1 Workflow and Decision Logic

The SMART-ALERT software was designed to review all transmissions uploaded to the SMART-ALERT clinic on CareLink every five minutes to ensure a 'real-time' notification to participants if new AF episodes were uploaded. The software's workflow was as follows:

1. **Automated Login and Patient Selection**

The SMART-ALERT software ran continuously in the cloud during the SMART-ALERT study. When the programme was initiated, it opened a Chrome internet browser and then it selected the CareLink webpage (www.europe.medtroniccarelink.net). It used study-specific login credentials to gain access to the remote monitoring platform. It would then navigate to the SMART-ALERT

clinic on the main dashboard (top right corner). After opening the clinic page, it selected the "All Patients" tab to display the full patient list (Figure 2-5). Each participant would then be selected sequentially to access their transmissions data for review. If no new episodes were detected, the software became inactive and repeated the process of sequentially selecting each participant and reviewing the episode log for new AF episodes every five minutes.

2. Data Extraction and Episode Identification

For each participant, the software accessed the "Quick Look" summary page, to retrieve participant data, including their phone number. It then proceeded to the "Episodes" tab, which had the summary table containing data from all arrhythmic episodes. This table displayed each individual episode with its episode ID, type of arrhythmia (e.g., AF, tachycardia, pause, bradycardia), date and time of arrhythmia detection, and episode duration.

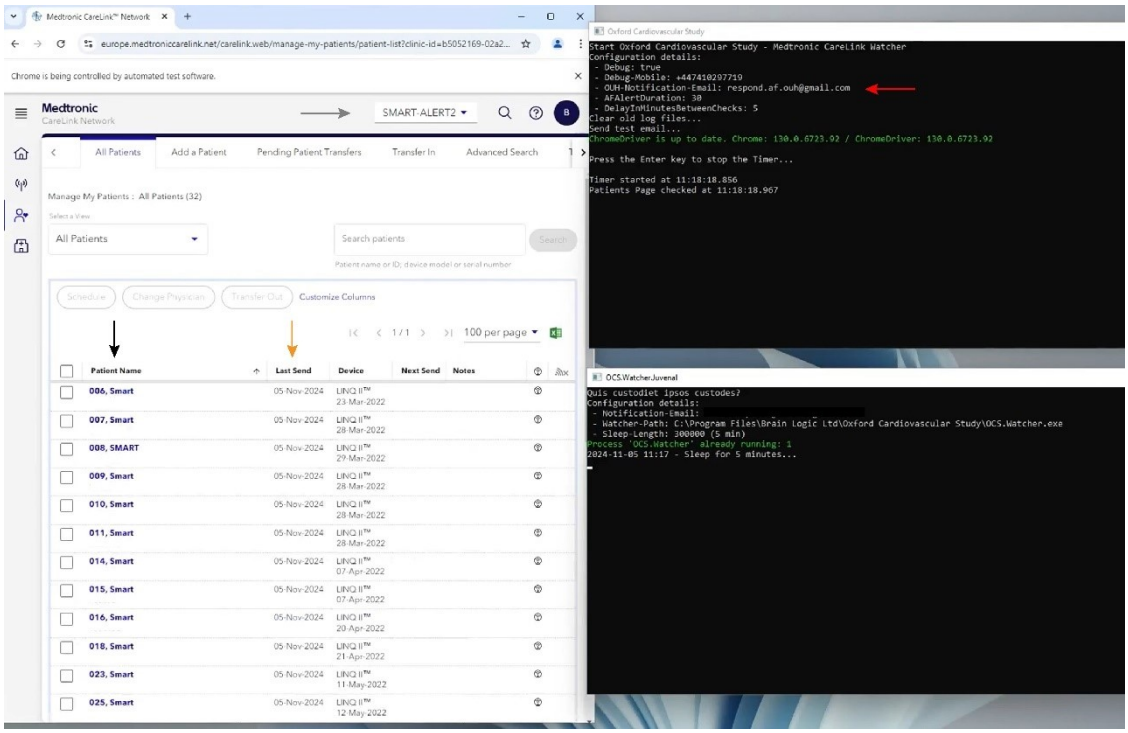


Figure 2-5. *Example of the SMART-ALERT software running. The left panel displays the SMART-ALERT clinic (grey arrow) with the list of participants enrolled in the SMART-ALERT study (black arrow). On the right, there is a column with the date of the latest data transmission to CareLink (orange arrow). The top-right panel shows the SMART-ALERT software running and it displays key features, such as email notifications to the research team of any alerts sent to participants. The red arrow highlights that the AF alert duration was set at 30 minutes. We set the delays between transmission checks at 5 minutes. The software also checks whether ChromeDriver is up to date before launching Chrome to prevent connectivity problems and failures to launch the extension.*

3. Decision Tree for SMS Notification

The software employed three-tier decision logic to determine whether the AF episode met the study criteria of the first episode of AF ≥30 minutes in a 24-hour period.

The first step was the arrhythmia identification filter, in which only episodes categorised as AF were considered for SMS notification. The second step was the timing validation process, where it compared the date and time of each detected episode against the timestamp of the last SMS notification sent, to prevent duplicate alerts being triggered for the same episode and confirm that more than 24-hour had elapsed since the last alert. The last step involved assessing threshold duration, by confirming whether the AF episode met or exceeded the SMART-ALERT study's predefined minimum duration of ≥30 minutes (Figure 2-6).

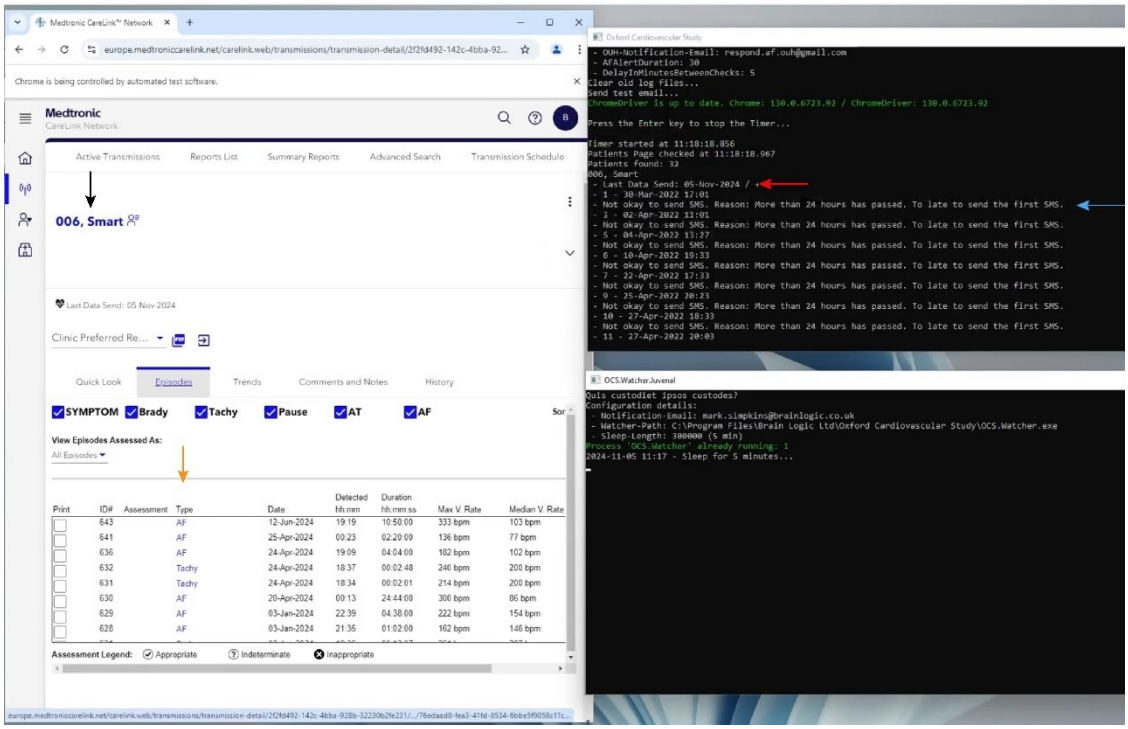


Figure 2-6. *Example of the SMART-ALERT software reviewing individual transmissions. The left-hand panel shows participant SMART006 (black arrow), with the "Episodes" tab selected, displaying a summary table with episode ID, type of episode, date of detection, and duration (orange arrow). The top-right panel shows the last data transmission for SMART006 (red arrow). The software reviewed date and duration of all AF episodes and applies the decision tree to determine whether an AF notification should be sent. No SMS alert was triggered in this case since more than 24 hours have elapsed from the first episode.*

4. SMS Notification and Database Entry

If an episode met all predefined criteria, it would trigger a standardised SMS to the participants registered phone numbers, with the following message: *"We have detected an episode of AF. Please acknowledge by replying to this SMS."* Participants would then acknowledge receipt of

the SMS by replying to the study number. The timestamp of the SMS sent by the SMART-ALERT software and the timestamp of the reply from participants were recorded in the MySQL database for monitoring and analysis.

For a successful AF notification and acknowledgement in the SMART-ALERT study, the LINQ II ICM needed to be within Bluetooth® range of the participant's smartphone. The MyCareLink Heart app had to be open in the background with a working internet connection to ensure the episode was uploaded to CareLink. The SMART-ALERT software had to be running, correctly identified the AF episode according to the study criteria (see Chapter 6) and triggered an SMS notification. Finally, the participant had to receive and acknowledge the SMS. This was the closed-loop alert system developed and tested, designed to enable real-time AF notification as part of a 'pill-in-the-pocket' OAC strategy.

Snippets from the SMART-ALERT software code can be found in Appendix A.

2.4.4 Apple Watch

The Apple Watch (Apple, Cupertino, CA) was the first FDA-approved smartwatch capable of recording SL-ECGs. This capability was first introduced in the Series 4 watch, released in 2018, by combining two electrodes, one on the back of the watch in contact with the wrist skin and the other embedded in the metal crown (Figure 2-7).

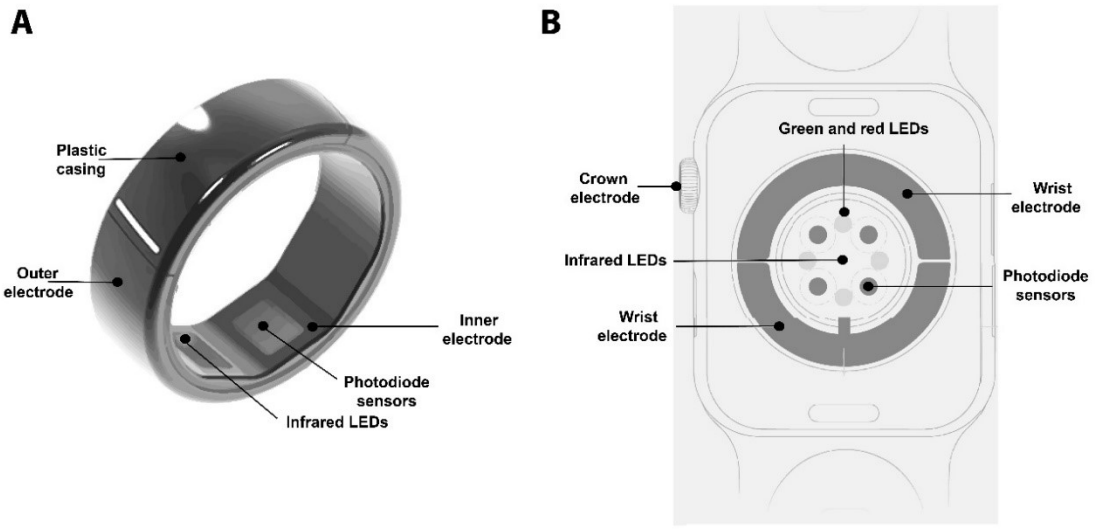


Figure 2-7. *Wearable devices.* ***(A)*** *Illustration of the Skylabs CART Ring with its key components, including the outer and inner electrodes for electrical sensing, infrared light-emitting diodes (LEDs), and photodiode sensors embedded within the metal casing.* ***(B)*** *Illustration of the Apple Watch highlighted the digital crown and wrist electrodes, and the optical sensor array used to collect photoplethysmography data.*

The Apple Watches tested were series 6 and series 7 with ECG algorithm version 1.0. The Watch comes in two sizes. In series 6, the case size can be either 40 and 44 mm and its series 7 case are slightly larger at 41 mm and 45 mm. Electrodes and infrared LEDs lights are located at the back of the Apple Watch and are designed to be in good contact with the skin on the wrist to collected PPG signals. The battery life of the Apple Watch is typically 18 hours and with fast charging the battery can reach 80% in 45 minutes.

2.4.4.1 AF Notifications during Ambulatory Monitoring

The Apple Watch's detection criteria for AF detection (irregular rhythm notifications) are not well defined. Apple documentation stated that if the device detected an irregular rhythm during a pulse check, it would initiate more frequent PPG sampling, typically multiple times per hour. The duration threshold for AF detection tested in the SMART-ALERT study (Chapter 6) was 30 minutes.

In the Apple Heart study, participants without a history of AF, the Apple Watch (series 1-3) used the following criteria: if 5 out of 6 pulse checks within a 48-hour period were irregular, participants who had received an AF notification and were sent a 7-day ambulatory monitor.[264] Only 2,161 (0.52%) participants received an Apple Watch and wore a monitor; however, only 86 participants had an AF alert notification by the Apple watch during this period. Nonetheless, in 72 (84%) this was confirmed as a True-AF episode on the monitor.

Wasserlauf *et al.* investigated the sensitivity of the Apple Watch (Series 5) in patients with known AF and with an ICM as the gold-standard.[265] They report an Apple Watch AF notification sensitivity for AF >1 hour was 60%, increasing to 78% for AF >12 hours. In the REACT-AF study (NCT05836987) which is partially funded by Apple Inc, the irregular rhythm notification have been reduced to 3 out of 5 pulse checks to capture shorter episodes; this study is currently recruiting in the US.

The Apple Watch communicates with the Apple smartphone via Bluetooth®. A list of irregular rhythm notifications can be accessed in the Health app. Examples of irregular rhythm notification alerts from the Apple Watch can be found in Figure 2-9.

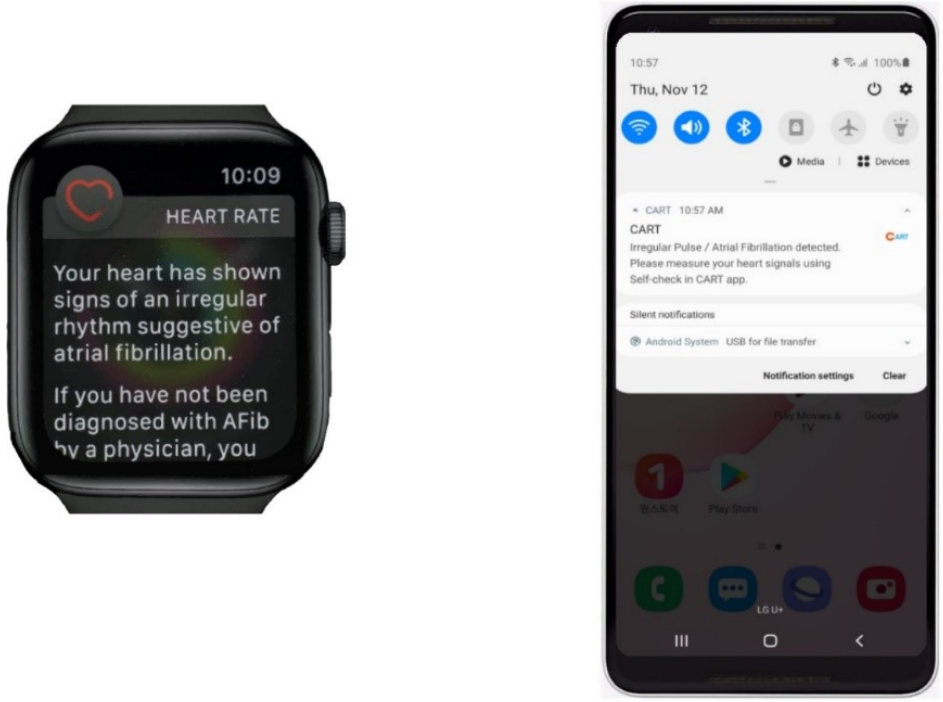


Figure 2-8. *Example of alert notification during AF episodes for the Apple Watch and the SkyLabs CART Ring (Chapter 6; SMART-ALERT study).*

2.4.4.2 Single-lead Electrocardiograms

The WEAR-TECH ECG study (Chapter 5) used the Apple Watch Series 6 (40 mm), and SMART-ALERT study (Chapter 6) participants used the Series 7 (41 mm). The Series 7 featured improved electrode sensors, which reportedly translated into an improved ECG recording quality and a lower rate of unclassified ECGs.[266]

Participants generated a high-quality 30-second ECG by placing a finger on the digital crown. The ECG waveform is displayed on the watch during the recording and automatically stored in the companion Health app, where it can be exported as a PDF file (Figure 2-9).

The Apple Watch's ECG algorithm in the Series 6 was designed to classify recordings into five possible outcomes: sinus rhythm, AF, heart rate below 50 bpm, heart rate above 120 bpm, and inconclusive (due to poor signal quality, excessive movement, or uninterpretable waveforms).

In Apple's validation study using ECG algorithm version 1.0, 588 patients were enrolled into either an AF or sinus rhythm cohort. The reported sensitivity for AF was 98.3% and specificity was 99.6% when unclassified episodes (12.2%) were excluded. However, if the analysis includes all SL-ECGs generated by the WATCH, the AF sensitivity dropped to 85%.[266,267]

A second validation study was conducted using the Apple Watch Series 7 and now with ECG algorithm version 2.0, which expanded the classification of high heart rate to 150 bpm. The aim was to reduce the number unclassified SL-ECGs due to a mean heart rate >120 bpms. This study enrolled a total of 546 patients and reported an AF sensitivity of 98.5% and specificity of 99.3%. The rate of unclassified ECGs was indeed lower at 7.1%.[267]

These clinical validation studies have not been externally peer-reviewed or published and are only available in Apple's documentation. Studies replicating Apple's methodology, which tested only patients in either AF or sinus rhythm, found similarly high sensitivity for automated AF detection.[268,269]

Figure 2-9. *Example of a 30-second SL-ECG from the Apple Watch, recorded in the WEAR-TECH ECG study (Chapter 5). On top, algorithm classified the SL-ECG as AF with mean the heart rate of 89 beats per minute. The paper speed is 25 mm/s and amplitude is 10mm/mV. The ECG algorithm version used was 1.0.*

2.4.5 CART Ring

The CART Ring (Skylabs, Seongnam-si, South Korea) is a CE-marked wearable device used in both the WEAR-TECH ECG study (see *Chapter 5*) and SMART-ALERT study (see *Chapter 6*). It collects PPG signals from the proximal phalanx of the finger.

The CART Ring's metal casing contains high-intensity LEDs and photodiodes in its lower aspect, which facilitate PPG signal acquisition (Figure 2-5). These signals are then processed by a deep learning algorithm based on a convolutional neural network to differentiate between a sinus rhythm and AF. The potential benefits of using a ring as a wearable device include better long-term compliance and, as the fingers are more vascular than the wrist, a higher signal-to-noise ratio and, therefore, improved diagnostic accuracy.[270]

The CART Ring is available in eight different sizes to accommodate different finger circumferences. For optimal signal acquisition, it should fit snugly on the proximal phalanx. The reported battery life is approximately 18 hours.

The CART Ring validation study included 100 participants undergoing elective direct current cardioversion and reported a 99% sensitivity and a positive predictive value of 94.3% for the PPG detection of AF episodes longer than 20 seconds.[270] These findings suggest strong diagnostic performance for short-term rhythm assessment in ideal condition, patients at rest and with either sinus rhythm or AF. However, independent 'real-world' data was needed to assess the true performance in ambulatory patients.

2.4.5.1 AF Notifications During Ambulatory Monitoring

Similar to the Apple Watch, the CART Ring does not record PPG signals continuously but instead collects and analyses data preferentially during rest periods. However, the AF detection notification criteria are not explicitly defined, and limited data is available on its detection performance in ambulatory patients.

Unlike the Apple Watch, it is possible to customise the AF detection duration threshold that triggers an AF pop-up notification on the user's smartphone. However, it remains unclear how many pulse checks with evidence of AF are required within a given time frame to generate an AF notification. For the SMART-ALERT study (Chapter 6), we used an AF notification threshold of 30 minutes, meaning that AF had to persist for at least 30 minutes before an alert was sent to the participant's smartphone (Figure 2-8).

2.4.5.2 Single-lead Electrocardiograms

The CART Ring can also generate high-quality 30-second SL-ECGs by placing a finger on the metal portion of the ring. The ECG and the PPG can be reviewed in the CART smartphone app (Figure 2-10). The PPG data are analysed in the cloud and classified into three possible outcomes: sinus rhythm, atrial fibrillation or unclassified. Unlike the Apple Watch, there is no documented upper or lower heart rate limit for classification.

There are no known contraindications for the CART Ring or Apple Watch, and potential adverse events only include skin reactions to the metal or silicone wrist bands.

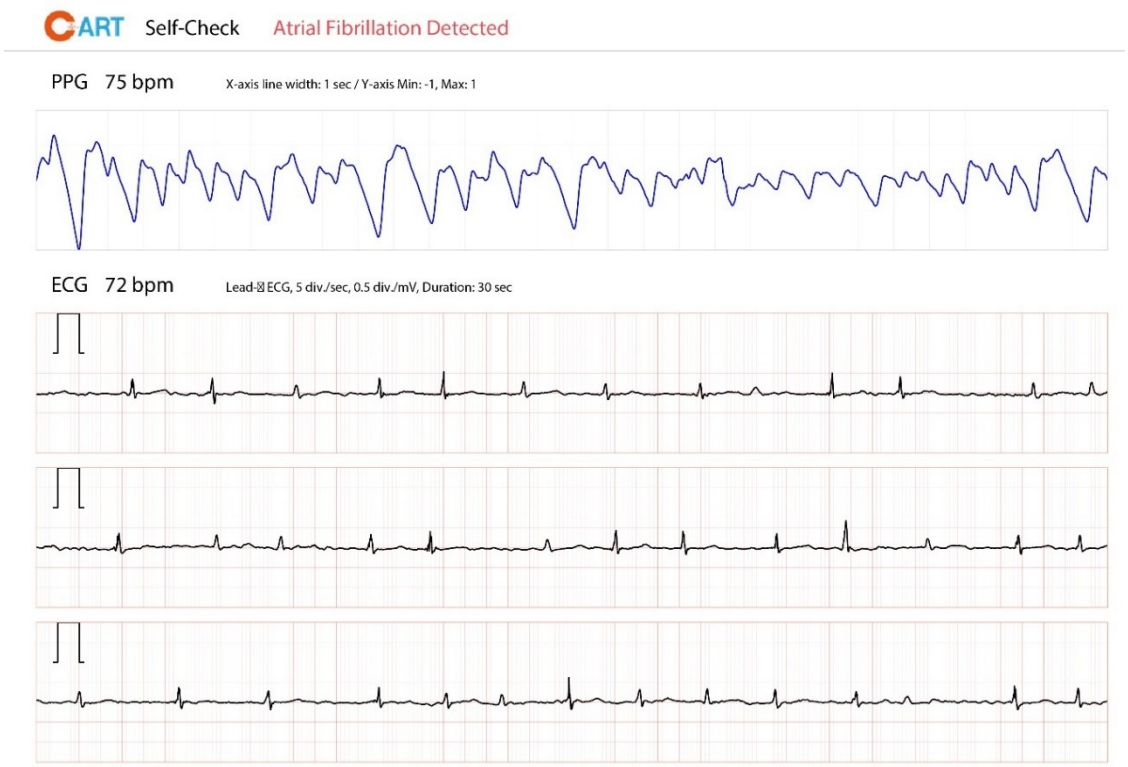


Figure 2-10. *Example of a 30-second SL-ECG from the CART Ring, recorded in the WEAR-TECH ECG study. On top, the self-check has correctly classified this rhythm as AF. Below there is the 30-second PPG signal and followed by the ECG rhythm strip displayed at 25 mm/s paper speed.*

2.5. Adjudication and Statistical Analysis Across all studies

I personally adjudicated all ECGs generated by the devices tested: Confirm Rx ICM, LINQ II ICM, Apple Watch and CART Ring. In the UK Confirm Rx study, a second reviewer (M.P) blinded to my adjudication reviewed a random sample (10%) of ECGs to calculate inter-observer variability. For the WEAR-TECH and SMART-ALERT studies, all ECGs from the devices tested were adjudicated by a second reviewer (A.S). Any disagreements were resolved by a third senior reviewer (T.R.B). The level of agreement between reviewers was calculated using the Cohen's kappa.

2.5.1 Statistical Analysis

The data collected was converted to a .csv format and all statistical analysis and plots were performed using R (version 4.0.3) software. For most statistical analysis *dplyr* and *gtsummary* packages were used, with plots generated with ggplot2 package.

Diagnostic performance was assessed at both an episode and patient levels, depending on study design, as follows:

The performance metrics in Chapters 4-6 were calculated as follows:

- **Sensitivity**: defined as the proportion of true-positive episodes correctly identified by the algorithm or physician interpretation as positive

$$\textbf{Sensitivity} = \frac{\text{True Positives}}{\text{True Positives} + \text{False Negatives}}$$

- **Specificity**: defined the proportion of true negative episodes correctly identified by device algorithm or physician interpretation as negative.

$$\textbf{Specificity} = \frac{\text{True Negatives}}{\text{True Negatives} + \text{False Positives}}$$

- **Positive Predictive Value (PPV):** defined as the proportion of positive classifications by the algorithm or physician interpretation that are true positive episode.

$$\textbf{Positive Predictive Value} = \frac{\text{True Positives}}{\text{True Positives} + \text{False Positives}}$$

- **Negative Predictive Value (NPV)**: defined as the proportion of negative classifications the algorithm or physician interpretation that are true negative episode.

$$\textbf{Negative Predictive Value} = \frac{\text{True Negatives}}{\text{True Negatives} + \text{False Negatives}}$$

- **Accuracy**: the overall proportion of correctly classified episodes.

$$\textbf{Accuracy} = \frac{\text{True Positives} + \text{True Negatives}}{\text{Total Number of Episodes}}$$

Study-specific methodology is discussed in-depth in the individual chapters.

3 Systematic Review and Meta-analysis: 'Pill-in-the-pocket' OAC

3.1 Publications and Abstracts

3.1.1 Publications

Briosa e Gala A, Pope MTB, Leo M, Sharp AJ, Tsoi V, Paisey J, Curzen N, Betts TR. "'Pill-in-the-pocket' oral anticoagulation guided by daily rhythm monitoring for stroke prevention in patients with atrial fibrillation: a systematic review and meta-analysis." Arrhythm Electrophysiol Rev. 2023 Mar 2;12:e05

AER Arrhythmia & Electrophysiology Review

SYSTEMATIC REVIEW

Atrial Fibrillation

'Pill-in-the-pocket' Oral Anticoagulation Guided by Daily Rhythm Monitoring for Stroke Prevention in Patients with AF: A Systematic Review and Meta-analysis

Andre Briosa e Gala [1,2] Michael Timothy Brian Pope,[1,2] Milena Leo,[1] Alexander James Sharp,[1] Victor Tsoi,[3] John Paisey,[3] Nick Curzen [2,3] and Timothy Rider Betts [3,4]

1. Department of Cardiology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK; 2. Faculty of Medicine, University of Southampton, Southampton, UK; 3. Wessex Cardiac Unit, University Hospital Southampton NHS Foundation Trust, Southampton, UK; 4. NIHR Biomedical Research Centre, Oxford, UK

Abstract

Aims: In patients with a low AF burden and long periods of sinus rhythm, 'pill-in-the-pocket' oral anticoagulation (OAC) may, taken as needed in response to AF episodes, offer the same thromboembolic protection as continuous, life-long OAC, while reducing bleeding complications at the same time. The purpose of this study is to systematically summarise available evidence pertaining to the feasibility, safety and efficacy of pill-in-the-pocket OAC. **Methods**: Medline and Embase were searched from inception to July 2022 for studies adopting a pill-in-the-pocket OAC strategy in AF patients guided by daily rhythm monitoring (PROSPERO/CRD42020209564). Outcomes of interest were extracted and event rates per patient-years of follow-up were calculated. A random effects model was used for pooled estimates. **Results**: Eight studies were included (711 patients). Daily rhythm monitoring was continuous in six studies and intermittent in two (pulse checks or smartphone single-lead electrocardiograms were used). Anticoagulation criteria varied across studies, reflecting the uncertainty regarding the AF burden that warrants anticoagulation. The mean time from AF meeting OAC criteria to its initiation was not reported. Adopting pill-in-the-pocket OAC led to 390 (54.7%) patients stopping OAC, 85 (12.0%) patients taking pill-in-the-pocket OAC and 237 (33.3%) patients remaining on or returning to continuous OAC. Overall, annualised ischaemic stroke and major bleeding rates per patient-year of follow-up were low at 0.005 (95% CI [0.002–0.012]) and 0.024 (95% CI [0.013–0.043]), respectively. **Conclusion**: Current evidence, although encouraging, is insufficient to inform practice. Additional studies are required to improve our understanding of the relationships between AF burden and thromboembolic risk to help define anticoagulation criteria and appropriate monitoring strategies.

Keywords

AF, anticoagulation, stroke, thromboembolism, rhythm monitoring

Disclosures: MTBP has received funding from Atucus Medical. NC has received funding from Boston Scientific, Haemonetics, HeartFlow, Backman Coulter, Abbott, Edwards, Biosensors, and is president of the British Cardiovascular Intervention Society. JP has received speaker's fees from Daiichi Sankyo. TRB has received funding from Abbott. All other authors have no conflicts of interest to declare.

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AF is the most common sustained cardiac arrhythmia and is seen as a health epidemic.[1] In Europe, one in three individuals aged ≥55 years will develop AF at some point in the future.[2] AF-related strokes account for approximately one-quarter of all strokes.[3,4]

Lifelong oral anticoagulation (OAC) remains the cornerstone of AF management, given it reduces stroke risk by two-thirds and mortality by one-quarter, but this is at the expense of increased major bleeding occurring.[5–7] Real-world data suggest a 5% yearly risk of a major bleeding event but, if the predicted annual stroke rate is above 1%, instigating OAC has a net clinic benefit.[6,8]

Guidelines recommend using risk scores, such as the CHA_2DS_2-VASc, to inform anticoagulation decisions.[9,10] However, these are based solely on clinical risk factors and do not include AF temporal patterns or burden.

A meta-analysis of almost 100,000 patients with AF showed that both the adjusted and unadjusted stroke and mortality risks are lower in paroxysmal AF.[11] Similarly, the yearly stroke rate was below 1% in non-anticoagulated patients with AF paroxysms of <23.5 hours' duration and a CHA_2DS_2-VASc score between 1 and 2, suggesting a lower stroke risk in association with short AF episodes.[12]

The justification for continuous, long-term OAC in such patients appears to be weaker and, furthermore, indefinite OAC may expose patients with short or infrequent AF episodes to a high bleeding risk relative to the more limited benefit in stroke reduction.

3.2 Abstract

Background: In patients with a low AF burden and long periods of sinus rhythm, 'pill-in-the-pocket' OAC may offer the same thromboembolic protection as continuous life-long OAC, whilst at the same time reducing bleeding complications.

Objective: The purpose of this study is to systematically summarise available evidence pertaining to the feasibility, safety, and efficacy of 'pill-in-the-pocket' OAC.

Methods: Medline and Embase were searched from inception to July 2022 for studies adopting a 'pill-in-the-pocket' OAC strategy in AF patients guided by daily rhythm monitoring (PROSPERO/CRD42020209564). Outcomes of interest were extracted and event rates per patient-years of follow-up were calculated. A random effects model was used for pooled estimates.

Results: Eight studies were included (711 patients). Daily rhythm monitoring was continuous in six studies and intermittent in two (pulse checks or SL-ECGs). OAC criteria varied across studies reflecting the uncertainty regarding AF burden that warrants anticoagulation. The mean time from AF meeting OAC criteria to its initiation was not reported. Adopting a 'pill-in-the-pocket' OAC led to 390 (54.7%) patients stopping OAC, 85 (12.0%) patients taking 'pill-in-the-pocket' OAC and 237 (33.3%) patients remaining or returning to continuous OAC. Overall, annualised ischaemic stroke and major bleeding rates per patient-year of follow-up were low, 0.005 (95% CI:0.002-0.012) and 0.024 (95% CI: 0.013-0.043), respectively.

Conclusion: Current evidence, although encouraging, is insufficient to inform practice. Additional studies are required to improve our understanding of the relationships between AF burden and thromboembolic risk and to help define anticoagulation criteria. Current monitoring tools are unsuitable for this alternative strategy The ideal solution is a closed-loop system with devices that can accurately detect AF, provide real-time notifications and integrate seamlessly with healthcare systems.

3.3 Introduction

The increase in availability of novel continuous and intermittent rhythm monitoring tools has led to interest in exploring a 'pill-in-the-pocket' OAC during periods of higher thromboembolic risk. While this approach is attractive, it is still unclear whether current evidence supports its implementation.

This chapter presents a systematic review and meta-analysis to determine the feasibility, safety and efficacy of rhythm-guided 'pill-in-the-pocket' OAC. The review examines the monitoring modalities used, the OAC criteria for initiation and discontinuation, and related clinical outcomes, including thromboembolic and bleeding complications. It provides a formal evaluation of whether 'pill-in-the-pocket' OAC is a viable alternative to continuous lifelong OAC, identify pitfalls and highlight key areas that require further investigation.

3.4 Methodology

3.4.1 Search Strategy

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement and was registered in PROSPERO (CRD42020209564).[271] The search strategy was designed in collaboration and conducted with the assistance of an experienced research librarian. I used MeSH terms and keywords to search Medline and Embase databases from inception to July 2022 *(*Appendix B, Figure S3-1 and S3-2). I conducted a manual review of reference lists, editorials, and review articles to identify secondary source documents not captured by the initial database search.

3.4.2 Study Selection and Data Extraction

Studies were only included if a daily rhythm monitoring strategy (intermittent or continuous) was employed to identify AF episodes and guide OAC decisions in patients with a previous diagnosis of AF. The exclusion criteria were as follows: (1) patients with valvular AF; (2) case reports, conference proceedings, commentary, and letters; and (3) editorials and review articles, although their reference lists were manually searched.

The results of the initial database search were exported to EndNote X7.0.1 and duplicate citations were removed. Two independent investigators (A.B.G and M.P) then proceeded to screen the remaining abstracts and, if appropriate, full text manuscripts were reviewed against the eligibility criteria. Any discrepancies were resolved by a third investigator (T.R.B). A standardised data extraction form was used.

Outcomes of interest were defined a *priori* as follow: (1) OAC utilisation or time on OAC; (2) all-cause mortality; (3) thromboembolic events; (4) major bleeding; (5) minor bleeding; and (6) intracranial haemorrhage.

The methodological quality of the studies was assessed using the Cochrane tool for assessing risk of bias for RCTs and the ROBIN-I tools for non-randomised studies. All studies were independently reviewed by two investigators (A.B.G and M.P) and any disagreements were settled by the senior investigator (T.R.B). Publication bias was assessed for the outcomes of interest by producing Funnel plots.

3.4.3 Data Analysis and Synthesis

Continuous variables were summarised by extracting mean and standard deviation, if available in the manuscript, or calculated from the reported medians and interquartile ranges using established statistical methods. Categorical variables were expressed as frequency and percentage to facilitate comparisons between studies. Outcomes of interest were extracted from each individual study and the event rate per year of follow-up estimated. When the total follow-up duration was not explicitly reported, it was calculated by multiplying the number of patients by the mean follow-up time in years.

All outcome data extracted were pooled using an inverse variance random-effect model as described by DerSimonian and Laird, which accounts for both within-study and between-study variability.[272] This approach led to a summary estimate of event rate per year of follow-up with accompanying 95% confidence interval (CI). If studies reported zero outcome events a continuity correction of 0.5 was applied, so that these studies could be included in the meta-analysis. Heterogeneity between studies was assessed by using the Cochrane's Q test and its magnitude was quantified using the I^2 statistic. The I^2 statistic represents the percentage of total variation that arises from heterogeneity rather than chance. Significance was set at 0.05 and all the analyses were two-sided. The statistical analysis and corresponding plots were performed using R statistical software version 4.0.3, with the metafor and meta packages (www.r-project.org).

3.5 Results

The Embase and Medline literature search identified 2799 unique publications. Of these, 2779 were excluded after screening the title and abstract. The remaining 20 full-text publications underwent comprehensive review against the eligibility criteria. Eight studies meet inclusion

criteria and were included for review (Figure 3-1).[67-69,187,216,217,239,240] Seven studies were prospective observational studies without a control group. Whilst TACTIC-AF was initially designed as a RCT with a control arm receiving uninterrupted OAC, its protocol was amended halfway through the study to a single-arm prospective study and patients from the control arm allowed to cross-over to 'pill-in-the-pocket' OAC.[199] iCARE-AF was a randomised controlled pilot study.[275]

Study quality ranged from overall low risk of bias in REACT.COM and Zuern *et al*. to moderate in the remaining studies (Table 3-1 and 3-2).[68,69] Confounding was rated as low in all studies except in the Mascarenhas *et al.* (2015, 2019) and Zado *et al*.[67,273,274] which were moderate. TACTIC-AF had a serious deviation from the protocol with one centre failing to follow OAC criteria and starting it inappropriately, which had a significant impact on the OAC rates.[199] Examination of funnel plots did not depict any significant concerns regarding publication bias (Appendix B, Figure S3-1).

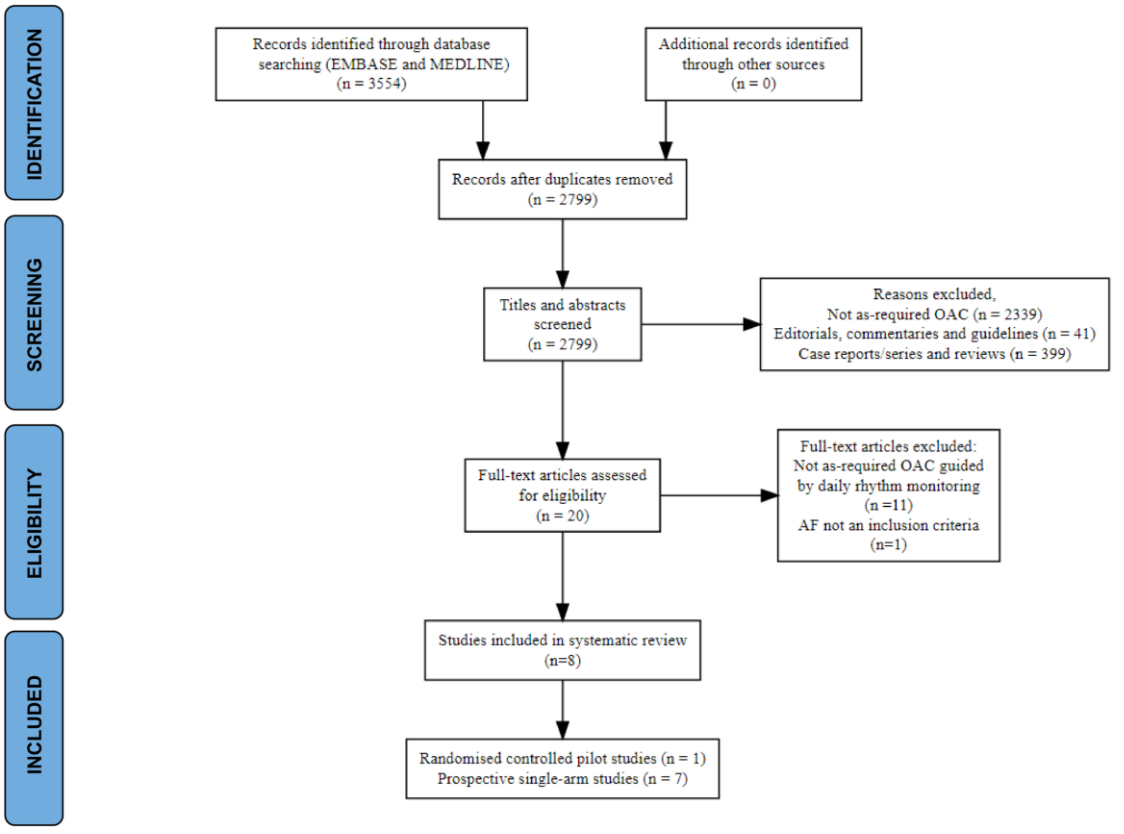

Figure 3-1. *PRISMA flow diagram. Reproduced with permission from Briosa e Gala et al.*[254]

A summary of included studies is displayed in Table 3-2.[67-69,199, 239, 273-275] Overall, 711 patients were on a 'pill-in-the-pocket' OAC strategy guided by daily rhythm monitoring. The follow-up

duration ranged from 0.8 years to 4.2 years, with a total of 1,396 years of patient follow-up. The mean age was 68.3 years, 67% were male, 73% had PAF and the mean CHA_2DS_2-VASc score was 2.2 (Appendix B, Table S3-3).

Table 3-1. *Risk of bias summary in 7 non-randomised studies included in this systematic review (ROBIN-I risk assessment tool). Reproduced with permission from Briosa e Gala et al.*[254]

Domain	Zuern *et al.*	Mascarenhas *et al.*	REACT.COM	TACTIC-AF	Zado et *al.*	Mascarenhas *et al.*	Prothenius *et al.*
Confounding	Low	Moderate	Low	Low	Moderate	Moderate	Low
Selection of participants	Low	Moderate	Low	Low	Moderate	Moderate	Low
Classification of intervention	Low	Moderate	Low	Low	Moderate	Moderate	Moderate
Deviation from intended interventions	Low	Low	Low	Serious	Low	Low	Low
Missing data	Moderate	Low	Low	Low	Low	Moderate	Moderate
Measurement of outcomes	Low	Low	Low	Low	Low	Low	Low
Selection of the reported result	Low	Moderate	Low	Moderate	Moderate	Moderate	Moderate
Overall bias	Low	Moderate	Low	Moderate	Moderate	Moderate	Moderate

Table 3-2. *Risk of bias summary of RCTs. Unclear risk of bias is largely due to lack of information regarding blinding of personnel and randomisation. iCARE-AF was a randomised pilot study.*

Domain	iCARE-AF
Random sequence generation	
Allocation concealment	
Blinding of participants and personnel	
Incomplete outcome data	
Selective reporting	
Other bias	

Table 3-3. *Summary of the main characteristics of studies included in this review. Adapted with permission from Briosa e Gala et al.*[254]

Study	Design	N	Follow-up†	CHA_2DS_2-VASc‡	AF Detection	Transmission	Anticoagulation Criteria	OAC Initiation	OAC Drugs
Zuern et al[69] (2015)	Single-centre prospective single-arm	65	2.6	2.8	ICM (Reveal XT)	- Daily	· ***Initiate OAC:*** Daily AF burden>1h · ***Stop OAC:*** (Optional) following repeat AF ablation and no evidence of AF after the blacking period.	Patient	Warfarin DOAC
Mascarenhas et al[67] (2015)	Single-centre case-observational	70	2.0	2.9	ICM (Reveal XT, LINQ)	- Monthly	· ***Initiate OAC*:**AF recurrence (not specified) · ***Stop OAC:*** AF <1% for ≥3 months	Research team	Warfarin & DOAC
REACT.COM[68] (2016)	Multicentre single-arm pilot	59	1.3	2.4	ICM (LINQ)	- Daily	· ***Initiate OAC:*** AF ≥ 1h · ***Stop OAC:*** No AF ≥ 1h in 30 days	Research team	DOAC
iCARE-AF[275] (2017)	Single centre prospective RCT pilot study	58	1.7[c]	2.5	iPhone 1-lead ECG	NA	· ***Initiate OAC:*** AF in 1-lead ECG (30s) · ***Stop OAC:*** AF <48h, after 48h; AF 2-7 days, after 7 days; AF > 7days: OAC	Research team	DOAC
TACTIC[199]¥ (2018)	Multicentre prospective, single-arm pilot	48	0.8	1.7[b]	PPM ICD	- Biweekly - Alerted (AF burden>6h)	· ***Initiate OAC:*** *AT/AF >6 min or >6h/24h* · ***Stop OAC:*** No *AT/AF >6 min or >6h/24h for 30 days*	Research team Patient	DOAC

Study	Design	N	Follow-up†	CHA_2DS_2-VASc‡	AF Detection	Transmission	Anticoagulation Criteria	OAC Initiation	OAC Drugs
Zado et al[274] (2019)	Single centre, prospective feasibility study	99	2.5	1.9	Pulse check	NA	· ***Initiate OAC:*** AF ≥ 1h suspected, repeat pulse assessment or ECG · ***Stop OAC:*** 2-4 weeks	Patient	DOAC
Mascarenhas et al[273] (2019)	Single centre prospective longitudinal case-observation study	145	4.2	2.9	ICM PPM CRT-D	NR	· ***Stop OAC:*** Low AF burden (<24h in 30 days for 3 months) · ***Initiate OAC:*** High AF burden (> 24h in 30 consecutive days) or Stroke/TIA	Research team	Warfarin DOAC
Pothineni et al[229] (2021)	Single-centre prospective study	196	0.6	2.0	CIED ICM	- Daily ICM transmission & - Twice daily pulse checks	· ***Initiate OAC:*** AF recurrence (criteria below) and OAC continued indefinitely · ***Stop OAC:*** no AF>2 minutes on ICM or >30sec on CIED after 6 weeks of blanking period	Patient Research team	DOAC

AF, atrial fibrillation. **AT**, atrial tachycardia. **CIEDs**, cardiac implantable electronic devices. **CRT-D**, cardiac resynchronisation therapy-defibrillator. **DOAC**, direct oral anticoagulants. **ICD**, implantable cardioverter-defibrillator. **ICM**, implantable cardiac devices. **NA**, not applicable. **NR**, not reported. **OAC**, oral anticoagulation. **PPM**, permanent pacemakers. **TIA**, transient ischaemic attack

†years, ‡ mean, ¥ Initially designed as a RCT, but the protocol was amended to a single-arm prospective study.

3.5.1 Rhythm Monitoring Strategies and Oral Anticoagulation Criteria

Two studies (128 patients) used intermittent rhythm monitoring (spot-ECGs and pulse checks) and in six studies (583 patients) continuous rhythm monitoring was employed with ICMs or CIEDs with an atrial lead.[67-69,199,239,273-275] Criteria used to initiate and discontinue OAC were heterogeneous, perhaps reflecting technical constraints from devices used and the uncertainty surrounding the AF episode duration that warrants anticoagulation (Table 3-3).

None of the studies reported the mean time from AF episode detection to patients starting OAC. Only three studies had patient-initiated OAC.[69,239,274] Zado *et al*. instructed patients to take OAC if pulse assessments revealed AF lasting one hour or, alternatively, short frequent episodes.[274] Pulse checks were performed only twice daily and asymptomatic episodes may have been missed. Similarly, in Pothineni *et al.* participants performed twice daily pulse checks but the duration that would trigger OAC was not described.[239]

In Zuern *et al*., patients performed daily manual ICM interrogation with a hand-held device which alerted them to take OAC.[69] The AF burden was counted every calendar day so there may have been delays but it is likely that, if compliant with study protocol, OAC was started within 24 hours. The remaining five studies had three rate-limiting steps: remote nightly transmissions, adjudication of all episodes during the next working day, and, if appropriate, contacting patients.[67,68,199,273,275] Complexity of remote transmission adjudication may have led to further delays. Investigators in iCARE-AF reviewed 30-second SL-ECGs and patients started OAC within one hour of adjudication, but it is unclear when this adjudication took place.[275]

3.5.2 Oral Anticoagulation Utilisation

Overall, adopting a 'pill-in-the pocket' strategy led to 390 (54.7%) patients not taking OAC during the study period and 85 (12.0%) patients only taking it intermittently following AF episodes (Figure 3-2). The remaining 237 (33.3 %) patients remained on or returned to continuous OAC, mostly due to a high AF burden or development of permanent AF.

Other reasons for OAC initiation included adverse events (three TIAs and one ischaemic stroke), other indications (13 patients), non-compliance with protocol (four patients) and patients' wishes (four patients).

Four studies assessed the total duration of anticoagulation. REACT.COM, TACTIC-AF, Zuern *et al.* and Pothineni *et al.* reported 94%, 75%, 60% and 20% reduction in time on OAC from a 'pill-in-the-pocket' strategy compared to standard of care (continuous OAC), respectively.[68,69,199,239]

However, inappropriate OAC due to a protocol violation in TACTIC-AF accounts for almost half of the time spent on OAC.[199]

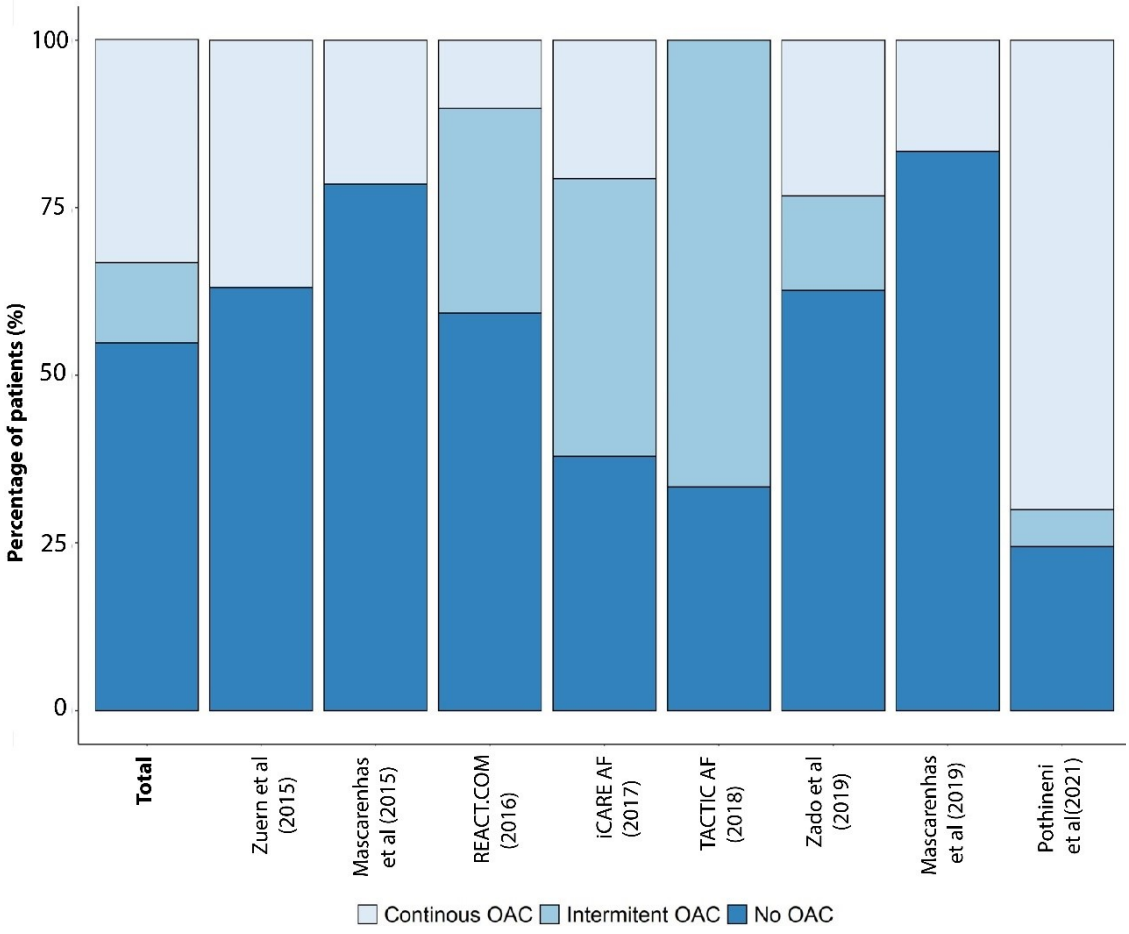

Figure 3-2. *OAC utilisation in studies using a 'pill-in-the-pocket' strategy. Reproduced with permission from Briosa e Gala et al.*[254]

3.5.3 Safety and Efficacy Outcomes

Adverse events in patients taking 'pill-in-the-pocket' OAC are described in detail in Table S3-4 in Appendix B.

3.5.3.1 Thromboembolic Events

Neurological events were defined in only two studies and independently adjudicated in three studies.[68,199,275] Only one patient (0.1%) had an ischaemic stroke. He was an 81-year-old man with a CHA_2DS_2-VASc score of 3 who was not taking OAC as he denied any pulse irregularity during pulse checks.

The overall annualised rate of ischaemic stroke and TIA was 0.005 (95% CI: 0.002-0.012) and 0.007 (95% CI :0.002-0.023) per patient-year of follow-up, respectively (Figure 3-3). High heterogeneity (I^2= 53%, p=0.04) was only observed in TIA rate. No systemic embolism events were reported.

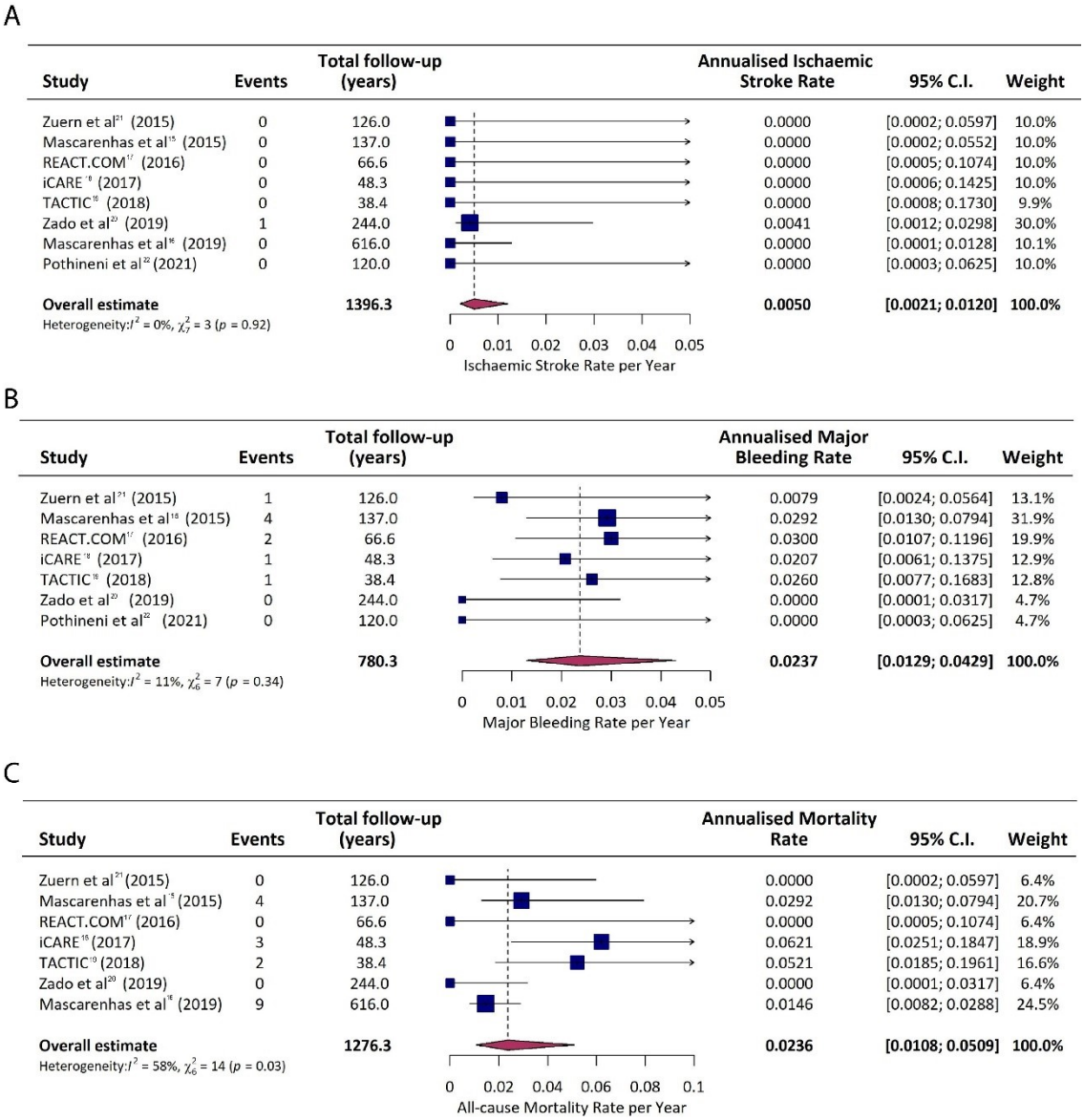

Figure 3-3. (A) *Annualised ischaemic stroke rate,* ***(B)*** *annualised major bleeding,* ***and (C)*** *annualised all-cause mortality rate across pooled studies. Reproduced with permission from Briosa e Gala et al.*[254]

3.5.3.2 Bleeding Complications

Major bleeding was reported in seven studies (566 patients).[67-69,199,239,274,275] A total of nine (1.6%) major bleeding episodes were reported over 780 patient-years of follow-up, representing an annualised major bleeding rate of 0.024 (95% CI: 0.012-0.043) per patient-year of follow-up. One

study reported bleeding events in 12 (8.5%) out of 145 patients, including nine gastrointestinal bleeds but it is unclear if these represent major or minor bleeding episodes.[273]

Two intracranial haemorrhages were reported, both in patients not taking OAC, corresponding to an overall rate of 0.0065 (95% CI: 0.0028-0.0148) per patient-years of follow-up (Figure 3-4).

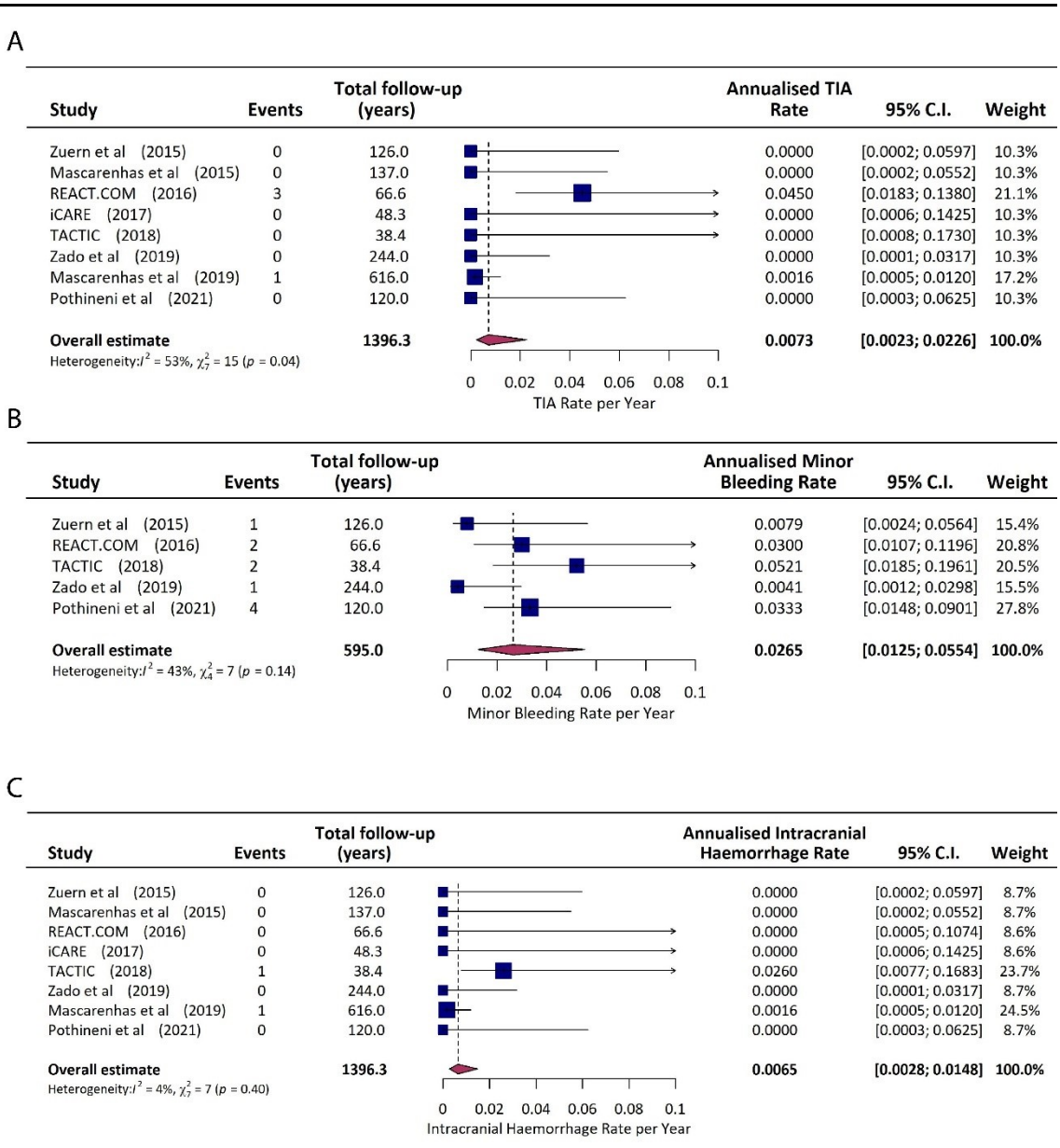

Figure 3-4. (A) *Annualised transient ischaemic attact (TIA) rate,* ***(B)*** *annualised minor bleeding rate, and* ***(C)*** *annualised intracranial haemorrhage. Reproduced with permission from Briosa e Gala et al.*[254]

3.5.3.3 All-cause Mortality

Of the 515 patients in seven studies on 'pill-in-the pocket' OAC there were 18 deaths from any cause. The annualised mortality rate ranged from 0 to 0.0621 with an overall estimate of 0.024

(95% CI: 0.018-0.051) deaths per patient-year of follow-up. We found moderate between-study heterogeneity (I^2= 58%). Of the 18 deaths, four (22.2%) were classified as cardiovascular (3 from heart failure and one following an intracranial haemorrhage) and 14 (77.8%) as non-cardiovascular. Pothineni *et al.* did not explicitly report the total number of deaths.[239]

3.6 Discussion

The main findings of this systematic review are:

1. Criteria for initiation and discontinuation of OAC varied widely reflecting the uncertainty regarding AF episode duration/AF burden and increase in thromboembolic risk.
2. The mean time from AF detection to initiation of OAC was not reported and only three studies had patient-initiated OAC.
3. In carefully selected patients with known AF and during a relatively short follow-up, 'pill-the-in-pocket' OAC strategy led to 54.7 % of patients never restarting OAC and 12 % of patients taking OAC only intermittently.
4. Annualised stroke rate (0.5% [95% CI: 0.2%-1.2%]) was low but the small number of patients, short follow-up and lack of control group precludes any conclusions regarding safety and efficacy of a 'pill-in-the-pocket' strategy.

The concept of 'pill-in-the-pocket' OAC is a potentially attractive alternative strategy for a subset of patients with infrequent AF episodes and low stroke risk who would otherwise be committed to life-long OAC with all its implications. However, the causal relationship between AF and stroke is still a matter of debate. Other essential unanswered questions are: (1) How quickly does OAC need to be initiated to prevent left atrial thrombus? (2) How long does thromboembolic risk last following an AF episode? (3) How to best monitor and alert patients during AF episodes?

3.6.1 How quickly does OAC need to be initiated to prevent left atrial thrombus?

It is biologically implausible that a universal cut-off exists or that the relationship between AF duration and stroke risk is linear. Yet, it may be possible to identify a range of AF burden associated with a steep increase in thromboembolic risk. Available data is conflicting, which explains the discrepancies in OAC criteria used in the studies included in this review.

Guidelines suggest that it is safe to proceed with cardioversion not on routine OAC without excluding an intracardiac thrombus in AF episodes lasting less than 48 hours, implying that only longer episodes create a prothrombotic 'milieu'.[22,276] There is however no RCT data to support this practice. In the FinCV study, included 7,600 cardioversions performed in 3,143 patients with AF <48 hours and reported a low thromboembolic rate (0.7%) which is similar to rates of patients

undergoing DCCV on OAC.[219,277] Importantly, the risk was lower in those with AF <12 hours compared to those with longer episodes (0.3% versus 1.1%), suggesting that AF duration may be a critical factor in determining thromboembolic risk.[278]

This assertion of a '48-hour window' has also been questioned by studies using long-term continuous rhythm monitoring. Large observational studies showed an increased risk with AF episodes ranging from 5 minutes in MOST, daily burden of 5.5 hours in TRENDS to 24 hours in studies by Botto *et al*., Capuci *et al.,* and post-hoc analysis of ASSERT.[171-174,183] From these data it is difficult to discern a clear cut-off for OAC, but most studies suggest multi-hour episodes rather than brief periods of AF.

3.6.2 How long does thromboembolic risk last following an AF episode?

The total duration of OAC required following an AF episode is also uncertain, but DCCV data provides important insights. Conversion from AF to sinus rhythm is followed by a period of mechanical dysfunction of the left atrium and appendage, also known as atrial stunning, leading to blood stasis despite organised atrial electrical activation, and contributing to increased thrombotic risk in the post-cardioversion period.[105] The severity and recovery of atrial function is dependent on the duration of the preceding AF episodes; brief episodes have a swift return to baseline function whilst longer episodes may take up to a month.[105,236] Most thromboembolic events occur within 10 days of DCCV; without OAC the 30-day thromboembolic rate ranges from 5-7% which is mitigated with OAC to <1%.[216-218,279] The conventional strategy of at least 4 weeks of OAC post-cardioversion is advocated by international guidelines to cover this vulnerable period.[1,22] Evidence from continuous rhythm monitoring from, Turakhia *et al.* and Singer *et al.*, reported that stroke risk returned to baseline after one month and it is at its highest within 5-days of the episode.[179,225] Taking this together, it is likely that, at most, a month of OAC is required in a 'pill-in-the-pocket' strategy.

3.6.3 How to best monitor and alert patients during AF episodes?

The litmus test for any new intervention is an adequately powered RCT with meaningful outcomes, such as thromboembolic events, major bleeding, and all-cause mortality. However, current evidence is insufficient to adequately inform how to design and conduct this trial. More work is needed to delineate OAC criteria, how quickly it should be started and for how long. Studies with long term AF monitoring in this cohort, with advanced neuroimaging to define the stroke mechanism, are warranted.[229]

Continuous rhythm monitoring is essential to deliver 'pill-in-the-pocket' OAC; patient reported AF symptoms are often unreliable.[280] Pulse palpation or even daily ECG checks are likely to miss AF episodes and do not provide reliable data regarding AF episode duration and burden and are not suited for a 'pill-in-the-pocket' strategy. The workflow in the six studies with continuous rhythm monitoring was suboptimal and lacks scalability.[67-69,199,273] Episodes were transmitted at best only once daily, investigators had to adjudicate all episodes and patients had to be contacted. This requires a huge manpower resource, REACT.COM had 24,000 transmissions from 59 patients, has high costs and will lead to delays in starting OAC.[68]

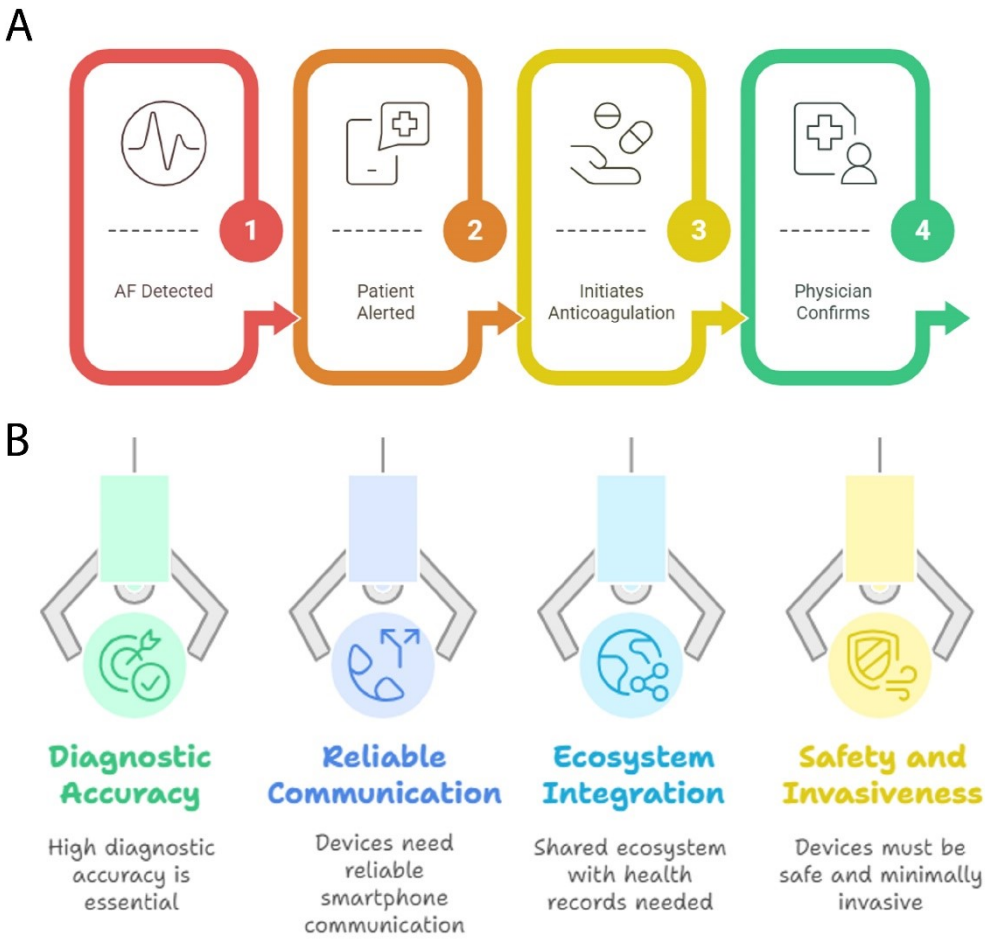

Figure 3-5. (A) *Closed-loop system to guide 'pill-in-the-pocket' OAC and* ***(B)*** *the ideal characteristics of the device and alert system used.*

The ideal solution is a closed-loop system with devices informing patients in 'real-time' of AF episodes, to reduce the time from AF detection to initiation of OAC. Four important conditions must be met. First, diagnostic accuracy must be extremely high to reduce the likelihood of inappropriate OAC. Second, devices must communicate regularly and reliably with patients'

smartphone to deliver alerts. Third, devices must have shared ecosystem with electronic health records/remote monitoring platforms to ensure physicians can adjudicate episodes and are aware if OAC is initiated. Finally, devices must be safe and minimally invasive.

Wearable devices have important limitations that reduce their potential value as an arbiter for the delivery of rhythm guided OAC. Specifically, motion artefacts are common and are responsible for high rates of FP detections.[72,73,281] Compliance is not well studied and is likely suboptimal due to the frequent need for battery recharging and patients may be reluctant to wear them overnight. Lastly, most are consumer facing devices without any integrated physician platforms for remote monitoring and adjudication.

Leveraging on advancements in ICMs technology is a more attractive strategy. The new iterations have improved diagnostic accuracy, particularly for longer AF episodes, connect to patients' smartphone via low-energy Bluetooth® and transmit device information to remote monitoring platforms with robust cybersecurity.[262,60] ICMs have a miniaturised profile and are minimally invasive. The SMART-ALERT study (NCT05207150), described in Chapter 6, investigated the accuracy of 'closed-loop' alerts from ICMs and two wearable devices (Apple Watch and CART Ring) during episodes of AF and how promptly patients respond to these alerts.[257]

3.6.4 Limitations

The present analysis is limited by the small number of patients included in most studies with notable heterogeneity in study methodology, baseline characteristics and criteria for both initiation and discontinuation of OAC. Moreover, there was no comparator in most studies except for iCARE-AF. 'Pill-in-the-pocket' relies on swift initiation of OAC; however, none of the studies report the mean time from AF detection to patients starting OAC raising doubts regarding the feasibility of the monitoring strategies used.

Studies without continuous rhythm monitoring may underestimate AF recurrence and thus overall OAC utilisation which is a key metric. Moreover, observational studies have inherent biases in their design and adverse events may be less rigorously collected than in an RCT; underreporting will affect overall event estimates. Nonetheless, this review provides a useful overview of different rhythm monitoring strategies, their pitfalls and applicability.

IMPACT did not meet the inclusion criteria as only 12% of patients recruited had AF and was therefore not included in this review.[45] It showed no difference in the primary endpoint (composite of stroke, systemic embolism, and major bleeding) between standard care and OAC guided by atrial tachycardia monitoring and was stopped early due to futility. This RCT has

important limitations. It recruited predominantly patients with poor ejection fraction and with a high number of co-morbidities (median CHA_2DS_2-VASc of 4), OAC algorithm was compliance and compliance was poor. VKA were used by most patients (80.9%) raising concerns regarding inadequate OAC due to its slow onset of action, prothrombotic effects during initiation, and narrow therapeutic window.

3.7 Conclusion

A 'pill-in-the-pocket' OAC strategy guided by daily rhythm monitoring challenges our current paradigm of stroke prevention in AF but current evidence, although encouraging, is insufficient to inform practice. To assess the risk-benefit of 'pill-in-the-pocket' OAC, an adequately powered RCT comparing it to continuous OAC (standard of care) in patients with infrequent AF episodes and low-to-moderate stroke risk is needed. It is, however, premature to proceed without additional studies that inform our understanding of the relationship between AF burden and thromboembolic risk and help delineate OAC criteria and how to best deliver them.

Continuous rhythm is essential for delivering 'pill-in-the-pocket' OAC, as patient-reported symptoms are unreliable and often miss AF episodes. Current monitoring tools are unsuitable for this alternative strategy as they do not provide direct-to-patient notifications, adjudication is labour-intensive and unscalable. The ideal solution is a closed-loop system with devices that can accurately detect AF, provide real-time notifications and integrate seamlessly with healthcare systems.

4 UK Confirm Rx study

4.1 Publications and Abstracts

4.1.1 Publications

Briosa e Gala A, Pope MTB, Leo M, Sharp AJ, Field D, Thomas H, Balasubramaniam R, Hunter R, Gardner RS, Wilson D, Gallagher MM, Ormerod J, Paisey J, Curzen N, Betts TR. *"Diagnostic performance of the Confirm Rx™ SharpSense AF detection algorithm in 'real-world' patients: UK Confirm Rx study."* **J Arrhythm**. 2024 Sep 3;40(5):1093–1101.

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ORIGINAL ARTICLE

Journal of Arrhythmia WILEY

"Real-world" performance of the Confirm Rx™ SharpSense AF detection algorithm: UK Confirm Rx study

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Abstract

Introduction: The novel Confirm Rx™ implantable cardiac monitor (ICM) with SharpSense™ technology incorporates a new P-wave discriminator designed to improve AF detection. This study aimed to evaluate the diagnostic performance of the Confirm Rx™ ICM in detecting AF episodes of varying durations.

Methods: We conducted a multicenter retrospective analysis of consecutive patients implanted with a Confirm Rx™ ICM (v1.2) across nine UK hospitals, all with documented AF lasting at least 6 min. Electrocardiograms (ECGs) were manually adjudicated by cardiologists. To account for intra- and inter-reviewer variability, a random sample of 10% of ECGs underwent additional review. Disagreements were resolved by a third reviewer. Diagnostic performance was determined by calculating the gross and patient-averaged positive predictive value (PPV) for AF episodes of different duration. The source of false positive (FP) detection was also categorized.

Results: Overall, 16,230 individual ECGs from 232 patients were included. The median AF episode duration was 14 min. R-wave amplitude remained stable during follow-up

4.1.2 Abstracts

Briosa e Gala A, Pope MTB, Leo M, Field D, Thomas H, Bala R, Hunter R, Gardner RS, Wilson D, Gallagher MM, Ormerod J, Paisey JR, Curzen N, Betts TR. *"Accuracy of AF burden detection with the new Confirm Rx™ with Sharp-sense technology."* **Oral presentation, European Heart Rhythm Association Congress 2022**

Briosa e Gala A, Pope MTB, Leo M, Field D, Thomas H, Bala R, Hunter R, Gardner RS, Wilson D, Gallagher MM, Ormerod J, Paisey JR, Curzen N, Betts TR. *"Diagnostic accuracy of the Confirm-Rx™ AF detection algorithm in 'real-world' patients: UK experience.*" **Poster Presentation, Heart Rhythm Sessions 2022**

Briosa e Gala A, Pope MTB, Leo M, Field D, Thomas H, Bala R, Hunter R, Gardner RS, Wilson D, Gallagher MM, Ormerod J, Paisey JR, Curzen N, Betts TR. *"Incidence of false-positive AF detection with the new Confirm Rx™ with Sharp-sense technology: UK experience"* **Poster presentation, Heart Rhythm Sessions 2022**

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4.2 Abstract

Background: The novel Confirm Rx ICM with SharpSense technology incorporates a new P-wave discriminator designed to improve AF detection. The performance of the new AF detection algorithm is unknown.

Objective: This study aimed to evaluate the diagnostic performance of the Confirm Rx ICM in detecting AF episodes of varying durations.

Methods: We conducted a multicentre retrospective analysis of consecutive patients implanted with a Confirm Rx ICM (v1.2) across nine UK hospitals, all with documented AF lasting at least six minutes. ECGs were manually adjudicated by cardiologists. To account for intra- and inter-reviewer variability, a random sample of 10% of ECGs underwent additional review. Disagreements were resolved by a third reviewer. Diagnostic performance was determined by calculating the gross and patient-averaged PPV for AF episodes of different duration. The source of FP detection was also categorised.

Results: Overall, 16230 individual ECGs from 232 patients were included. The median AF episode duration was 14 minutes. R-wave amplitude remained stable during follow-up (0.52±0.27 mV [initial] vs 0.54±0.29 mV [end of follow-up], p=0.10). The gross and patient-averaged PPV were 75.0% and 67.0%, respectively. Diagnostic performance (gross) increased with progressively longer AF episodes: 88.0% for ≥ 1 hours, 97.3% for 6 hours and 100% for 24 hours. The main source of FP during tachycardia was T-wave oversensing (54.2%), whilst in non-tachycardic episodes it was predominantly ectopy (71.2%). The AF burden precision was excellent (93.3%). Confirm Rx performance was significantly better in men than women, with rates of 83.8% and 64.3%, respectively.

Conclusion: The Confirm Rx ICM diagnostic performance was modest for all AF episodes (75%), with accuracy increasing for longer AF episodes and reaching 100% PPV for AF ≥24 hours. Ectopy remains the largest source of FP detections. R-wave amplitude and diagnostic performance were higher in men than in women.

4.3 Introduction

AF diagnosis relies on ECG documentation of irregularly irregular R-R intervals without any discernible P-waves.[1,2] Twelve-lead ECGs, Holter monitors, patches and event recorders are routinely employed to detect AF episodes. However, the unpredictable nature of AF results in a relatively low diagnostic yield from intermittent monitoring when compared to prolonged continuous rhythm monitoring with ICMs.[37,282] Recently, there has been an increased focus in expanding the indications for ICMs and employing them following cryptogenic strokes and for monitoring AF burden and recurrence after catheter ablation and cardiac surgery.[36,61-65,283]

Despite their high sensitivity in detecting AF episodes, ranging between 88-96%, previous generations of ICMs were limited by the high number of FP episodes.[47-52] All transmissions require careful adjudication to confirm if episodes are correctly classified as AF, which, given the large volume of data collected, is resource-intensive and time-consuming. Moreover, the SARS-CoV-2 pandemic has accelerated the adoption of digital solutions, including increased use of remote monitoring of cardiac devices, leading to further strain on already busy device clinics.[284] Therefore, the diagnostic utility of ICMs relies on accurate and timely detection of clinically significant arrhythmias whilst minimising FPs.

Technological advancements have led to minimally invasive ICMs with improved connectivity, remote monitoring capabilities, refined AF algorithms aimed at reducing FP episodes and streamlining workflow. The Confirm Rx ICM exemplifies this progress, using wireless telemetry (Bluetooth® and Wi-fi/cellular technology) to communicate with the myMerlin smartphone app and transmit data to its secure remote monitoring platform (Merlin Patient Care Network). However, the app only transmits data, it does not provide patients with details regarding the number or type of arrhythmic episodes detected.[60]

The Confirm Rx was the first ICM to communicate directly with a smartphone app, creating opportunities for novel management strategies and it is particularly relevant for 'pill-in-the-pocket' OAC. However, if this ICM were used to directly alert patients without manual adjudication, its diagnostic accuracy, particularly how well it can avoid PF detections, would be critical to avoid inappropriate OAC.

To evaluate the suitability of the Confirm Rx for rhythm-guided OAC strategies, this multicentre retrospective 'real-world' study evaluated its diagnostic performance in detecting AF episodes of varying durations.[255]

4.4 Methodology

This multicentre retrospective study included consecutive patients from nine UK hospitals: Oxford University Hospitals NHS Foundation Trust, East Suffolk and North Essex NHS Foundation Trust, Northumbria Healthcare NHS Foundation Trust, University Hospitals Dorset NHS Foundation Trust, Barts Health NHS Trust, Golden Jubilee National Hospital, Worcestershire Royal Hospital, St George's University Hospitals NHS Foundation Trust, and Milton Keynes University Hospital. The inclusion criteria were as follows: Confirm Rx ICM with SharpSense technology (version 1.2) with at least one episode AF ≥6 minutes and more than 90 days of follow-up.

The ASSERT study showed increased thromboembolic risk in patients with device-detected AF ≥6 minutes and subsequent studies using ICMs, such as REVEAL-AF and LOOP studies, used the same cut-off of ≥6 minutes for clinically significant AF episodes.[175,285,286]

De-identified data from Merlin.net remote monitoring database was extracted and adjudicated by researchers at the Oxford University Hospitals. All study participants signed a Merlin.net™ Patient Care Network consent form at the time of their ICM implant agreeing to have their data de-identified, pseudonymised and analysed for research purposes.

The study was registered and endorsed by the HRA (ID 297175) and received REC exemption under the category of research limited to the previously collected, non-identifiable information.

4.4.1 Device Characteristics and AF algorithm

The Confirm Rx implant procedure and specifications including its AF algorithm which now incorporates SharpSense are described in detail in Chapter 2 (Methodology; Section 2.4 Study Devices).

4.4.2 Episode Adjudication and Statistical Analysis

All AF episodes included a corresponding 120-second SL-ECG and heart rate scatterplot which was considered representative of the whole episode. One reviewer (A.B.G., CCDS certified) adjudicated all recordings (episodes categorised by the Confirm Rx as AF) and classified them as 'True-AF' or 'FP'. To account for intra-reviewer variability, a random sample of 10% of stored ECGs was re-adjudicated by the same reviewer (A.B.G., CCDS certified). Similarly, this random sample was adjudicated by a second reviewer (M.P., CCDS certified) to assess inter-reviewer variability. Any disagreement was resolved by a third reviewer (T.R.B.).

The level of agreement between reviewers was calculated using the Cohen's kappa and, as per convention, values over 0.80 were considered excellent agreement. All reviewers were blinded to ICM indications.

Sensitivity and specificity cannot be calculated from this dataset as there is no other device used as gold standard, such as a Holter monitor. Instead, diagnostic accuracy was determined by calculating gross positive PPV and patient-averaged PPV for AF episodes of different durations (6 minutes, 10 minutes, 30 minutes, 1 hour, 3 hours, 6 hours, 12 hours and 24 hours).

The gross PPV was computed by dividing all True-AF episodes by the total number of AF episodes (True-AF and FP) detected by the Confirm Rx ICM. This method assumes that each episode was an independent event. Conversely, patient-averaged PPV was derived by first calculating the gross PPV for each patient and then averaging across all patients. This dual approach allows for both population-level and patient-centred interpretations of the diagnostic accuracy. I repeated this analysis for predefined subgroups according to reason for monitoring, sex, and R-wave amplitude to identify factors that may influence diagnostic performance.

To characterise the potential mechanisms leading to misclassification of AF, FP episodes were divided into five categories: undersensing, oversensing, noise, atrial/ventricular ectopy or a combination of any of the above.

The total AF burden (proportion of time in AF) was computed as the sum of the duration of all AF episodes (True-AF and FP) detected by the Confirm Rx ICM divided by the total duration of follow-up. In contrast, True-AF burden only included True-AF episodes and was calculated by dividing the duration of all True-AF episodes by the total duration of follow-up. AF burden precision was calculated by dividing the True AF burden by the total AF burden. As before, sub-analysis was performed for precision of AF burden for each ICM implant indication and stratified by AF episode duration.

4.5 Results

Between August 2018 to August 2021, 232 consecutive patients from nine UK hospitals met the inclusion criteria. A total of 16,230 individual ECG recordings were adjudicated, with excellent intra- and inter-observer agreement with Cohen's Kappa values of 0.85 and 0.87, respectively.

The study cohort was 46% male with a median age of 67 years (IQR 56-77), and the median duration of follow-up was 18 months (IQR 10-22). Implant indications are described in Table 4-1, which shows syncope as the most common reason for monitoring (65.1%) and a minority of patients (2.6%) had an ICM for AF management.

Table 4-1. *Baseline demographics of participants and episode characteristics. Reproduced with permission from Briosa e Gala et al.*[255]

Patients, *n*	232
Males, *n (%)*	111 (48%)
Age (years), median *(IQR)*	67 (56-77)
Follow-up (months), *median (IQR)*	18 (10-22)
Number of AF episodes	16,230
Number AF episodes per patient, *median (IQR)*	10 (3-58)
Implant indication:	
• **AF management**	6 (2.6%)
• **Suspected AF**	15 (6.5%)
• **Palpitations**	36 (15.5%)
• **Syncope**	151 (65.1%)
• **Other**	24 (10.3%)
Episode duration (min), *median (IQR)*	14 (8.7-31.9)
R-wave amplitude (implant), mean ± SD	0.52 ± 0.27 mV
R-wave amplitude (follow-up), mean ± SD	0.54 ± 0.29 mV

The median AF episode duration was 14 minutes (IQR 9-32), and only 15.1% (2,441 episodes) of AF episodes were ≥ 1 hour in 76 patients. Notably, in the AF management cohort nearly half of the episodes were ≥ 1 hour.

The distribution of age and sex according to implant indication can be found in Table 4-2, with patients with Palpitations being younger (median age 54 years) compared to AF management (median age 70 years). Patient with an ICM for Syncope and AF management were more likely to be women (64.8% and 52.1%, respectively), with men having higher rates of ICM implants for Suspected AF (61.5%) and Other (54.9%) indications.

Table 4-2. *Confirm Rx ICM Implant indications according to age and sex. Reproduced with permission from Briosa et al.*[255]

	Palpitations	**AF Management**	**Syncope**	**Suspected AF**	**Others**
Age *(years)*	54 (37-67)	70 (63-76)	72 (57-82)	67 (57-67)	64 (57-77)
Sex					
• Female	3 (50%)	12 (52.1%)	22 (64.8%)	5 (38.4%)	64 (42.1%)
• Male	3 (50%)	11 (47.8%)	12 (35.2%)	8 (61.5%)	78 (54.9%)

4.5.1 Overall AF Detection Performance

Overall, the gross PPV was 75.0%, and patient-averaged PPV was 67.0% for AF≥ 6 minutes (Table 4-3 and Figure 4-1). There was stepwise increase in the diagnostic performance (gross PPV) with progressively longer AF episodes: 88.0% for ≥ 1 hour, 97.3% for ≥ 6 hours, 99.2% ≥ 12 hours and 100% for ≥ 24 hours. (Table 4-3). Similarly, patient-averaged PPV also showed an improvement in AF episodes of longer duration and reaching 100% for AF ≥ 24 hours.

Table 4-3. *Diagnostic performance of the Confirm Rx ICM with SharpSense Technology for AF episodes of different duration. Reproduced with permission from Briosa e Gala et al.*[255]

Episode duration	Number of AF episodes detected	Number of True AF episodes	Number of Patients with True AF	PPV (gross)	PPV (patient-averaged)
≥ 6 minutes	16,230	12,171	188	75.0%	67.0%
≥ 10 minutes	10,805	8,289	162	76.7%	73.5%
≥ 30 minutes	4,268	3,518	115	82.4%	82.2%
≥ 1 hour	2,441	2,148	76	88.0%	83.4%
≥ 3 hours	1,073	1,015	48	94.6%	95.7%
≥ 6 hours	622	605	35	97.3%	98.3%
≥ 12 hours	371	368	22	99.2%	98.1%
≥ 24 hours	160	160	14	100%	100%

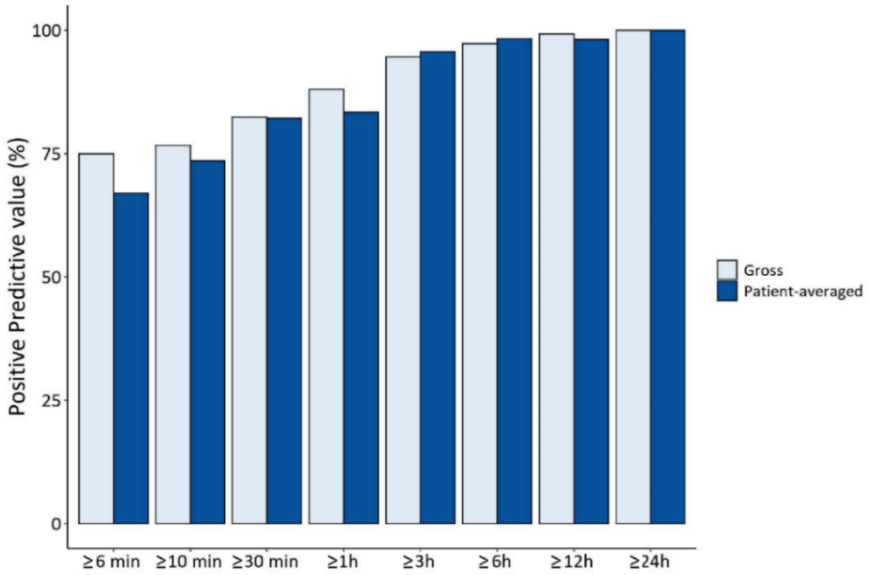


Figure 4-1. *Confirm Rx ICM AF detection performance according to AF episode duration. Reproduced with permission from Briosa e Gala et al.*[255]

4.5. AF Detection Performance Stratified by Indication

Table 4-4 reveals important differences in the total number of AF episodes detected and True-positive between cohorts. The AF management cohort, despite having the lowest number of AF episodes (155) and monthly recordings per patient (1.6), exhibited a significantly higher PPV (95.5% True-AF episodes) compared to other groups ($p<0.001$).

Conversely, the Palpitations (PPV of 56.6%) and Suspected AF (PPV of 44.0%) cohorts had the lowest PPV, but a substantially higher frequency of monthly AF episodes recorded (5.1 and 5.8 recordings/patient/month, respectively) (Appendix C, Figure 4-1).

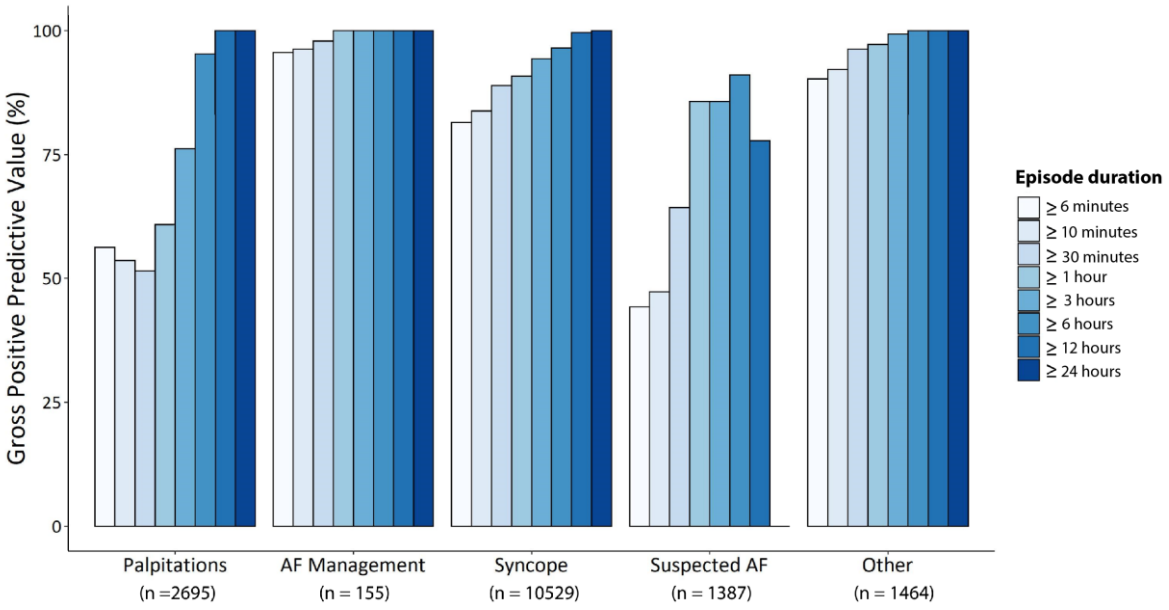


Figure 4-2. *Confirm Rx ICM AF detection performance for different episode durations and stratified by implant indications.* *Reproduced with permission from Briosa e Gala et al.*[255]

Importantly, as shown above in Figure 4-2, despite these variations in PPV between cohorts, the overall trend of improved AF detection with longer episode duration remained consistent across all cohorts.

Further details on PPV stratified by implant indications and for different AF durations can be found in Appendix C, Table S4-1.

Table 4-4. *Diagnostic performance of the Confirm Rx ICM with SharpSense Technology as a function of different implant indications. Reproduced with permission from Briosa e Gala et al.*[255]

	Reason for monitoring					Total
	Palpitations	AF Management	Syncope	Suspected AF	Other	
Number of episodes of AF detected	2,695	155	10,529	1,387	1,464	16,230
Number of True positive episodes	1,516	148	8,573	614	1,320	12,171
Gross PPV	56.3%	95.5%	81.4%	44.3%	90.2%	75.0%
Patient-averaged PPV	69.3%	81.7%	67.1%	55.2%	65.0%	67.0%

4.5.3 Impact of R-wave Amplitude on AF Detection

R-wave amplitude measurements remained stable with no significant changes from initial implant to end of follow-up (0.52±0.27 mV vs 0.54± 0.29 mV, p=0.10).

There was a sex-based difference in both R-wave amplitude and diagnostic accuracy (Appendix C, Table S4-2). Men had statistically higher median R-wave amplitude compared to women, 0.65 mV and 0.41mV, respectively (p <0.01).

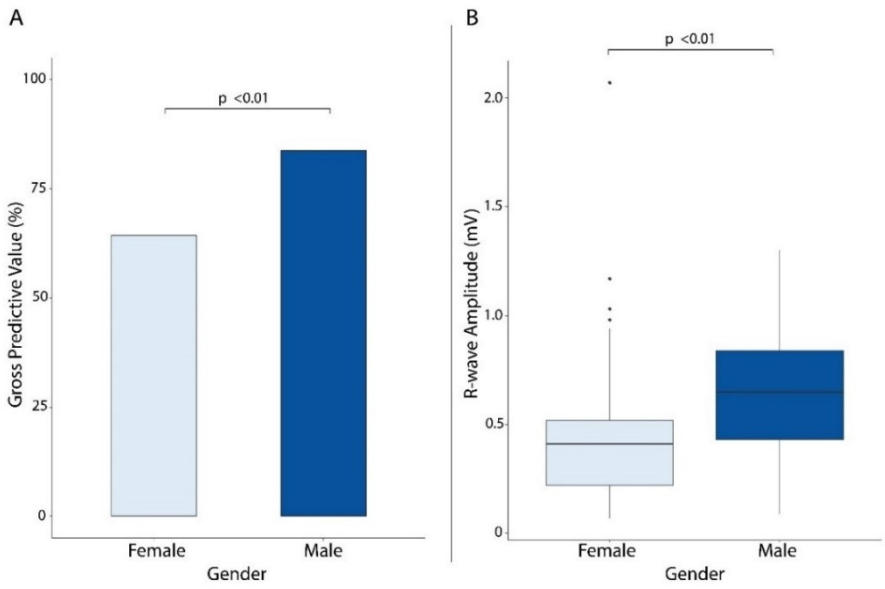


Figure 4-3. (A) *Sex-based comparison of gross positive predictive value (PPV) for the Confirm Rx. (**B**) Sex-based comparison of R-wave amplitude for the Confirm Rx. Reproduced with permission from Briosa e Gala et al.*[255]

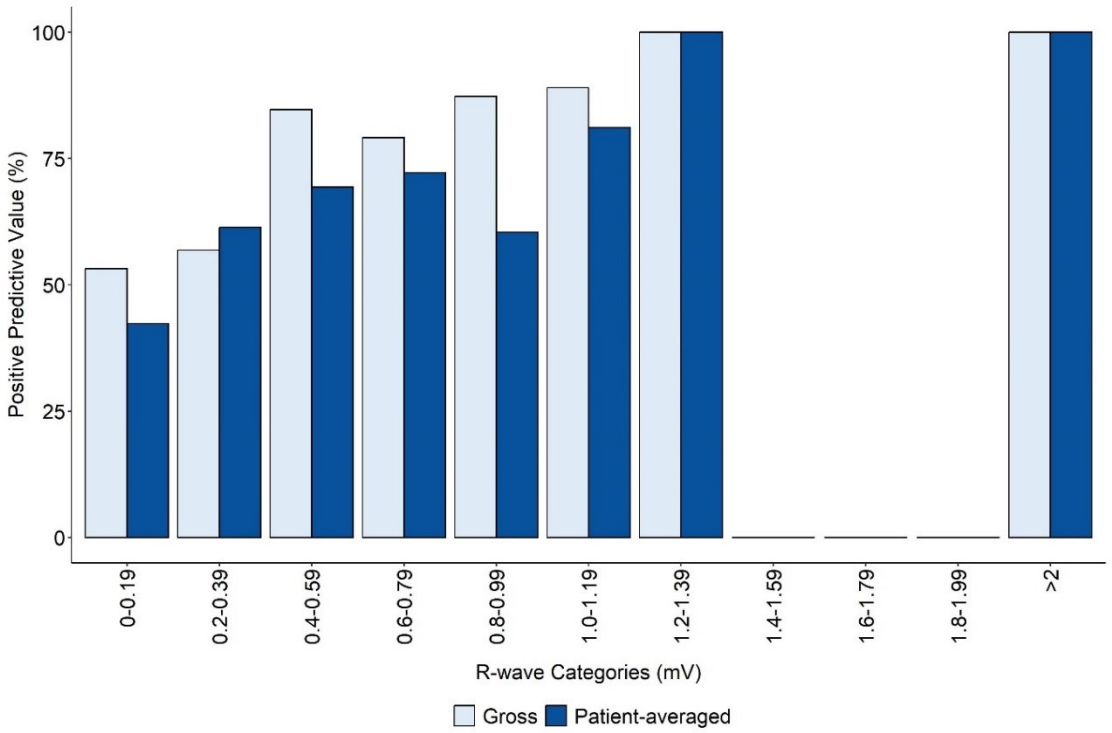


Figure 4-4. *Diagnostic performance of the Confirm Rx ICM AF detection algorithm stratified by 0.2 mV increments in R-Wave amplitude. Reproduced with permission from Briosa e Gala et al.*[255]

This difference correlated with detection performance, as men had overall higher PPV for AF detection (83.8%) compared to women (64.3%) (Figure 4-3A). A noticeable trend of greater gross PPV with higher R-wave amplitude increments of 0.2 mV was observed and is depicted in Figure 4-4.

Episodes with R-wave amplitudes <0.2 mV had the lowest gross PPV of 53.2%, and at the end of the spectrum episodes with R-wave >1.2 mV achieved a perfect PPV (100%).

4.5.4 False-Positive Episodes

A quarter (4,074) of all episodes classified as AF by the Confirm Rx were FP detections in 162 (69.8%) patients. Figures 4-5A displays the mechanism of FP detections, showing that atrial and ventricular ectopy accounted for approximately half (51.0%) of FP episodes, followed by oversensing (19.7%) and combination (26.4%).

Interestingly, the predominant cause of FP was not consistent across implant indications, with statistically significant difference in the rate and distribution of FP episodes (Appendix C, Table S4-3, Figure S4-3). For example, 87.5% of FP episodes in patients with an ICM for Suspected AF were due to oversensing. However, for all other implant indications, the predominant source of

FP was atrial or ventricular ectopy and accounted for at least half of the FP episodes observed (Figure S7). Sex differences can be found in supplementary Figure S4-2 in Appendix C.

4.5.5 AF Detection during Tachycardia

The Confirm Rx AF detection performance was poorer during episodes of tachycardia (mean heart rate>100 bpm) when compared to normal heart rates (52.1% vs 20.0%, p<0.01; Figure 4-5B). T-wave oversensing emerged as the primary factor for FP detections during tachycardia, particularly in the setting of atrial tachycardia/flutter with rapid ventricular response where the occasional T-wave oversensing led to an irregular pattern and, consequently, the ICM interpreted this as an AF episode.

Interestingly, despite the inclusion of a new P-wave discriminator into the AF detection algorithm, atrial and ventricular ectopy continued to be the leading cause of (70.8%) for FP events in non-tachycardic episodes.

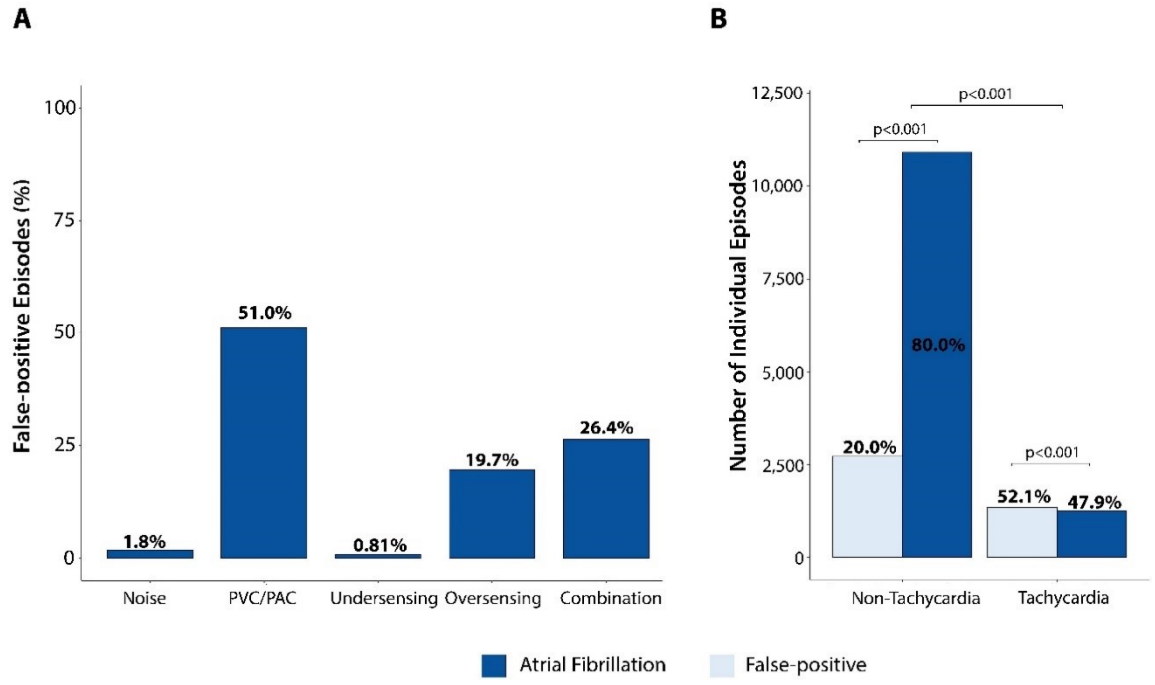


***Figure 4-5**. **(A)** Source of FP detections for the 4,074 incorrectly classified by the Confirm Rx as AF. **(B)** FP episodes in non-tachycardic versus tachycardic episodes defined as mean heart rate ≥ 100 bpm **AF**, atrial fibrillation. **PAC**, premature atrial contraction. **PVC**, premature ventricular contraction. Reproduced with permission from Briosa e Gala et al.[255]*

4.5.6 AF Burden

Over more than 325 patient-years of follow-up, a total of 26,137 hours of AF episodes were recorded, representing a total AF burden of 0.92% in the study cohort. However, a breakdown of these episodes revealed that 24,404 hours (or 0.86% of the follow-up) represented true AF ("True-AF" burden), resulting in an AF burden precision of 93.3%.

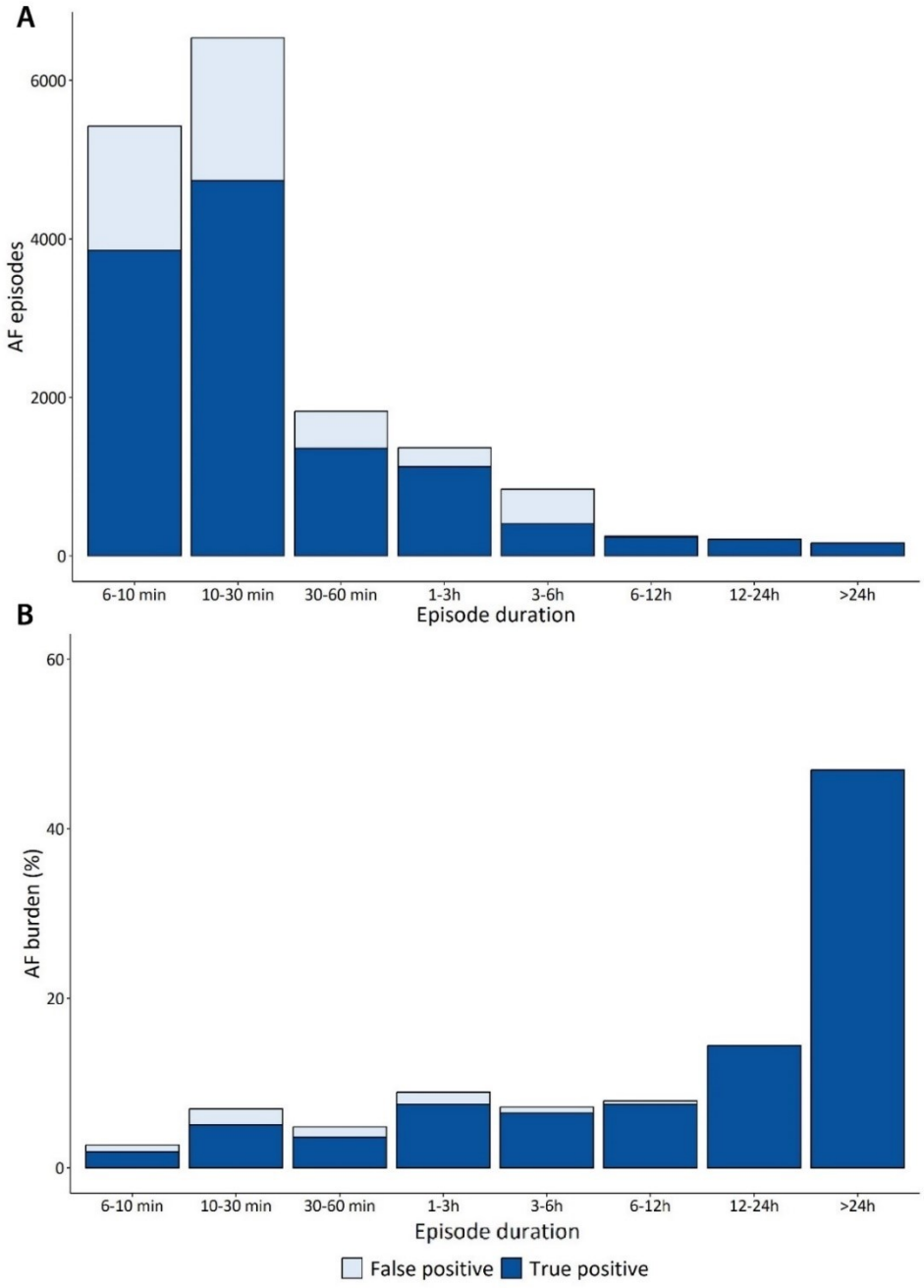


Figure 4-6. (A) *Diagnostic performance of the Confirm Rx as a function of episode duration.* ***(B)*** *Contribution of AF episodes of different duration to overall AF burden. Reproduced with permission from Briosa e Gala et al.*[255]

Most AF episodes (84.5%) were <1 hour, and although approximately a quarter of them were FP, they contributed little to the overall AF burden. In contrast, AF episodes ≥3 hours accounted for 76.4% of time spent in AF and, of these, the proportion of True-AF episodes was very high (98.5%). This unequal contribution of longer episodes to the total burden accounts for the high precision of estimated burden by these devices (Figure 4-6). At a patient-level, the precision of True-AF burden was lower at 82.9%.

4.6 Discussion

The main findings of this 'real-world' study are: (1) the overall diagnostic performance (gross PPV) was 75.0% and was highest with longer AF episodes; (2) the gross PPV was higher in men (83.8%) compared to women (64.3%); (3) despite a new P-wave discriminator, the dominant mechanism of FP is atrial and ventricular ectopy (51%); and (4) the estimated AF burden for the whole cohort was excellent (93.3%).

Accurate and reliable R-wave sensing is essential in AF detection algorithms to minimise FP detection arising from oversensing, undersensing, ectopy or noise. This study found that the miniaturisation of the Confirm Rx ICM allows for a faster and less invasive procedure without compromising signal acquisition. The mean R-wave amplitude observed in this study (0.54 mV was comparable to the DETECT-AF study, which used an older, larger generation ICM (SJM Confirm) with a different implantation technique (0.52 mV).[47]

The UK Confirm Rx study highlights the importance of an adequate R-wave amplitude in accurate detection. Episodes with R-waves <0.25 mV had significantly greater incidence of FP due to oversensing (35.4% of patients), likely as a result from increased sensitivity settings required in the context of low R-wave amplitudes. Noise and undersensing had minimal contribution to FP events (2.6%). Further supporting the role of R-wave amplitude in detection was the observed increase diagnostic accuracy with higher R-waves.

The observed lower median R-wave amplitude in women compared to men is in line with prior work.[287] The difference in cardiac signal amplitude and morphology between sexes may be attributed to several factors: suboptimal device positioning (particularly when placed too superficially rather than adjacent to the fascia and muscle layer), laxity of tissue influencing the size of the pocket, and anatomical variations. Another possible contributing factor is female breast tissue which may lead to signal attenuation and lower R-wave amplitude if the ICM is not implant in an appropriate position. These factors may provide an explanation for the higher number of FP in women from ectopy and a combination of ectopy and undersensing when

compared to men. This is the first study to reveal sex-based difference in the diagnostic performance of the Confirm Rx ICM.

Women had a higher number of ICMs implants for Syncope but a lower number for Suspected AF. Although the difference in implant indication between sexes was not significant, it may have influenced the number and distribution FP detection patterns and should be taken into account when interpreting these results.

The refined AF detection algorithm with SharpSense Technology may explain the incremental improvement in the AF diagnostic performance for AF episodes of longer duration. DETECT-AF reported the SJM Confirm without SharpSense had an overall gross PPV of 62.8% and patient-averaged PPV of 60.7% for AF >5 minutes.[47] In contrast, the new SharpSense algorithm evaluated in the UK Confirm Rx study showed higher performance metrics for AF >6 minutes at an episode-level and patient-level, with PPV of 75.0% and 67.0%, respectively.

Importantly, this study demonstrated a gradual reduction in the proportion of FP episodes with episodes of longer duration. AF episodes >1 hour had a PPV of 88.0% for all indications, with it being higher in patients with known AF.

Despite its wide use, good quality data on the Confirm Rx ICM AF detection algorithm is sparse. Ip *et al.* randomised 142 patients to either a Reveal-LINQ ICM or a Confirm Rx ICM.[260] Twenty patients experienced 1,597 episodes of AF ≥ 6 minutes detected by the Confirm Rx, and the patient-averaged PPV was 38%. A publication by Gardner *et al.* showed that rationalising ECG adjudication to up to three "key ECGs" lowers the adjudication burden, but it did not provide any data on the overall Confirm Rx performance.[288]

The SMART Registry, sponsored by Abbott, was an international prospective observational study (NCT03505801) recruiting 1,400 patients to assess the safety of Confirm Rx ICM. Surprisingly, the diagnostic performance of Confirm Rx is not a predefined outcome measure; preliminary analysis only reports the incidence of true arrhythmias (47.5% of patients) rather than providing data on performance metrics.[289]

Positive predictive value varies according to the prevalence of AF in the population being studied and AF algorithm settings. The Confirm Rx ICM with SharpSense Technology had a similar performance for AF detection to published data on the Reveal LINQ ICM, using similar methodology. Mittal *et al.* reported a gross PPV of 77.5% following the analysis of 13,199 episodes ≥6 minutes categorised by the LINQ as AF.[262] Incremental performance was observed in AF ≥ 1 hour and, as the authors noted, should guide decisions on programming AF duration thresholds to reduce the FP episode rate. Nonetheless, Afzal *et al.* demonstrated that approximately 99% of

ICMs enrolled in Medtronic's remote monitoring platform use nominal settings rather than being tailored to patients' needs.[290] Moreover, in a 4-week period the rate of FP transmissions from LINQ ICMs using nominal setting (AF ≥2 minutes) ranged from 46% in patients with known AF to 86% in those a cryptogenic stroke as their implant indication.

In a subset of patients, such as those with cryptogenic stroke, AF detection would result in OAC for secondary stroke prevention, and it is, therefore, reasonable that programming is more aggressive (lower AF duration threshold, increased sensitivity) and accepts a larger number of FP episodes. In contrast, following catheter ablation and/or changes in medication the focus should be burden reduction and symptom-rhythm correlation. In research settings, the efficacy of catheter ablation success rates is judged on the freedom of AF of >30 seconds; however, in a clinical setting it may be preferable to set alerts at a longer duration to reduce alert burden or even rely on manual transmission during symptomatic episodes.[53,291]

The Confirm Rx ICM AF burden counter includes all episodes, regardless of duration threshold set for the device, and, importantly, it is not updated following adjudication. This means that FP will still be counted towards overall AF burden. This is an important technical limitation of the ICM which is often overlooked. Yet, with SharpSense Technology, the UK Confirm Rx study demonstrated a reduction in the rate of FP detections and, as longer episodes, which are far more accurate, dominate in AF burden, the device gives a reasonable estimation of the 'True-AF' burden.

P-wave discriminator analysis is not provided during adjudication, which would be potentially useful to clinicians. In many cases, P-waves were distinctly present during episodes of atrial ectopy and sinus arrhythmia that were incorrectly labelled by the Confirm Rx ICM AF. It is therefore unclear whether the P-wave discriminators cannot detect these small deflections or if P-waves are incorrectly stacked during the analysis looking for a consistent P- wave pattern, which is a parameter used to reduce FP detection. Conversely, other episodes lacked visible P-waves, nonetheless the heart rate scatterplot clearly showed a regularly irregular pattern in keeping with ectopy. Therefore, the main technical challenge appears to be low P-wave amplitude in many ECGs recoded. This reinforces the rationale for optimising for R-wave amplitudes, as patients with low R-wave signals, the comparatively smaller P-waves will often be indiscernible.

Studies have consistently shown that the ectopy is the primary source of FP episodes despite ICMs including P-wave discriminators into ICM algorithms.[260,290,292] As AF detection has traditionally on R-R interval analysis, ICMs are essentially designed for accurate detection of R-waves and, as such, the recommended implant location is the left parasternal 4th intercostal space

with the device injected roughly at a 45-degree angle. Both the Confirm Rx and LINQ ICMs have incorporated P-wave discriminators to augment their AF detection accuracy, but their current implant location is not optimised a good P-wave signal. Indeed, a small study comparing P-wave visibility in patients with Confirm Rx and Reveal-LINQ ICMs found that in almost 30% of patients the P-wave was not visible.[293] Perhaps a less conventional position at the atrial level to improve P-wave sensing without compromising R-waves, as seen in some ECG patches, may yield better results and is worth exploring. For example, the Carnation Ambulatory Monitor is designed to capture a good quality P-wave, and it is placed more medially near the sternum to cover the atria. A small comparative study of the Carnation monitor and the Zio-XT patch revealed that ECGs were more visible (100% vs 16%), in large part owing to a superior P-wave signal quality.[294]

An advantage of the Confirm Rx ICM, which makes it particularly attractive to a 'pill-in-the-pocket' OAC strategy is the potential connectivity capabilities. Namely, it was the first ICM to communicate with a smartphone app via Bluetooth® which then transmits episode data to its remote monitoring platform (Merlin.net). Initial findings from an American registry shows a high uptake with 97% of 5,666 patients registering the ICM to the smartphone app and 92% having used it for at least one data transmission.[60] Using smartphones instead of traditional bedside monitors is more versatile, allowing for the potential for real-time transmissions of AF episodes. The mean time from patient-activated episodes to these being available on the remote platform was only 2.9 minutes; however, automatic transmission still occurred roughly once a day (mean time 18.5 hours).[60]

4.6.1 Technical Barriers to 'Pill-in-the-pocket' OAC

As described in detail in Chapter 3, REACT.COM enrolled 59 patients who, over a mean follow-up of 1.3 years, generated 24,004 ICM transmissions requiring adjudication.[68] In the event of an AF episode >1 hour the research team contacted patients directly to initiate OAC. This workflow is challenging, time-consuming, expensive, and lacks scalability. The improved connectivity of the Confirm Rx ICM offers the potential for 'pill-in-the-pocket' OAC, if there was real-time AF episode transmission to its remote monitoring platform.

However, it is important to understand the Confirm Rx ICM current limitations. The existing architecture only transmits patient-activated episodes in real-time.[60] Automated detections are typically only uploaded to the remote monitoring platform once a day, around 6 am. This causes a time delay between detecting AF and clinicians accessing the episode.

There are no direct alerts to patients or any information in the smartphone app regarding the type of episode detected. Alerts from physicians to patients would have to be sent only after the

episode data is upload to Merlin.net. Therefore, to implement 'pill-in-the-pocket' OAC would require a substantial change to current Confirm Rx and smartphone app design and architecture and, after extensive discussion with the manufacturers, it became clear that this was not feasible within our timelines. This resulted in a different ICM, the LINQ II ICM, being used SMART-ALERT study (Chapter 6) which investigated real-time AF detection and alerts.[257]

Although the AF episode duration threshold that requires OAC is unknown, REACT.COM used a cutoff of AF ≥ 1hour to guide OAC decisions.[68,199] In this scenario, the Confirm Rx ICM with a PPV of 88% may be a reasonable trade-off for implementing direct AF notification to patients. This would mean that approximately one in eight patients would start OAC inappropriately, likely for only a few days, until adjudication identified a FP and OAC was stopped. This strategy would delay the time from AF detection to start of OAC, accepting that some patients would have inappropriate OAC for a limited period. However, since these patients would otherwise be on lifelong OAC, any adverse effects of being on OAC for a few days should be minimal.

4.6.2 Limitations

First, a 'gold-standard' ambulatory ECG monitor was not available; hence, other important performance metrics, such as sensitivity and specificity, cannot be determined from this dataset. However, DETECT-AF reported a high sensitivity for AF episodes and thus, it is not likely that many AF episodes were missed.[47] PPV is a very useful parameter of diagnostic performance and can be used to compare the Confirm Rx to other ICMs. Furthermore, the limited duration of available ambulatory monitoring tools (up to 14 days) restricts examination of more prolonged AF episodes and assessment of cumulative AF burden which was the aim of this study.

Second, the dataset had limited datapoint on baseline characteristics, such as body mass index and implant location, which could affect the overall quality of ECG recordings and sensed R-waves. This has, of course, important implications when interpreting the difference observed between men and women with regards to diagnostic performance and R-wave amplitude.

Third, the first 120 seconds of the ECG were considered representative of the entire episode when estimating AF episode performance and AF burden.

Finally, this study reflects UK practice where syncope is the commonest indication for an ICM. The PPV for each cohort according to the reason for monitoring should be interpreted with caution due to the imbalance in patient numbers.

4.7 Conclusions

The diagnostic performance of the AF algorithm in the novel Confirm Rx ICM with SharpSense technology was 75%, with the stepwise increase in the accuracy for longer AF episodes. Confirm Rx ICM performance was significantly better in men than women, with rates of 83.8% and 64.3%, respectively. R -wave parameters were excellent and remained stable during follow-up. Overall, the Confirm Rx ICM AF detection demonstrates an improved performance compared to its previous iteration. However, ectopy still accounts for most FP episodes despite the introduction of P-wave discriminators.

In the context of a 'pill-in-the-pocket' OAC strategy, the Confirm Rx ICM offers several advantages: (1) the high diagnostic accuracy for longer AF episodes may permit direct to patient notification allowing for a small percentage of FP detection; (2) better connectivity via a smartphone app, and (3) accurate AF burden estimation.

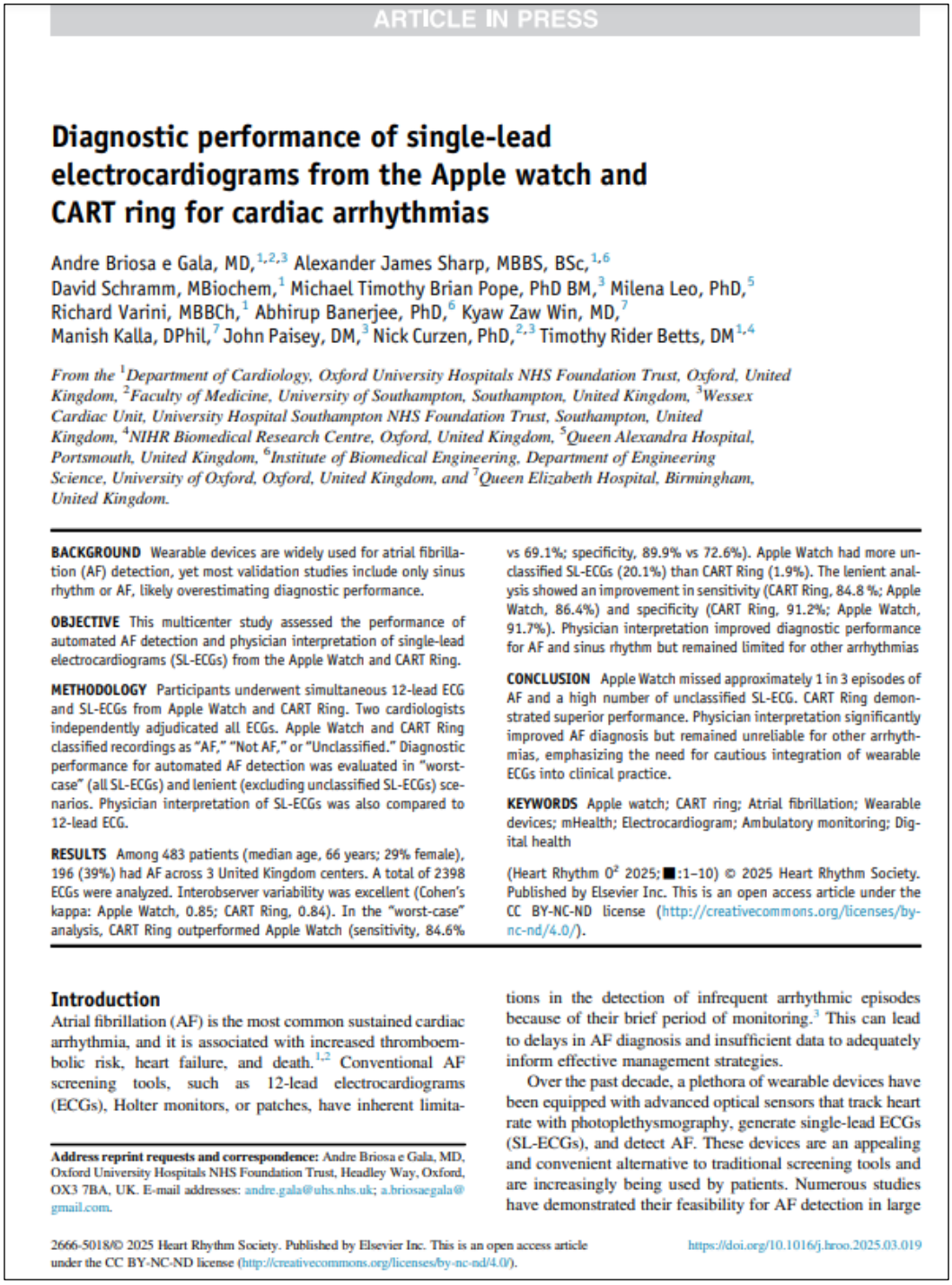
However, the major barrier for its use in a ‘pill-in-the-pocket’ OAC approach is that episode uploads to the remote monitoring platform only occur once daily, which hinders ‘real-time’ AF notifications to patient and needs to be addressed. Without timely data transmissions, there would be significant delays in AF notifications and, consequently, OAC initiation. This important limitation must be address before the Confirm Rx ICM can be employed effectively in this context.

5 WEAR-TECH ECG study

5.1 Publications and Abstracts

5.1.1 Publications

Briosa e Gala A, Sharp AJ, Schramm D, Pope MTP, Leo M, Varini M, Banerjee A, Win KZ, Kalla M, Paisey J, Curzen N, Betts TR. Diagnostic Performance of Single-Lead Electrocardiograms from the Apple Watch and CART Ring for Cardiac Arrhythmias. **Heart Rhythm O2** 2025 Mar 26;6(6):808-817



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Diagnostic performance of single-lead electrocardiograms from the Apple watch and CART ring for cardiac arrhythmias

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BACKGROUND Wearable devices are widely used for atrial fibrillation (AF) detection, yet most validation studies include only sinus rhythm or AF, likely overestimating diagnostic performance.

OBJECTIVE This multicenter study assessed the performance of automated AF detection and physician interpretation of single-lead electrocardiograms (SL-ECGs) from the Apple Watch and CART Ring.

METHODOLOGY Participants underwent simultaneous 12-lead ECG and SL-ECGs from Apple Watch and CART Ring. Two cardiologists independently adjudicated all ECGs. Apple Watch and CART Ring classified recordings as "AF," "Not AF," or "Unclassified." Diagnostic performance for automated AF detection was evaluated in "worst-case" (all SL-ECGs) and lenient (excluding unclassified SL-ECGs) scenarios. Physician interpretation of SL-ECGs was also compared to 12-lead ECG.

RESULTS Among 483 patients (median age, 66 years; 29% female), 196 (39%) had AF across 3 United Kingdom centers. A total of 2398 ECGs were analyzed. Interobserver variability was excellent (Cohen's kappa: Apple Watch, 0.85; CART Ring, 0.84). In the "worst-case" analysis, CART Ring outperformed Apple Watch (sensitivity, 84.6% vs 69.1%; specificity, 89.9% vs 72.6%). Apple Watch had more unclassified SL-ECGs (20.1%) than CART Ring (1.9%). The lenient analysis showed an improvement in sensitivity (CART Ring, 84.8 %; Apple Watch, 86.4%) and specificity (CART Ring, 91.2%; Apple Watch, 91.7%). Physician interpretation improved diagnostic performance for AF and sinus rhythm but remained limited for other arrhythmias

CONCLUSION Apple Watch missed approximately 1 in 3 episodes of AF and a high number of unclassified SL-ECG. CART Ring demonstrated superior performance. Physician interpretation significantly improved AF diagnosis but remained unreliable for other arrhythmias, emphasizing the need for cautious integration of wearable ECGs into clinical practice.

KEYWORDS Apple watch; CART ring; Atrial fibrillation; Wearable devices; mHealth; Electrocardiogram; Ambulatory monitoring; Digital health

(Heart Rhythm O2 2025;■:1–10)

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and it is associated with increased thromboembolic risk, heart failure, and death.[1,2] Conventional AF screening tools, such as 12-lead electrocardiograms (ECGs), Holter monitors, or patches, have inherent limitations in the detection of infrequent arrhythmic episodes because of their brief period of monitoring.[3] This can lead to delays in AF diagnosis and insufficient data to adequately inform effective management strategies.

Over the past decade, a plethora of wearable devices have been equipped with advanced optical sensors that track heart rate with photoplethysmography, generate single-lead ECGs (SL-ECGs), and detect AF. These devices are an appealing and convenient alternative to traditional screening tools and are increasingly being used by patients. Numerous studies have demonstrated their feasibility for AF detection in large

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2666-5018/

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5.1.2 Abstracts

Briosa e Gala A, Sharp AJ, Schramm D, Ries W, Pope MTB, Leo M, Paisey J, Curzen N, Betts TR. *"Single lead ECGs with wearable technology: diagnostic performance in patients with cardiovascular disease."* **Oral presentation, European Heart Rhythm Association Congress 2023**

Briosa e Gala A, Sharp AJ, Schramm D, Ries W, Pope MTB, Leo M, Paisey J, Curzen N, Betts TR. *"Automated atrial fibrillation detection with a smartwatch and smart-ring in individuals with cardiovascular disease"* **Oral presentation, European Heart Rhythm Association Congress 2023**

Briosa e Gala A, Sharp AJ, Schramm D, Ries W, Pope MTB, Leo M, Paisey J, Curzen N, Betts TR. *"Wearable technology for atrial fibrillation detection: a comparison of the Apple Watch and the CART Ring in patients with cardiovascular disease."* **Poster presentation, Heart Rhythm Sessions 2023**

Briosa e Gala A, Sharp AJ, Schramm D, Ries W, Pope MTB, Leo M, Paisey J, Curzen N, Betts TR. *"Diagnostic accuracy of the Apple Watch and CART Ring for detecting atrial arrhythmias."* **Poster presentation, Heart Rhythm Sessions 2023**

5.2 Abstract

Background: Wearable devices are increasingly widely used for AF detection, yet most validation studies only included patients in either sinus rhythm or AF, likely overestimating diagnostic performance. The 'real-world' performance of these devices on an unselected cohort with a broad range of cardiac rhythms is uncertain.

Objective: This multicentre study assessed the performance of automated AF detection and physician interpretation of SL-ECGs from the Apple Watch and CART Ring against the gold standard 12-lead ECG in patients with a broad range of cardiac rhythms.

Methodology: Participants underwent simultaneous 12-lead ECGs and SL-ECGs from an Apple Watch and a CART Ring. Wearable device recordings are classified as "AF", "Not AF", or "Unclassified". Diagnostic performance for automated AF detection was evaluated in 'worst-case' (all SL-ECGs included) and lenient (unclassified SL-ECGs excluded) scenarios. Physician interpretation of SL-ECGs for all cardiac rhythm was compared to 12-lead ECG.

Results: Among 483 patients (median age 66 years, 29% female) across 3 UK centres, 196 (39%) had AF. A total of 2,398 ECGs were analysed with excellent interobserver agreement. In the 'worst-case' analysis, the CART Ring outperformed the Apple Watch (sensitivity: 84.6% vs. 69.1%; specificity: 89.9% vs. 72.6%). The Apple Watch had significantly more unclassified SL-ECGs (20.1%) compared to the CART Ring (1.9%). The lenient analysis showed improved performance for both devices in sensitivity (CART Ring 84.8%, Apple Watch 86.4%) and specificity (CART Ring 91.2%, Apple Watch 91.7%). Physician interpretation improved diagnostic performance for AF and sinus rhythm but remained suboptimal for other cardiac arrhythmias

Conclusion: The Apple Watch missed approximately one in three episodes of AF and generated a high number of unclassified SL-ECGs. The CART Ring demonstrated superior performance in automated AF detection. Physician interpretation significantly improved AF diagnosis but was unreliable for other arrhythmias, emphasising the need for caution when integrating wearable SL-ECGs into routine clinical practice.

5.3 Introduction

Recent advances in sensor technologies and signal processing have led to a plethora of relatively low-cost wearable devices, such as watches, bands and rings, capable of tracking heart rate via PPG and generating SL-ECGs.[75,295] Wearable devices are a more convenient alternative to traditional screening devices and increasingly are being used by patients outside the healthcare setting to detect AF.

The Apple Watch was the first FDA-approved smartwatch to record SL-ECGs. In Apple's clinical validation study with 545 patients, it reported that its Series 6 watch (algorithm version 1.0) had 98% sensitivity and 99% specificity for AF detection.[266] Similarly, the CART Ring is the first CE-marked (Conformité Européenne) ring capable of recording a 30-second SL-ECG to its companion app by placing a finger in its metal casing. The ring is designed to maximise comfort and to improve adherence. The clinical validation study of the CART Ring SL-ECGs, funded by Skylabs, also reported excellent diagnostic metrics for AF detection, with a sensitivity of 99.6%.[270]

Many wearable devices, including the Apple Watch and CART Ring, collect PPG data in ambulatory patients and can trigger automatic irregular rhythm notifications. The Apple Heart Study, STROKESTOP and Fitbit Heart Study have demonstrated the feasibility of wearable devices in AF screening of large populations.[264,39,296] However, in the vast majority of devices, PPG tracings cannot be reviewed by physicians, which may generate uncertainty regarding the rhythm diagnosis.

In contrast, SL-ECGs provide 30-second rhythm strips that can be formally reviewed by physicians. Spot-check SL-ECGs may therefore be a valuable tool in guiding a 'pill-in-the-pocket' strategy by confirming the presence of AF following an irregular rhythm notification, which, in most devices, does not generate a PPG tracing to be reviewed.

Many validation studies comparing SL-ECGs to 12-lead ECGs have primarily included patients with either sinus rhythm or AF.[77,78,268,297] Consequently, there is a potential risk of overestimating diagnostic performance by excluding other clinically relevant arrhythmias, which may be important sources of both FP detections. Their utility in a 'real-world' setting remains uncertain.

The WEAR-TECH ECG study was a prospective investigator-initiated multicentre study comparing automated AF detection and physician interpretation of SL-ECGs from two wearable devices (the Skylabs CART Ring and the Apple Watch Series 6) to a 12-lead ECG for different cardiac rhythms.[256]

5.4 Methods

5.4.1 Study Design and Participants

Study design, ethics approval and funding, are described in detail Chapter 2.

5.4.2 Study Aim

The primary objective was to compare the Apple Watch Series 6 (watchOS 7.0.2, Watch6,1, Algorithm Version 1.0) and the Skylabs CART Ring AF detection algorithms' diagnostic accuracy against simultaneous 12-lead ECGs.

Secondary objectives included: comparing the diagnostic performance for other atrial arrhythmias (atrial flutter and atrial tachycardia [AT]); assessing physician rhythm interpretation of SL-ECGs compared with 12-lead ECGs; comparing interobserver agreement between physicians interpreting SL-ECGs; determining the proportion and distribution of unclassified recordings from each device.

5.4.3 Study Procedures

The WEAR-TECH ECG study was conducted in three tertiary UK hospitals: Oxford University Hospitals NHS Foundation Trust, Queen Elizabeth Hospital and University Hospital Southampton NHS Foundation Trust.

There were only two main inclusion criteria. First, adults (> 18 years old) undergoing a routine 12-lead ECG as part of their routine care. Second, a documented history of cardiovascular disease, broadly defined as any condition affecting the cardiac and vascular system. Recruitment took place across diverse clinic settings, including inpatient wards, outpatient clinics, catheterisation labs and coronary care units. Exclusion criteria included the presence of tattoos, which could interfere with device signal acquisition, and participant inability to operate the wearable devices.

The Robust Randomisation app (RRapp) developed by the Icahn School of Medicine at Mount Sinai was used to randomly assign participants in a 1:1 fashion to one of two investigation groups (Figure 5-1). Group 1 underwent SL-ECG recording with the SkyLabs CART Ring first, followed by the Apple Watch, while Group 2 underwent the Apple Watch recording first, followed by the SkyLabs CART Ring.

Study devices characteristics, including how to generate an SL-ECG are described in detail in Chapter 2.

All SL-ECG recordings were performed simultaneously with a 30-second standard 12-lead ECG. If the initial recording was unreadable due to artefact, a second recording was allowed. An ECG machine with a sweep speed of 25 mm/s and an amplitude of 10 mm/mV on millimetric paper was used to record the 12-lead ECGs. Participants performed wearable devices recording according to the instruction manuals, with the research team providing demonstrations.

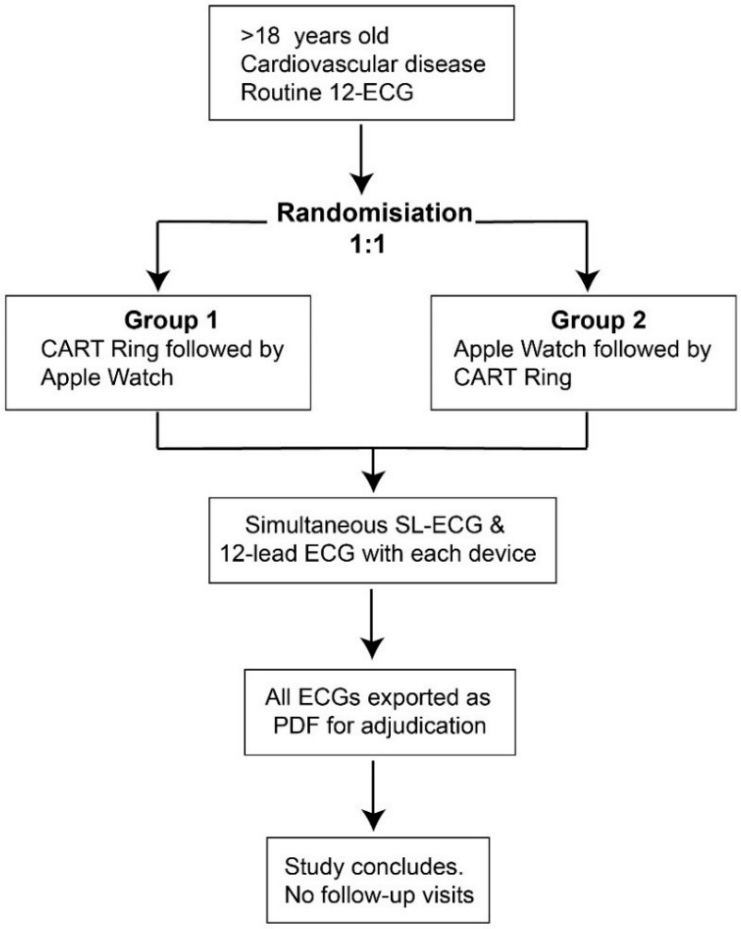

Figure 5-1. *WEAR-TECH ECG study flow chart. Reproduced with permission from Briosa e Gala et al.*[256]

After completing the SL-ECG recordings with both devices, participation in the study was completed; no follow-up visits were required. All SL-ECG recordings from the wearable devices were stored in their respective smartphone app and subsequently exported in PDF format and anonymised for adjudication. The 12-lead ECGs were automatically exported in PDF format to the participant's electronic patient records.

5.4.4 ECG adjudication and Statistical analysis

Two independent cardiologists (A.B.G. and A.S.) adjudicated all ECG recordings, by assigning a rhythm diagnosis which included the following options: AF, sinus rhythm, atrial flutter/AT, ectopy, heart block, junctional rhythm or ventricular tachycardia. All adjudicators were blinded to participants' data. The principal investigator (T.R.B.) resolved any disagreements.

The Apple Watch and CART Ring classified SL-ECG recordings as follows: "AF", "Not AF" (sinus rhythm by the Apple Watch), and "Unclassified". The unclassified SL-ECGs are further labelled by the Apple Watch into four sub-categories: (1) "Poor recording", (2) "Heart rate over 120 beats per minute", (3) "Heart rate below 50 beats per minute", and (4) "Inconclusive".

Adjudicators were also required to rate the SL-ECGs quality on a three-point scale: 1 (high quality, confident diagnosis with minimal artefact), 2 (intermediate quality, probable diagnosis despite artefact), and 3 (uninterpretable, poor quality).

Automated AF detection algorithms were evaluated against the 12-lead ECG (reference standard). The algorithm performance was evaluated using two analytic approaches to account for the impact of unclassified SL-ECGs on the diagnostic metrics. The first, termed the 'worst-case' scenario analysis, reflects a real-world scenario where unclassified ECGs cannot be interpreted. In this approach, unclassified SL-ECGs by the wearable devices were categorised as FP detections if the corresponding 12-lead ECG did not show AF.

Conversely, if the 12-lead ECG confirmed AF, it was labelled as a FN episode. This analysis was designed to provide a lower-bound estimate of the automated AF detection algorithm performance. The second approach, 'lenient analysis', reflects ideal testing conditions, as often used in validation studies, and excluded all unclassified SL-ECGs.

A separate analysis for atrial arrhythmias was performed by grouping AF, atrial flutter, and AT as a single entity for both algorithm detection and physician interpretation. For this analysis, correct detection meant that the automated algorithm and physician interpretation of SL-ECGs identified an atrial arrhythmia. This approach acknowledges the clinical significance of detecting any form of atrial arrhythmia, even if the subtype was misclassified. Finally, I investigated the diagnostic performance of physician interpretation of SL-ECGs for all other cardiac rhythms, reflecting a common clinical scenario where physicians are asked to interpret SL-ECGs for a rhythm diagnosis.

The diagnostic performance metrics for each device were assessed in four domains: sensitivity, specificity, PPV and NPV.

SL-ECGs generated by the study devices were exported in PDF format, with timestamps used to subsequently match them with their corresponding 12-lead ECG.

All statistical analyses were performed using R (version 4.1.3) software. The Cohen's kappa coefficient was used to assess the level of interobserver agreement, and values greater than 0.80 are, by convention, considered excellent interobserver agreement. The Shapiro–Wilk test was used to first assess the distribution of the data. Means and standard deviations summarised data with Gaussian distributions, whilst non-normally distributed variables were reported using medians and interquartile ranges. Categorical data was summarised with frequencies and percentages.

For comparisons involving paired categorical data, such as when comparing metrics between study devices, McNemar's test was employed. For subgroup analyses with small sample size or frequency, Fisher's exact test was used instead. Finally, all statistical tests were two-tailed, and a p-value <0.05 was considered statistically significant. All plots and figures were generated in R using the ggplot2 package.

5.5 Results

Over a 12-month period from December 2021 to December 2022, 508 participants with cardiovascular diseases were recruited across three centres. Ten participants were excluded due to suboptimal 12-lead ECG recordings and a further 15 participants had evidence of ventricular pacing. The final study cohort comprised of 483 participants and 2,398 ECGs. Median age of participants was 66 years (IQR, 57-75) and 29% were female.

History of AF was recorded in 60.8% of participants and 11.8% had a history of atrial flutter or AT. Ninety-seven percent were Caucasian and the 12-lead ECG presenting rhythm was AF in 194 (40%) of participants. Participants with AF were older (67 vs 65, p = 0.041) and had higher rates of other co-morbidities, such as ischaemic heart disease, congestive heart failure and stroke. The cohort with AF had also significantly higher rates of anticoagulants and antiarrhythmic drugs.

Detailed baseline characteristics of participants are presented in Table 5-1.

The level of agreement between adjudicators was 91.7% for Apple Watch and 89.7% for CART Ring SL-ECG interpretations. Interobserver variability was excellent: Cohen's kappa values of 0.85 for the Apple Watch and 0.84 for the CART Ring.

There was no statistically significant difference (p = 0.70) between the diagnostic quality of SL-ECGs, with 78.1% and 79.3% of recordings graded as of high diagnostic quality (Table 5-2). The

CART Ring generated a higher number of SL-ECGs deemed uninterpretable by the adjudicators when compared to the Apple Watch (3.8% vs 1.6%, respectively).

Table 5-1. *Baseline characteristics and demographics for the final cohort and according to the presenting rhythm on the 12-lead ECG (AF vs non-AF rhythms). Reproduced with permission from Briosa e Gala et al.*[256]

Characteristics	Total (N=483)	AF (N=194)	Not AF (N=288)	p-value
Age, median (Q1-Q3)	66 (57—75)	67 (60—74)	65 (54—75)	0.041
Female sex, no (%)	139 (29%)	57 (29%)	57 (29%)	0.9
BMI, median (Q1-Q3)	27.8 (24.9—32.5)	28.9 (25.7—32.9)	27.5 (24.5—31.6)	0.06
Ethnicity, n (%)				
Caucasian	469 (97%)	192 (98%)	277 (96%)	0.6
Co-morbidities, n (%)				
Ischaemic Heart Disease	113 (22.6%)	20 (10%)	88 (31%)	<0.001
Myocardial Infarction	68 (13.7%)	12 (6.2%)	55(19%)	<0.001
Atrial Fibrillation	292 (60.8%)	182 (93%)	110 (38%)	<0.001
Atrial Tachycardia/Flutter	59 (11.8%)	22 (11%)	37 (12%)	0.9
Congestive Cardiac Failure	101 (21%)	53 (27%)	48 (17%)	0.008
Hypertension	153 (32%)	69 (35%)	84(29%)	0.2
Valvular Heart Disease	86 (18%)	46 (24%)	40 (14%)	0.009
Cardiac Surgery	50 (10%)	22 (11%)	28 (9.7%)	0.7
Stroke/TIA	29 (6.0%)	20 (10%)	9 (3.1%)	0.02
Diabetes Mellitus	34 (7.0%)	16 (8.2%)	18 (6.3%)	0.5
Anticoagulation, n (%)				
DOACS	250 (51.7%)	110 (36%)	140 (49%)	<0.001
Warfarin	20 (4.0%)	12 (6.2%)	8 (2.6%)	0.07
Rate control drugs, n (%)				0.006
Beta-blocker	245 (50.7%)	140 (72%)	105 (36%)	
Calcium-channel blocker	20 (4.0%)	12 (6.2%)	8 (2.6%)	
Digoxin	12 (2.8%)	6 (3.1%)	6 (2.2%)	
Antiarrhythmic drugs, n (%)				0.016
Amiodarone	42 (8.7%)	21 (7.3%)	21 (11%)	
Dronedarone	2 (0.4%)	—	2 (0.7%)	
Flecainide	23 (4.8%)	4 (2.1%)	19 (9.8%)	
Propafenone	2 (0.4%)	1 (0.5%)	1 (0.3%)	
Sotalol	19 (3.9%)	12 (6.2%)	7 (2.4%)	

AF, atrial fibrillation. **BMI**, body mass index. **DOACS**, direct oral anticoagulants. **ECG**, electrocardiogram. **TIA**, transient ischaemic attack.

Table 5-2. *Distribution of the diagnostic quality of Apple Watch and CART Ring SL-ECGs rated by both adjudicators. Reproduced with permission from Briosa e Gala et al.*[256]

	Apple Watch (n=483)	CART Ring (n=483)	P-value
High	381 (78.1%)	386(79.3%)	0.70
Intermediate	89 (20.3%)	78 (16.9%)	0.19
Uninterpretable	7 (1.6%)	17 (3.8%)	0.04

5.5.1 Diagnostic Performance for AF Detection

The automated AF detection algorithms demonstrated important differences in their performance as depicted in Table 5-3 and Figure 5-2. In the 'worst-case' analysis, which included all SL-ECGs, the Apple Watch had 69.1% sensitivity (95% CI: 62.3–75.2) and 72.6% specificity (95% CI: 67.1–77.4). The CART Ring had better performance for AF detection with a sensitivity of 84.6% (95% CI: 78.9–89.0) and specificity of 89.9% (95% CI: 85.9–92.9), both statistically significant (p <0.01).

Table 5-3. *Diagnostic performance of the AF detection algorithm and physician-interpretation of SL-ECGs for AF using the 12-lead ECG as gold standard*. *Adapted with permission from Briosa e Gala et al.*[256]

Device	AF detection	N	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Apple Watch	Algorithm (Worst-case)	483	69.1% (62.3-75.2)	72.6% (67.1-77.4)	62.9% (56.2-69.1)	77.7% (72.4-82.3)
	Algorithm (Lenient)	386	84.8% (78.4-89.6)	91.7% (87.4-94.6)	87.6% (81.4-91.9)	89.7% (85.1-93.0)
	Physician (all ECGs)	483	95.4 (91.4-97.5)	89.6% (85.6-92.6)	86.0% (80.8-90.0)	96.6% (93.7-98.2)
CART Ring	Algorithm (Worst-case)	483	84.6% (78.9-89.0)	89.9% (85.9-92.9)	85.1% (79.4-89.4)	89.6% (85.6-92.6)
	Algorithm (Lenient)	474	86.4% (80.8-90.5)	91.2% (87.3-93.9)	86.8% (81.3-90.9)	90.8% (86.9-93.7)
	Physician (all ECG)	483	94.3% (90.1-96.8)	88.9% (84.8-92.0)	85.1% (79.7-89.3)	95.9% (92.8-97.7)

AF*, atrial fibrillation.* ***CI****, confidence intervals.* ***ECG****, electrocardiogram.* ***NPV****, negative predictive value.* ***PPV****, positive predictive value.* ***SL-ECG****, single-lead electrocardiogram.*

Both devices showed improvement in the performance of the automated AF detection in the lenient analysis, with the exclusion of unclassified SL-ECGs (97 in the Watch group and 9 in the Ring group). The Apple Watch showed an increase in sensitivity by 15.1% and in specificity by 19.1% compared to the 'worst-case' analysis. However, there was no significant difference in sensitivity between the two devices (84.8% vs. 86.4%) in the lenient analysis. FP AF detections in the Apple Watch group were largely due to atrial flutter/AT (62.5%) and sinus rhythm (31.3%). CART Ring showed a similar pattern, with atrial flutter/AT accounting for 60% and sinus rhythm with ectopy for 13.3%. (Appendix D, Table S5-1).

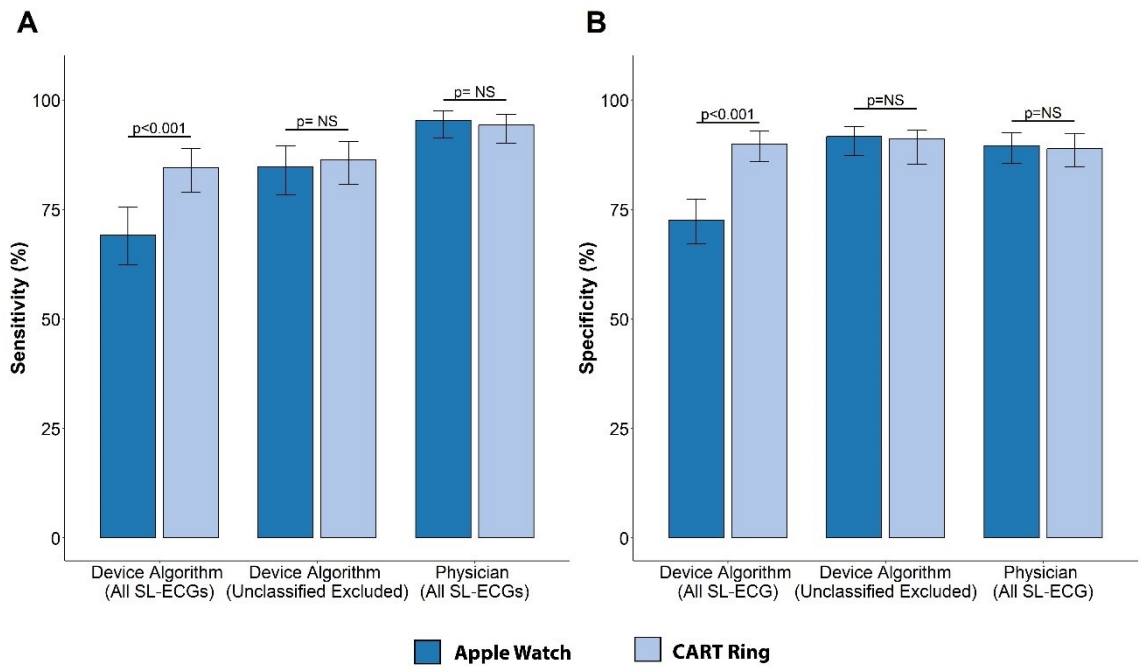

Figure 5-2. *Diagnostic performance of the Apple Watch and CART Ring for AF detection compared to a 12-lead ECG.* ***(A)*** *presents sensitivity, and* ***(B)*** *depicts specificity, across three categories: the worst-case scenario analysis (including all SL-ECGs), the lenient analysis (excluding unclassified ECGs), and physician interpretation of SL-ECGs. Reproduced with permission from Briosa e Gala et al.*[256]

Physician interpretation of SL-ECGs improved AF detection across both devices. Interpretation of SL-ECGs from the Apple Watch demonstrated slightly higher sensitivity of 95.4% (95% CI: 91.4–97.5) compared to the CART Ring [94.3% (95% CI: 90.1–96.8)], but the specificity of the Apple Watch (89.6% [95% CI: 85.6–92.6]) closely matched that of the CART Ring (88.9% [95% CI: 84.8–92.0]).

5.5.2 Unclassified ECGs

The Apple Watch had 20.1% (97) unclassified SL-ECGs compared to only 1.9% (9) of those recorded by the CART Ring (Table 5-4). In the Apple Watch, 62% were classified as "Inconclusive", with 72% of these showing either AF or sinus rhythm in the corresponding 12-lead ECG. Twenty-four per cent of unclassified SL-ECGs resulted from heart rates out of diagnostic range (<50 bpm or >120 bpm) and the remainder were due to "poor recordings".

The CART Ring had considerably lower number (9) of unclassified SL-ECGs, with poor quality recordings found largely in AF (44%) and sinus rhythm (33%) tracings. Physician interpretation correctly identified the rhythm on 76.2% (74) of unclassified Apple Watch and 66.7% (6) of unclassified CART Ring SL-ECGs.

Table 5-4. *Classification of unclassified SL-ECGs from the Apple Watch and CART Ring compared to corresponding rhythms identified on 12-lead electrocardiogram. Reproduced with permission from Briosa e Gala et al.*[256]

12- Lead ECG	Apple Watch				CART Ring
	HR < 50 bpm (N=16)	HR > 120 bpm (N=8)	Inconclusive (N=61)	Poor recording (N=12)	Poor Recording (N=9)
Atrial fibrillation	1 (6.2%)	3 (38%)	28 (45%)	5 (42%)	4 (44%)
Sinus rhythm	9 (56%)	1 (12%)	16 (27%)	6 (50%)	3 (33%)
Atrial Flutter/AT	1 (6.2%)	4 (50%)	11 (18%)	—	2 (22%)
Sinus rhythm with ectopy	1 (6.2%)	—	4 (6.7%)	1 (8.3%)	—
AF with complete heart block	—	—	—	—	—
Complete heart block	3 (19%)	—	1 (1.7%)	—	—
Ventricular tachycardia	—	—	1 (1.7%)	—	—
Junctional rhythm	—	—	—	—	—

AT*, atrial tachycardia.* ***Bpm****, beats per minutes.* ***ECG****, electrocardiogram.* ***CHB,*** *complete heart block.*

5.5.3 Diagnostic Performance for Atrial Arrhythmias

Of 242 participants with SL-ECGs showing atrial arrhythmias, 194 had AF and 48 had atrial flutter/AT. In the 'worst-case' scenario analysis for atrial arrhythmias, the CART Ring exhibited superior sensitivity of 77.2% (95% CI: 69.5-80.3) compared to 59.3% (95% CI: 53.0–65.2) for the

Apple Watch (Figure 5-3, Appendix D Table S5-1). This trend mirrors the CART Ring's advantage observed in automated AF detection.

The diagnostic performance of automatic detection for atrial arrhythmias was lower than for AF as the algorithm is designed to detect an irregularly irregular rhythm and atrial tachycardia can be regular or have limited irregularity. When unclassified SL-ECGs were excluded (lenient analysis), it resulted in a marked increase in sensitivity of the Apple Watch to 75.8% (95% CI: 69.2-81.3) and specificity to 96.9% (95% CI: 93.5-98.6) making it comparable to the CART Ring. Physician interpretation of SL-ECGs, once again, improved diagnostic performance considerably for both the Apple Watch and CART Ring, with sensitivities of 96.2% and 90.8%, respectively.

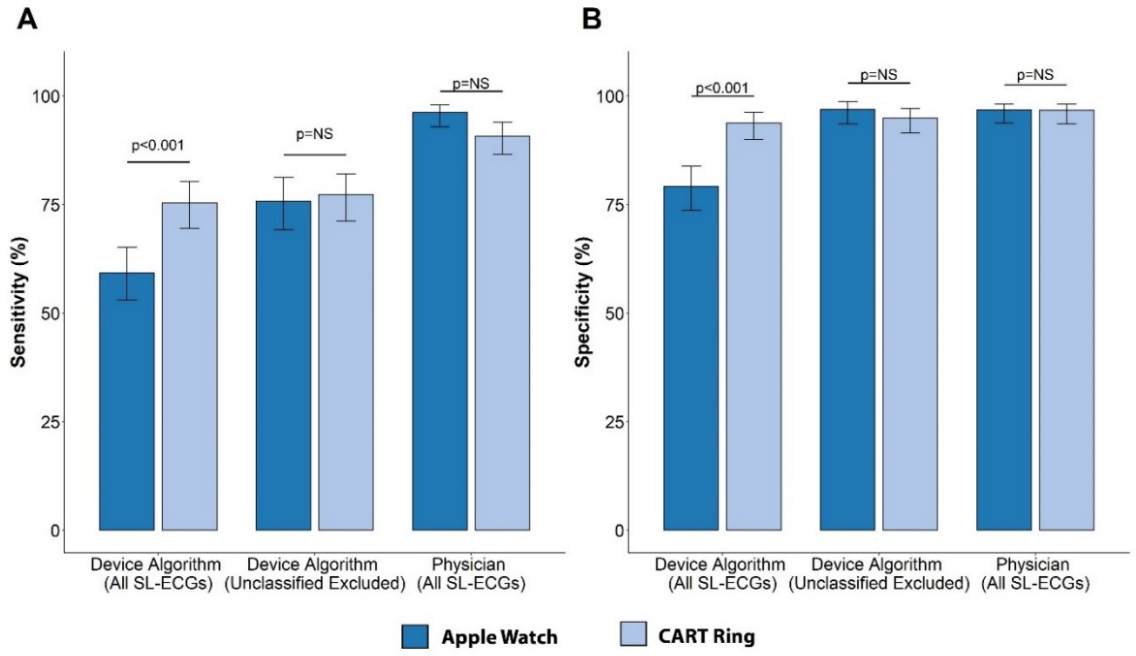

Figure 5-3. *Diagnostic performance of the Apple Watch and CART Ring for atrial arrhythmias compared to a 12-lead ECG.* ***A)*** *shows sensitivity, and* ***(B)*** *shows specificity in three analytic categories: the worst-case scenario analysis (including all SL-ECGs), the lenient analysis (excluding unclassified ECGs), and physician interpretation of SL-ECGs*. *Reproduced with permission from Briosa e Gala et al.*[256]

Of the 48 atrial flutter/AT ECGs, 24 had variable AV nodal conduction with an irregular ventricular rate. The Apple Watch identified 9 (38%) as AF compared to 13 (54%) using the CART Ring. In AT with regular ventricular rates, the Apple Watch classified only 1 (4.2%) as AF, 11 (46%) as unclassified, and 12 (50%) as sinus rhythm. In contrast, the CART Ring categorised 19 (79%) atrial flutter/AT with regular rate as sinus rhythm.

5.5.4 Physician Interpretation for Other Cardiac Rhythms

Figure 5-4 summarises the results of physician interpretation of SL-ECGs, depicting the distribution of true positives, FP, and FN across all cardiac rhythms.

A

Physician Interpretation Apple Watch SL-ECG	12-Lead ECGs: AF (n=194)	AT/Flutter (n=48)	Sinus rhythm (n=214)	Sinus rhythm & ectopy (n=17)	AF CHB (n=2)	CHB (n=5)	VT (n=1)	Junctional rhythm (n=1)
AF	**185 (95.4%)**	24 (50%)	5 (2.4%)	1 (5.8%)	–	–	–	–
AT/Flutter		**18 (37.5%)**	2 (0.9%)		–	–	–	–
Sinus rhythm	1 (0.5%)	6 (12.5%)	**197 (92.1%)**	6 (35.4%)	1 (50%)	4 (80%)	–	–
Sinus rhythm & ectopy	2 (1%)	–	9 (4.2%)	**10 (58.8%)**	–	–	–	1 (100%)
AF CHB	–	–	–	–	**1 (50%)**	–	–	–
CHB	–	–	–	–	–	**1 (20%)**	–	–
VT	–	–	–	–	–	–	–	–
Junctional rhythm	–	–	–	–	–	–	–	–
Uninterpretable	5 (2.6%)	–	1 (0.5%)	–	–	–	1 (100%)	–

B

Physician Interpretation CART ring SL-ECG	12-Lead ECGs: AF (n=194)	AT/Flutter (n=48)	Sinus rhythm (n=213)	Sinus rhythm & ectopy (n=17)	AF CHB (n=2)	CHB (n=5)	VT (n=1)	Junctional rhythm (n=1)
AF	**183 (94.3%)**	26 (54.2%)	5 (2.3%)	1 (5.9%)	–	–	–	–
AT/Flutter	–	**11 (22.9%)**	1 (0.5%)	–	–	–	1 (100%)	–
Sinus rhythm	1 (0.5%)	6 (12.5%)	**186 (87.3%)**	7 (41.2%)	2 (100%)	4 (80%)	–	1 (100%)
Sinus rhythm & ectopy	3 (1.5%)	4 (8.3%)	11 (5.2%)	**9 (52.9%)**	–	1 (20%)	–	–
AF CHB	–	–	–	–	–	–	–	–
CHB	–	–	–	–	–	–	–	–
VT	–	–	–	–	–	–	–	–
Junctional rhythm	–	–	–	–	–	–	–	–
Uninterpretable	7 (3.6%)	1 (2.1%)	9 (4.2%)	–	–	–	–	–

Figure 5-4. *Physician interpretation of SL-ECGs from the Apple Watch* ***(A)*** *and CART Ring* ***(B)*** *compared to rhythms identified on 12-lead ECGs. AF, atrial fibrillation. AT, atrial tachycardia. CHB, complete heart block. VT, ventricular tachycardia. Reproduced with permission from Briosa e Gala et al.*[256]

Sensitivity for sinus rhythm was excellent: 91.6% (95% CI: 88.1–95.1) for the Apple Watch and 92.1% (95% CI: 88.7–95.5) for the CART Ring. However, other arrhythmias, such as atrial flutter and ventricular ectopy, were frequently misclassified, leading to an overall poor diagnostic performance for non-AF arrhythmias. The CART Ring had double the number of SL-ECGs classified as uninterpretable by the adjudicators compared to the Apple Watch (19 [3.8%] vs. 9 [1.8%]; p= 0.085). The performance metrics for physician interpretation of all cardiac rhythm can be found in Appendix D, Table S5-2.

5.5.5 Impact of SL-ECG quality

The diagnostic quality of SL-ECG recordings had a significant impact on automated rhythm detection and physician interpretation (Figure 5-5).

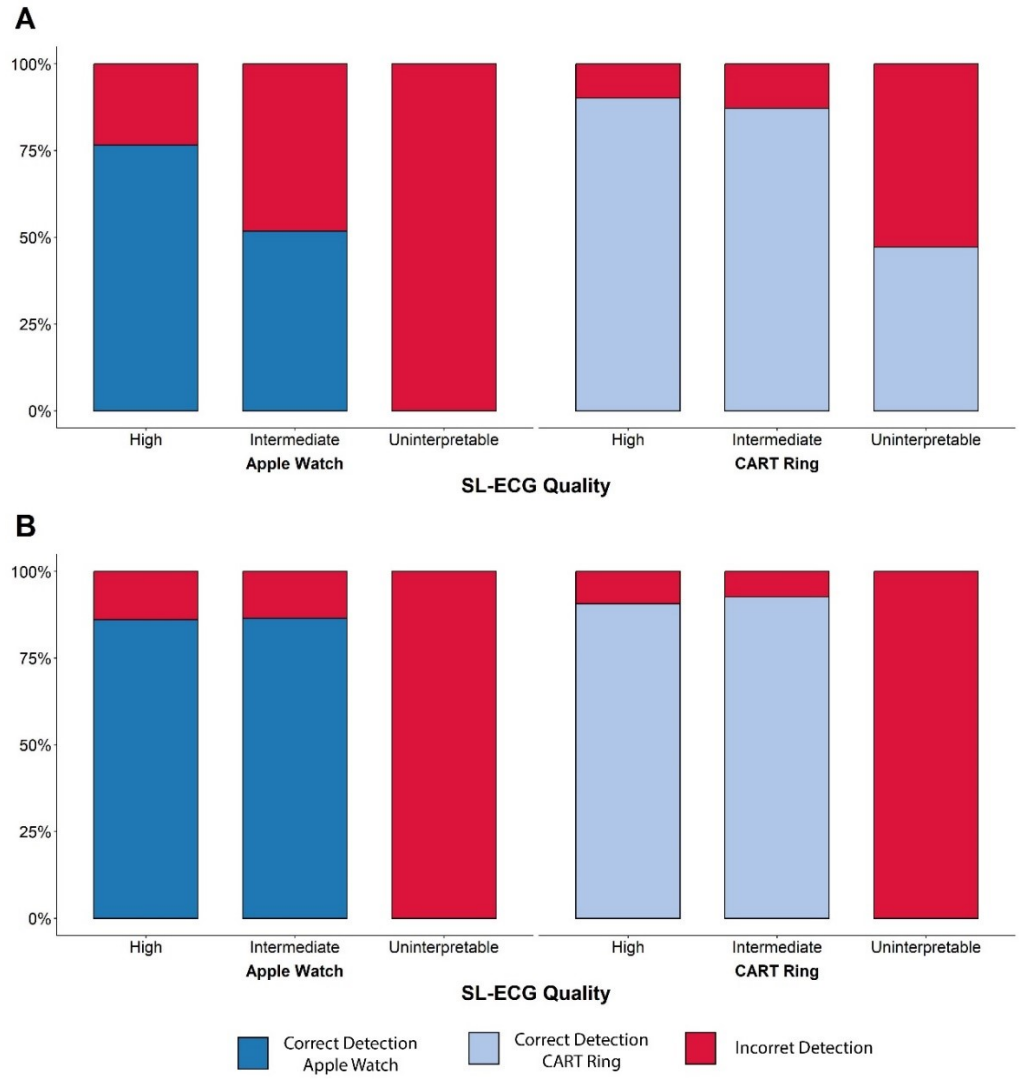

Figure 5-5. *Percentage of correct rhythm identification of SL-ECGs from the Apple Watch and CART Ring, stratified by diagnostic SL-ECGs quality rated by the adjudicators (high, intermediate, uninterpretable).*

(A) *Automated device detection for "AF" vs "Not AF" (all SL-ECGs included), and* ***(B)*** *depicts physician interpretation accuracy encompassing all cardiac rhythms (all SL-ECGs included). Reproduced with permission from Briosa e Gala et al.*[256]

For high-quality SL-ECGs, the CART Ring automated detection was superior to the Apple Watch (90.1% vs 76.1%, p <0.001). With intermediate-quality SL-ECGs, the Apple Watch's accuracy declined substantially to 49.5%, whilst the CART Ring only dropped by 3.5% with an overall accuracy of 86.6% (p<0.001). Interestingly, a higher proportion of unclassified SL-ECGs from the Apple Watch were graded as of high quality compared to the CART Ring (55% vs 33%, respectively).

Physician interpretation for all cardiac rhythms was robust for both devices, with correct rhythm diagnosis in over 80% of cases and only modest reduction between high- and intermediate-quality recordings (Appendix D, Table S5-3).

5.6 Discussion

This large multicentre study offers valuable insights into the diagnostic performance of the Apple Watch and CART Ring in a 'real-world' cohort of participants with a broad range of cardiac rhythms. Important diagnostic metrics for automated AF detection, such as sensitivity and specificity, were lower than previously reported. The Apple Watch missed one in three patients who were in AF under the 'worst-case' analysis. In contrast, the CART Ring outperformed the Apple Watch by demonstrating greater diagnostic reliability for automated AF detection. Nonetheless, its diagnostic performance was lower than that reported in its clinical validation study.[270]

The key strengths of this study include the broad range of arrhythmias, simultaneous wearable device testing against a 12-lead ECG, restricting the number of SL-ECG attempts, and creating a rigorous and clinically relevant testing environment.

Several clinical validation studies of wearable devices have employed methodologies that may artificially increase their diagnostic performance by offering participants very favourable testing conditions.[268,266,267] Some examples include only testing for AF or sinus rhythm, excluding unclassified ECGs from their analysis, and not reporting the number of SL-ECG attempts permitted.[77,78] Interestingly, Racine *et al.* followed a similar methodology to the WEAR-TECH ECGs study by including patients with cardiac rhythms beyond AF and sinus rhythm.[298] This single centre study included 729 patients showed an overall sensitivity of 69% for the Apple Watch Series 5.

Cardiologist interpretation of SL-ECGs showing AF and sinus rhythm was excellent across both devices. These results are consistent with previous studies highlighting the superiority of Cardiologist assessment over automated AF algorithms.[75] Therefore, the WEAR-TECH findings further reinforce the 2020 European Society of Cardiology AF guidelines, which, for the first time, recognised physician-interpreted SL-ECGs from wearable devices as diagnostic of AF.[22]

However, despite a large proportion of high-quality SL-ECGs, physician interpretation of non-AF rhythms was challenging. The heavily filtered nature of SL-ECGs often obscures key electrocardiographic features such as P-waves, whose presence and timing relative to the QRS is essential for correct ECG interpretation. As a result, both adjudicators found it difficult to accurately diagnose other atrial arrhythmias and heart blocks. In contrast, atrial and ventricular ectopy were generally easier to identify, as their detection primarily relies on QRS timing and morphology. While case reports have shown the potential usefulness of SL-ECGs from wearable devices in the detection of other cardiac rhythms, these findings underscore the need for caution when interpreting SL-ECGs which should ideally be corroborated by a 12-lead ECG.[299, 300]

An important finding was the high rate of unclassified (20.1%) Apple Watch SL-ECGs, consistent with previous studies that reported rates between 19% and 28%.[269,298] A recent study involving 247 participants and testing 5 smartwatches found that, despite several software updates and increased user familiarity, the reduction in inconclusive SL-ECGs over a 2-year period was only modest.[247] Moreover, Pepplinkhuizen *et al.* demonstrated that repeating further device recordings following an unclassified SL-ECG generated by the Apple Watch reduced the overall number of unclassified readings; however, this came at the cost of lower accuracy and an increase in FP detections.[301]

In contrast, the CART Ring demonstrated a significantly lower rate (1.8%) of unclassified SL-ECGs. Despite excluding far fewer SL-ECGs, there was no statistically significant difference in the rates of FP detections between the Watch and the Ring in the lenient analysis (Figure 5-3). Interestingly, among the 97 SL-ECGs unclassified by the Apple Watch, the CART Ring automated algorithm correctly identified the rhythm in 72% of cases. This improved performance may be attributed to the superior signal quality from its sensors, which record from the finger rather than the wrist. Moreover, the CART Ring does not analyse the SL-ECG traces on the device. Instead, it transmits the collected data to the cloud for analysis with the outcome subsequently uploaded to the smartphone.[270] Therefore, it avoids the physical constraints that a small device might have on processing power and leverages machine learning to improve its algorithm.

Automated AF detection algorithms rely primarily on heart rate variability to detect an irregular rhythm; hence, fast or slow heart rates or the presence of ectopy, lead to both FN and FP detections. This extends beyond AF, with poor automated detection observed for all atrial arrhythmias, which is particularly evident for regular atrial arrhythmias. Physician interpretation of atrial flutter/AT demonstrated poor sensitivity across both devices: 37.5% (95% CI, 25.2–51.6) for the Apple Watch and 22.9% (95% CI, 13.3–36.5) for the CART Ring, which has important implications for the clinical use of wearable devices in AF management.

When considering wearable devices for rhythm monitoring, there are three common clinical scenarios: general arrhythmia detection, post-AF ablation, and rhythm-guided anticoagulation. Each scenario has its own challenges with important trade-offs between diagnostic performance and convenience and accessibility which must be weighed.

Freedom from atrial arrhythmias is the key outcome measure following catheter ablation, and wearable devices are increasingly leveraged to monitor for arrhythmia recurrence and assess ablation success.[302,303] The inability to accurately detect atrial flutter or AT further undermines the utility of wearables in monitoring treatment success. Additionally, recurrence of atrial arrhythmias often informs subsequent catheter ablation strategies, making accurate differentiation between AF and other atrial arrhythmias critical for procedure planning, including choices of electro-anatomical mapping and ablation technologies.[302,304,305]

These observations have direct implications for a 'pill-in-the-pocket' OAC strategy. As discussed in Chapter 3, for wearable devices to be used to inform changes in OAC strategy, either initiation or discontinuation, they must have a high level of diagnostic accuracy.[254] The current generation of devices tested in a controlled environment setting under physician supervision was suboptimal: the Apple Watch missed approximately one in three AF episodes, and the CART Ring missed one in seven. Given that AT/Flutter are common in AF patients with rates of up to 20% of patients, and carry a similar thromboembolic risk, under-detection is also problematic.[306,307]

The 'pill-in-the-pocket' OAC strategy lends itself well to patients that have undergone catheter ablation as freedom from atrial arrhythmia in PAF patients is approximately 80%.[193,308] However, post-ablation atypical flutters are common and therefore are an important barrier to the safe implementation of this strategy in this cohort using spot-check SL-ECGs to confirm the presence of an atrial arrhythmia that would warrant OAC.[309] It is premature to rely on automated detection but hybrid models that combine AF notifications from PPG in ambulatory patients followed by a SL-ECG which is, at a later stage, interpreted by a physician may offer a safe and scalable solution.

The SMART-ALERT study in Chapter 6 moves beyond AF detection with 30-second SL-ECGs and evaluates whether real-time AF notifications from wearable devices compared to ICMs in ambulatory patients are a viable option to offer rhythm-guided OAC decisions.[257]

5.6.1 Limitations

The WEAR-TECH ECG study had several limitations. First, the study cohort included older adults with cardiovascular disease, limiting the generalisability of findings to younger individuals who increasingly use wearable devices. Second, the higher prevalence of atrial arrhythmias within our study cohort had an impact on performance metrics, such as PPV and NPV; these should be interpreted with caution. Third, the study deliberately limited the number of SL-ECGs to two per device for each patient which may have led to a higher number of unclassified ECGs. However, our unclassified rates are in keeping with prior studies without these restrictions. This scenario provides a more realistic and practical assessment of real-world usability of wearable devices.

Fourth, I should underscore that the SL-ECGs were recorded under physician supervision, which likely led to better technique and resulted in high-quality SL-ECG traces. Outside rigorous testing conditions, during routine use there may be a greater variability in the signal quality, potentially leading to a higher rate of unclassified ECGs than reported. Finally, the adjudication was performed by two cardiologists which strengthens the validation; however, it also introduces the potential for human error despite the high interobserver agreement reported**.**

5.7 Conclusion

The CART Ring outperformed the Apple Watch in automated AF detection, showing a higher sensitivity for AF detection (84.6% vs. 69.1%, respectively). Whilst physician interpretation significantly improved diagnostic accuracy for both AF and sinus rhythm, performance for non-AF arrhythmias was suboptimal for both wearable devices.

This study evaluated automated AF detection from 30-second SL-ECGs in an optimal testing environment, but the diagnostic performance fell short. The Apple Watch missed approximately 1 in 3 AF episodes and the CART Ring 1 in 7 — inadequate for a 'pill-in-the-pocket' OAC strategy which requires high diagnostic certainty. Therefore, the combination of modest AF and poor AT/atrial flutter detection suggest that these wearable devices cannot be used in isolation to inform OAC decisions.

More broadly, this chapter highlights the importance of validating wearable technologies, not only from a technical perspective, but also in the clinical context in which they are intended to be

used. A hybrid model combining automated detection with physician interpretation may offer a compromise to balance accessibility with improved diagnostic accuracy.

The results presented in this chapter form a technical rationale for the SMART-ALERT study (Chapter 6), which goes beyond the SL-ECGs' performance by evaluating the feasibility of real-time AF notifications compared to ICMs in ambulatory patients, potentially offering a more clinically viable pathway for incorporating wearable technology into rhythm-guided OAC decisions.

6 SMART-ALERT Study

6.1. Publication and Abstracts

6.1.1 Publications

Briosa e Gala A, Sharp AJ, Schramm D, Ries W, Pope MTB, Leo M, Paisey J, Curzen N, Banerjee A, Betts TR. *"Real-time Smartphone Alerts During Atrial Fibrillation Episodes with Implantable Cardiac Monitors and Wearable Devices: SMART-ALERT study."* **Heart Rhythm.** 2025 Apr 15:S1547-5271(25)02331-8.

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HeartRhythm

The Official Journal of the Heart Rhythm Society, The Cardiac Electrophysiology Society, and The Pediatric & Congenital Electrophysiology Society

Heart Rhythm Society SM

Real-time *smart*phone *alert*s during atrial fibrillation episodes with implantable cardiac monitors and wearable devices: SMART-ALERT study

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ABSTRACT

BACKGROUND Atrial fibrillation (AF) is a major cause of stroke, with dynamic thromboembolic risk during and shortly after episodes. Implantable cardiac monitors and wearable devices have emerged as tools for real-time AF detection, yet their comparative performance in supporting anticoagulation strategies remains underexplored.

OBJECTIVE This single-center feasibility study investigated the performance of real-time AF detection and notification for episodes lasting longer than 30 minutes.

METHODS Phase 1 evaluated the integration of an implantable cardiac monitor and bespoke cloud-based software (SMART-ALERT) in sending automated short message service notifications (n = 50) for episodes uploaded within 24 hours. Phase 2 evaluated the Apple Watch (n = 23) and the CART Ring (n = 23) detecting and notifying participants of AF episodes. The primary outcome was the successful AF notification rates via (1) SMART-ALERT software and (2) wearable devices. Secondary outcomes included acknowledgment rates, notification times, and adherence.

RESULT Among 4943 AF episodes detected in 31 participants, the SMART-ALERT software successfully notified 511 of 691 eligible AF episodes (74%), with a 99.6% acknowledgment. In contrast, wearable devices showed poor notification performance: the Apple Watch identified 76 of 389 episodes (19.5%); and the CART Ring, 72 of 474 (15.1%). This performance difference was partly explained by suboptimal device adherence (Apple Watch: 66.3%; CART Ring: 23.9%), with 24.6% and 55.7% of AF episodes missed because of devices not being worn.

CONCLUSION The SMART-ALERT system demonstrated the feasibility of real-time AF detection and automated notifications, achieving a 74% notification success but facing important connectivity challenges. Wearable devices showed poor notification rates (<20%) and adherence, highlighting significant technical barriers to their current use in clinical AF monitoring.

KEYWORDS Apple Watch; Atrial fibrillation; CART Ring; Wearable devices; Anticoagulation

(Heart Rhythm 2025;■:1–11)

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting millions worldwide and associated with a 5-fold increase in stroke risk.[1,2] Lifelong oral anticoagulation (OAC) is the cornerstone of AF management, reducing stroke risk by two-thirds but at the expense of 5% annual risk of major bleeding. Bleeding complications often affect anticoagulation adherence and lead to a decline in quality of life.[3–5] Current international guidelines recommend risk scores, such as the CHA_2DS_2-VASc score, to guide anticoagulation

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1547-5271/$-see front matter

6.1.2 Abstracts

Briosa e Gala A, Sharp AJ, Schramm D, Ries W, Pope MTB, Leo M, Paisey J, Curzen N, Banerjee A, Betts TR. *"Automated Continuous Rhythm Monitoring with Implantable Cardiac Monitor and Real-time Smartphone Alerts During AF Episodes: SMART-ALERT study."* **Poster presentation, European Heart Rhythm Association Congress 2024.**

Briosa e Gala A, Sharp AJ, Schramm D, Ries W, Pope MTB, Leo M, Paisey J, Curzen N, Banerjee A, Betts TR. *"SMART-ALERT: Real-time Smartphone Alerts During AF Episodes with Implantable Cardiac Monitors and Wearable Devices."* **Oral presentation, European Heart Rhythm Association Congress 2025**

6.2 Abstract

Background: AF is a major cause of stroke, with new evidence suggesting a dynamic thromboembolic risk during and shortly after episodes. ICMs and wearable devices are increasingly used for AF detection, but their comparative performance and role in supporting 'pill-in-the-pocket' OAC strategies is under-investigated.

Objective: This single-centre feasibility study investigated the performance of real-time AF detection and notification for episodes >30 minutes of three devices: SMART-ALERT software integrated with an ICM, Apple Watch and CART Ring.

Methods: Phase 1 evaluated the integration of ICM and bespoke cloud-based software (SMART-ALERT) in sending automated SMS notifications (n=50) for episodes uploaded within 24 hours. Phase 2 evaluated an Apple Watch (n=23) and CART Ring (n=23) detecting and notifying participants of AF episodes. Primary outcome was the successful AF notification rate via (1) SMART-ALERT software and (2) wearable devices. Secondary outcomes included acknowledgement rates, notification times, and adherence.

Result: Among 4,943 AF episodes detected in 31 participants, the SMART-ALERT software successfully notified 511/691 eligible AF episodes (74%), with a 99.6% acknowledgment. In contrast, wearable devices showed poor notification performance: the Apple Watch identified 76/389 episodes (19.5%) and the CART Ring 72/474 (15.1%). This performance difference was partly explained by suboptimal device adherence (Apple Watch: 66.3%; CART Ring: 23.9%), with 24.6% and 55.7% of AF episodes missed due to devices not being worn.

Conclusion: The integration of the SMART-ALERT software with an ICM demonstrated feasibility of real-time AF detection and automated notifications, with 74% notification success rate but further work is required to improve connectivity challenges. In contrast, wearable devices showed poor notification rates (<20%) and adherence which hinders their adoption as AF monitoring tools.

6.3 Introduction

New evidence suggests that thromboembolic stroke risk is dynamic, increasing during and shortly after AF episodes and then decreasing during periods of sinus rhythm.[179,310] In patients with low stroke risk profiles, brief episodes of AF, lasting minutes to hours, are associated with lower thromboembolic event rates compared to prolonged AF episodes lasting days.[231] This observed temporal relationship between AF and thromboembolic events has driven interest in a 'pill-in-the-pocket' OAC strategy, which limits OAC only to periods of high thromboembolic risk. Patients would therefore take OAC only during an AF episode and for a brief period following restoration of sinus rhythm.

This novel approach could provide comparable stroke prevention to using continuous OAC whilst significantly reducing the time on OAC and, consequently, lowering bleeding risk and healthcare costs.[212] Early studies, such as REACT.COM and TACTIC-AF, demonstrated that this approach is feasible in carefully selected patients who had continuous rhythm monitoring with ICMs and cardiac implantable electronic devices.[68,199] However, as highlighted in the meta-analysis results in Chapter 3, such a strategy would require accurate, minimally- or non-invasive monitoring tools with good adherence and scalability.[254]

There are other important barriers to a 'pill-in-the-pocket' OAC strategy: the need for reliable real-time AF detection and prompt patient notifications.[254] Current minimally-invasive technologies have important limitations. ICMs offer both continuous monitoring and a high sensitivity for AF detection, but current workflow relies on manual adjudication of all episodes, which is resource intensive and limits their scalability. In contrast, wearable devices, such as smartwatches and rings, are relatively inexpensive near-continuous monitoring tools, but their AF detection and adherence is not well studied.

While both technologies are promising, their ability to support real-time AF detection and automated patient notifications is still uncertain, with limited data on their implementation in clinical settings.

The SMART-ALERT study evaluated two approaches for detecting and notifying patients of AF episodes >30 minutes duration: (1) an ICM integrated with a bespoke software (SMART-ALERT), and (2) two wearable devices (Apple Watch and CART Ring).

There is no consensus on the AF duration threshold that warrants OAC, with studies proposing cutoffs from 5 minutes to 24 hours due to an observed increase in thromboembolic risk.[167] While REACT.COM and Zuern et al used a 1-hour threshold, we selected 30 minutes as a pragmatic

balance, long enough to capture episodes for a robust evaluation of the study devices without generating excessive alerts from shorter, potentially less clinically relevant episodes that could compromise patient engagement.

6.4 Methods

Ethical approval and funding are described in detail in Chapter 2 (Methodology; Sections 2.2 Ethical Approval and Funding).

6.4.1 Study Design

This feasibility study was conducted in two distinct phases, each lasting three months (Figure 6-1). In Phase 1, all participants had a LINQ II ICM implanted and programmed to detect and store all AF episodes lasting longer than 30 minutes. Data from the ICMs were transmitted via Bluetooth® to the Medtronic MyCareLink smartphone app, which used an internet connection to transfer the episodes to their cloud-based remote monitoring platform (CareLink). This transmission occurred at least once an hour if the device was within range. Episodes could only be transmitted if the smartphone app was open and running in the background.

The bespoke SMART-ALERT software system monitored all transmissions in CareLink every five minutes for new AF episodes (Chapter 2 Methodology; Sections 2.4 Study Devices). If a new AF episode was uploaded, the software would automatically trigger an SMS notification to participants based on predefined criteria (Figure 6-2):

1. AF episode ≥30 minutes
2. First episode within a 24 hour-period
3. AF episode uploaded to CareLink within 24 hours of its onset (Figure 6-3).

Participants were instructed to acknowledge receipt of the SMS notifications by replying promptly to the research team's telephone number. The SMART-ALERT software recorded timestamps in its database for the date and time of AF episode detection, SMS sent, and participant reply.

Failure to upload an AF episode to CareLink occurred in the following circumstances: smartphone did not have an active Bluetooth connection or internet connection, the ICM was not in range, the smartphone app was closed, or the smartphone was turned off. AF episodes were stored in the ICM until all conditions were met for upload. Similarly, scheduled maintenance on the CareLink platform prevented the SMART-ALERT software from accessing participant data.

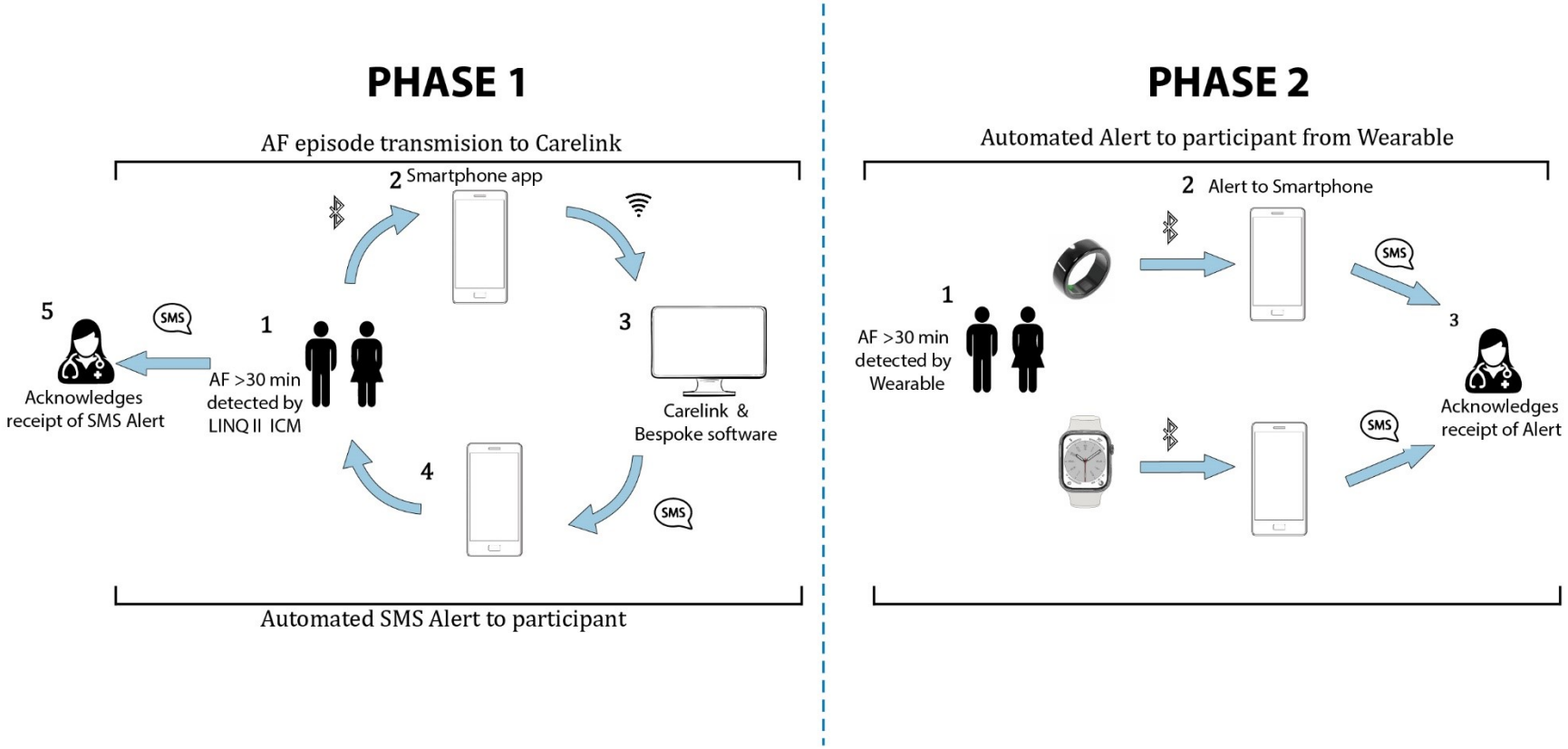

Figure 6-1. *SMART-ALERT study design. Reproduced with permission from Briosa e Gala et al.*[257]

To prevent excessive notifications, in case of multiple AF >30-minute episodes within the same 24 hour-period, only the first episode would lead to an automatic SMS notification to the study participant.

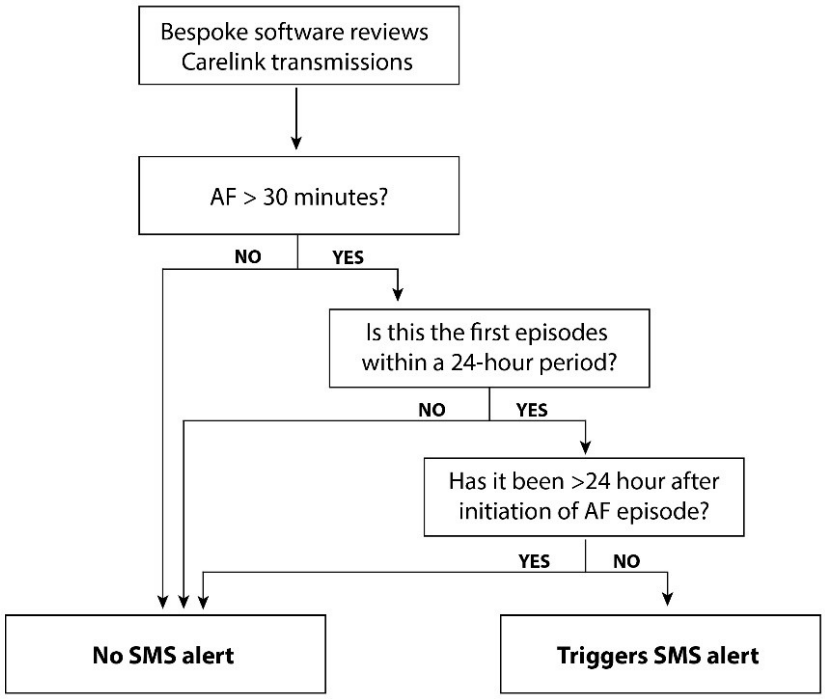

Figure 6-2. *SMART-ALERT software decision tree diagram used to generate automated SMS alerts during phase 1. Reproduced with permission from Briosa e Gala et al.*[257]

In Phase 2, participants continued to have the ICM implanted, but the SMART-ALERT software did not trigger SMS notifications. Instead, the ICM was used as the reference standard to investigate the AF detection performance of both wearable devices. Participants allocations depended upon their smartphone's operating system. The Apple Watch was allocated to those with an iOS device (iPhone) whilst the CART-Ring was compatible with both iOS and Android. Participants were encouraged by the research team to always wear their wearable device during Phase 2 of the study and enable Bluetooth® connection.

During this phase, the wearable devices detected AF and sent notifications directly to the participants' smartphone. Unlike Phase 1, there were no restrictions on the number of alerts per day that a participant could receive. Device settings were defined by the manufacturers and could not be changed by the research team.

The CART Ring's AF detection was set at 30 minutes, whilst the Apple Watch's detection criteria were less explicitly defined in Apple documentation (see Chapter 2). However, based on published data, the watch was expected to identify and notify users of AF episodes lasting at least 30 minutes in optimal conditions (patients at rest). As in Phase 1, participants were also asked to confirm receipt of these notifications by replying promptly to the study telephone number.

The SMART-ALERT study only evaluated monitoring technologies. No treatment decisions were made by the research team, but episode data were shared with their clinicians upon request. Moreover, all participants continued their standard of care medications, including OAC if this was indicated.

6.4.2 Study Devices

Study devices (LINQ II ICM, Apple Watch Series 7, and CART Ring) are comprehensively described in Chapter 2. This includes the implant procedure, AF detection metrics, and device settings for the LINQ II ICM, as well as AF notifications and wearable device performance and their settings.

6.4.3 Inclusion Criteria and Outcomes

The main inclusion criteria were adults (≥18 years old) with PAF who experienced frequent episodes, defined as at least one but fewer than 15 episodes per month, or persistent AF requiring recurrent cardioversions. This cohort was selected to ensure a sufficient number of AF episodes to evaluate the devices' detection and alerting performance. All participants were required to have an Apple iOS or Android smartphone compatible with the Medtronic MyCareLink app, which enabled communication with the LINQ II ICM. There were three main exclusion criteria: permanent AF, contraindications for an ICM, or visual or physical impairments that would prevent them from interacting with smartphone notifications

The primary outcome for Phase 1 was the performance of the SMART-ALERT software in sending automated real-time SMS notifications that met the study criteria, which was measured as the percentage of successful SMS notifications sent.

In Phase 2, the primary outcome was the performance of wearable device (Apple Watch and CART Ring) in detecting AF episodes lasting longer than 30 minutes and sending notifications to participants. Performance was defined as the percentage of ICM-detected AF episodes ≥30 minutes that resulted in a notification from the wearable device. While the CART Ring was programmed to notify users of AF episodes longer than 30 minutes, Apple's detection criteria were less explicitly defined, but its performance was evaluated against the same 30-minutes threshold. This was calculated for all AF episodes and at a patient-level.

Secondary endpoints were the following: percentage of notifications that were acknowledged, time from AF detection to acknowledgment in both phases, wearable device adherence, and patient questionnaires. Wearable device performance metrics assessed included FP and FN rates, and PPV). A FP detection was defined as an AF notification generated by a wearable device when no AF episode ≥ 30 minutes was recorded by the ICM within the same time. Conversely, a false-negative detection was defined as AF episodes ≥ 30 minutes captured by the ICM without a corresponding AF notification from the wearable device. The PPV was also calculated for wearable device notifications.

Heart rate data was used as a surrogate to investigate wearable device adherence. Heart rate data were reviewed in rolling 10-minutes windows. If heart rate data were available within a 10-minute window, the device was considered as being worn. A cutoff of three or more consecutive 10-minutes windows with no heart rate recordings was used to determined that the wearable was not being used. This was an attempt to account for lack of heart rate data arising from movement, signal dropout or other interruptions despite the wearable device being in use.

Adherence was calculated as the mean daily wear time and percentage of total time. Daytime (7 am to 9 pm) and night-time (9 pm-7 am) wear time was also computed and expressed as a percentage of total available time. A separate analysis of AF detection was performed to determine whether any AF episodes were missed due to wearable device non-use.

All interactions, including timestamps of detected episodes and participant acknowledgments, were logged in the software database for subsequent analyses.

At the end of the follow-up, I administered a structured questionnaire to all participants to assess their experience and satisfaction with each monitoring approach. I also asked for open-ended feedback suggestions for improvement, barriers to device adherence, and how to optimise alert systems.

6.4.4 Adjudication and Statistical Analysis

The SMART-ALERT software created a database in Excel format with timestamps of SMS alerts sent to study participants and the subsequent acknowledgements that were received. The participants' phone numbers served as identifiers to match the SMART-ALERT software alerts with participants' acknowledgements.

All AF episodes detected by the LINQ II ICM with available ECG recordings on CareLink were exported in PDF format.

Similarly, data from the wearable devices was exported to retrieve AF alert notification logs, heart rate data, and SL-ECGs. For the Apple Watch, these data were available in the Health app and exported in HTML format and later converted in CSV format for analysis. While for the CART Ring data was obtained in Excel format directly from Skylabs. All available ECGs were adjudicated by two cardiologists (A.B.G) and (A.S) who remained blinded to participants' data. The principal investigator (T.R.B) resolved any disagreements between adjudicators.

All statistical analysis were conducted using R version 4.1.3 and supported by a trained statistician (A.B). Frequencies and percentages were used to summarize categorical data. For continuous variables, normality was first determined with the Shapiro-Wilk test. Gaussian distributions were reported as mean and standard deviations.

For non-Gaussian distributions, median and interquartile ranges were used instead. When comparing performance between devices, paired t-tests were employed for continuous variables and Chi-square tests for categorical variables. As per convention, statistical tests were two-tailed and significance set at 0.05. All plots were generated in R using the ggplot2 package.

6.5 Results

A total of 50 participants were enrolled and had a LINQII ICM implanted between December 2021 to August 2022. The median age of participants was 62 (IQR 57-69) years, 30% were female, and 76% had a prior diagnosis of PAF and 68% were established on OAC. The median CHA_2DS_2-VASc and HAS-BLED scores were both 1.

The baseline characteristics of the study participants are summarised below in Table 6-1.

***Table 6-1**. Patient characteristics at time of enrolment and at the beginning of Phase 2. Reproduced with permission from Briosa e Gala et al.[257]*

Characteristics	Total (N = 50)	Apple Watch (N=23)	CART Ring (N=23)
Age — yr	62 (57—69)	62 (60—70)	62 (54—68)
Female sex — no. (%)	15 (30%)	8 (35%)	6(26%)
BMI — median (IQR)	26.8 (24.9- 30.2)	26.8 (24.9- 30.2)	26.8 (24.9- 30.2)
Paroxysmal AF — no. (%)	38 (76%)	19 (83%)	17 (74%)
AF duration (months) — median (IQR)	42 (24-68)	48 (24-96)	27 (26-30)
AF symptoms frequency — no. (%)			
• No symptoms	1 (2.0%)	1 (4.3%)	—
• Most days	9 (18%)	4(17%)	5 (23%)
• Most weeks	32 (64%)	8 (35%)	9(41%)
• Most months	8 (16%)	10 (43%)	8 (53%)
CHA_2DS_2-VASc — median (IQR)	1 (0—3)	1 (1—3)	1 (0—2)
HAS-BLED — median (IQR)	1 (0–1)	1 (0–1)	1 (0–1)
Hypertension — no. (%)	13 (26%)	6 (26%)	6 (26%)
Ischaemic Heart Disease — no. (%)	5 (10%)	3 (13%)	1 (4.3%)
Vascular Heart Disease — no. (%)	1 (2%)	1 (4.3%)	—
Heart Failure — no. (%)	10 (20%)	2 (8.7%)	7 (30%)
Previous Stroke/TIA — no. (%)	6 (12%)	3 (13%)	3 (13%)
Previous Ablation — no. (%)	24 (52%)	12 (52%)	12 (52%)
Previous Cardioversion — no. (%)	11 (22%)	7 (30%)	4 (17%)
Rate control drugs — no. (%)	33 (64%)	12 (51.6%)	18 (78.3%)
• Beta-blocker	30 (60%)	10 (43%)	17 (74%)
• Calcium-channel blockers	1 (2%)	—	1 (4.3%)
• Digoxin	1 (2%)	1 (4.3%)	—
• Others	1 (2%)	1 (4.3%)	—
Anti-arrhythmic drugs — no. (%)	26 (52%)	13 (57%)	15 (65.7%)
• Class Ic	17 (34%)	8 (35%)	12 (35%)
• Amiodarone	3 (6%)	—	2 (8.7%)
• Sotalol	6 (12%)	5 (22%)	1 (4.3 %)
Oral anticoagulation — no. (%)	34 (68%)	16 (70%)	14 (61%)
• DOAC	15 (30%)	15 (65.7%)	14 (61%)
• Warfarin	1 (2%)	1 (4.3%)	—
Normal EF — no. (%)	44 (88%)	21 (91%)	19 (83%)
Sinus rhythm — no. (%)	46 (92%)	22 (96%)	21 (91%)

***AF**, Atrial fibrillation. **BMI**, Body mass index. **DOAC**, Direct oral anticoagulants. **EF**, Ejection fraction. **TIA**, Transient ischaemic attack.*

The initial study protocol planned a target follow-up of three months for each phase; however, there were several participants who remained in Phase 1 for a slightly longer period (up to four months) due to logistical constraints from scheduling conflicts and device availability. This resulted in an overall follow-up of 6.8 ± 1.2 months, longer than initially planned.

Forty-six participants progressed to Phase 2 (Figure 6-3) and were assigned a wearable device (Apple Watch or CART Ring) depending on the operating system of their respective smartphones. Two participants asked to have their ICM removed during phase 1 and another two participants were in persistent AF and the clinical team decided to pursue a rate control strategy and, therefore, they were not offered a wearable device.

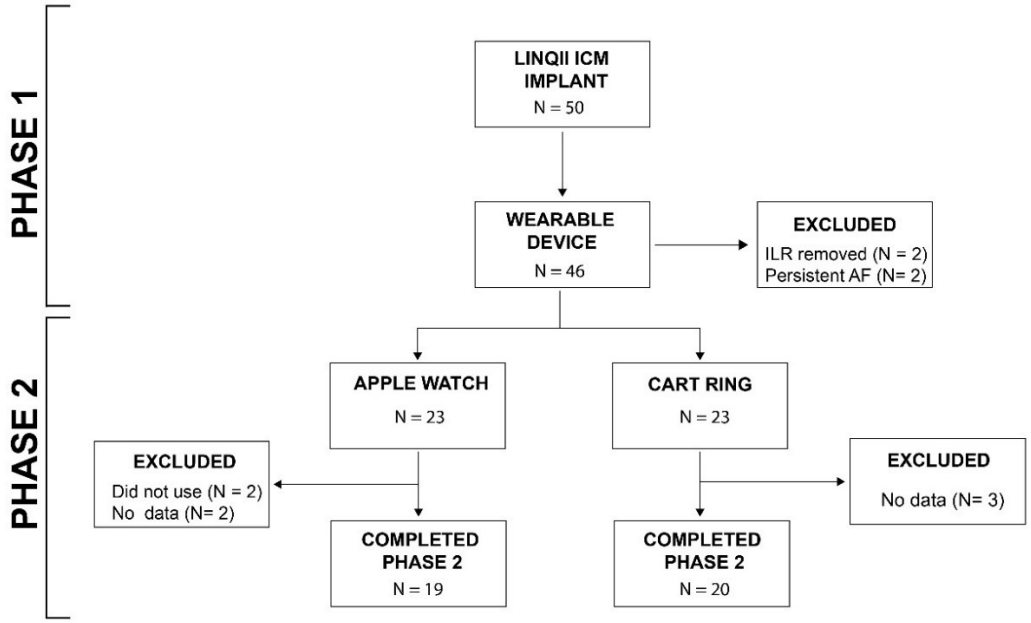

Figure 6-3. Study workflow. *Reproduced with permission from Briosa e Gala et al.*[257]

The LINQ II ICM detected 4,943 AF episodes lasting longer than 30 minutes in 31 participants. This figure includes all AF episodes stored on the ICM, irrespective of time of upload to CareLink.

Over the total duration follow-up, 919 AF episodes detected by the LINQ ICM that met the alert criteria had a corresponding ECG. Adjudication of these episodes revealed a PPV for AF of 99.5% for the LINQ II ICM.

Episode characteristics captured by the LINQ II ICM in both phases are shown in detail in Table 6-2.

Table 6-2. *Characteristics of AF episodes detected by the LINQ II ICM. Reproduced with permission from Briosa e Gala et al.*[257]

	Phase 1	Phase 2†	
	LINQ II ICM (N=50)	**Apple Watch (N=19)**	**CART Ring (N=20)**
AF episodes detected by ICM	4080	389	474
AF episodes meeting criteria for Notification	691‡	389	474
AF episodes with ECG	460	293	295
True AF episodes	458 (99.5%)	293(100%)	292 (99.0%)
Number of Patients with at least one AF episode	31	13 (68.4%)	9 (45%)
Episode duration (minutes), median (IQR)	80 (180)	82 (390)	66 (62)
Follow-up (months), mean±SD	3.3±1.3	4.3±1.3	3.5±1.2

AF*, Atrial fibrillation.* ***ECG,*** *electrocardiogram.* ***IQR****, interquartile range.* ***SD****, standard deviation.*
† Includes only participants who completed Phase 2. Of the 46 participants allocated a wearable device, two did not use it, and five had no analysable data.
‡ Number of AF episodes meeting the criteria for the bespoke software alert (first episode within a 24-hours period).

6.5.1 AF Notification Rates

In Phase 1, the bespoke SMART-ALERT software successfully triggered automated SMS notifications for 511 of the 691 AF episodes (74%) that met the three predefined criteria (Figure 6-4A). In Phase 2, using the ICM as the gold-standard for AF detection, the Apple Watch alerted participants of 76 of 389 AF episodes (19.5%) lasting ≥30 minutes compared to the CART Ring, which alerted 72 of 474 AF episodes (15.1%).

Success rates for AF alerts at the patient-level were as follows: 65.7% for the SMART-ALERT software, 27.9% for the CART Ring, and 25.0% for the Apple Watch.

The Apple Watch generated 109 AF notifications in total, of which 76 were true positives, yielding a PPV of 69.7%. In contrast, the CART Ring produced 349 AF notifications, of which only 72 were true positives, resulting in a lower PPV of 20.6% ($p < 0.001$; Figure 6-4B). The CART Ring had a significantly higher rate of FP detection compared to the Apple Watch (79.4% vs. 30.3%, respectively, $p<0.0001$).

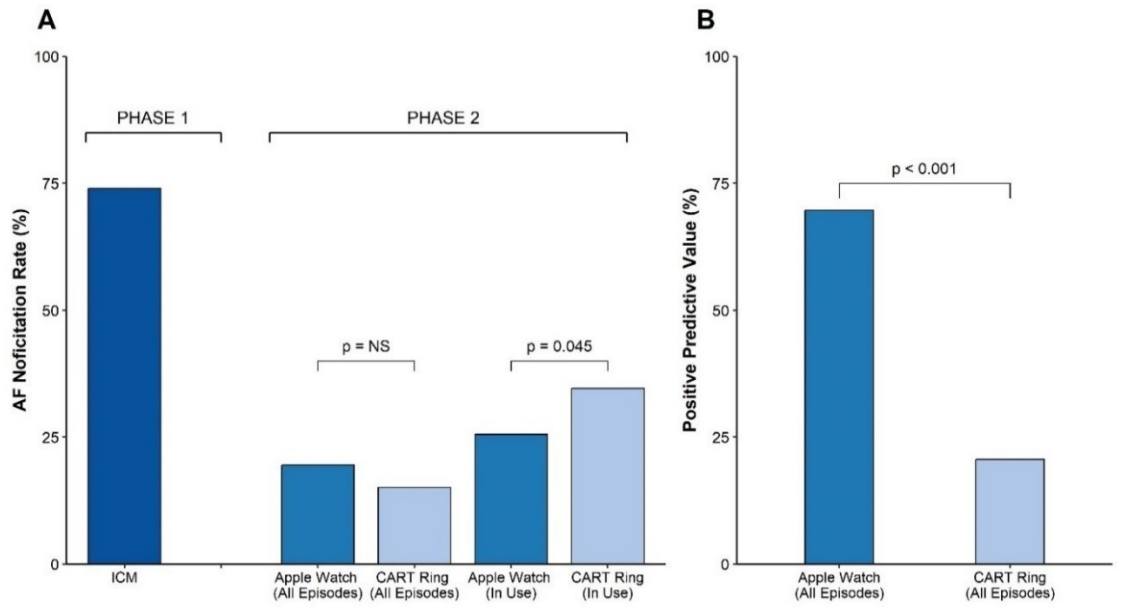

Figure 6-4.(A) *Percentage of successful AF notifications sent in the ICM cohort (Phase 1) and in the Apple Watch and CART Ring cohorts (Phase 2).* ***(B)*** *Positive predictive value of AF notifications by the wearable devices during Phase 2.* ***AF****, atrial fibrillation.* ***ICM****, implantable cardiac monitor.* ***NS****, non-significant (p ≥0.05) Reproduced with permission from Briosa e Gala et al.*[257]

6.5.2 Wearable Devices Adherence and Impact on Detection

Participants given the Apple Watch demonstrated higher adherence, with an average time worn of 66.3% (Figure 6-5A) and a mean daily wear time of 16.0±6.8 hours (Appendix E, Table S6-1). Moreover, the Watch mean wear time was consistent across daytime (67.3%) and nighttime (63.5%) periods (Figure 6-6, B-C.) In comparison, participants using the CART Ring had a significantly lower adherence rate of 23.9%, with a mean daily wear time of 5.73 ± 7.96 hours, but with higher use overnight than during the day (32.1% vs 19.0%; p = 0.008). Nine CART Rings failed and required replacement after 4 to 6 weeks, which had an impact on the adherence rates observed.

Wearable device adherence significantly influenced AF notification rates in Phase 2. The Apple Watch was not worn during 24.6% of AF episodes, whilst the CART Ring was not worn during 55.7% of episodes.

If AF notification performance were only restricted to episodes when the wearables were worn, the Apple Watch had a notification rate of 25.5% (74 of 293 episodes) and 34.6% (66 of 210 episodes) for the CART Ring (Figure 6-4A).

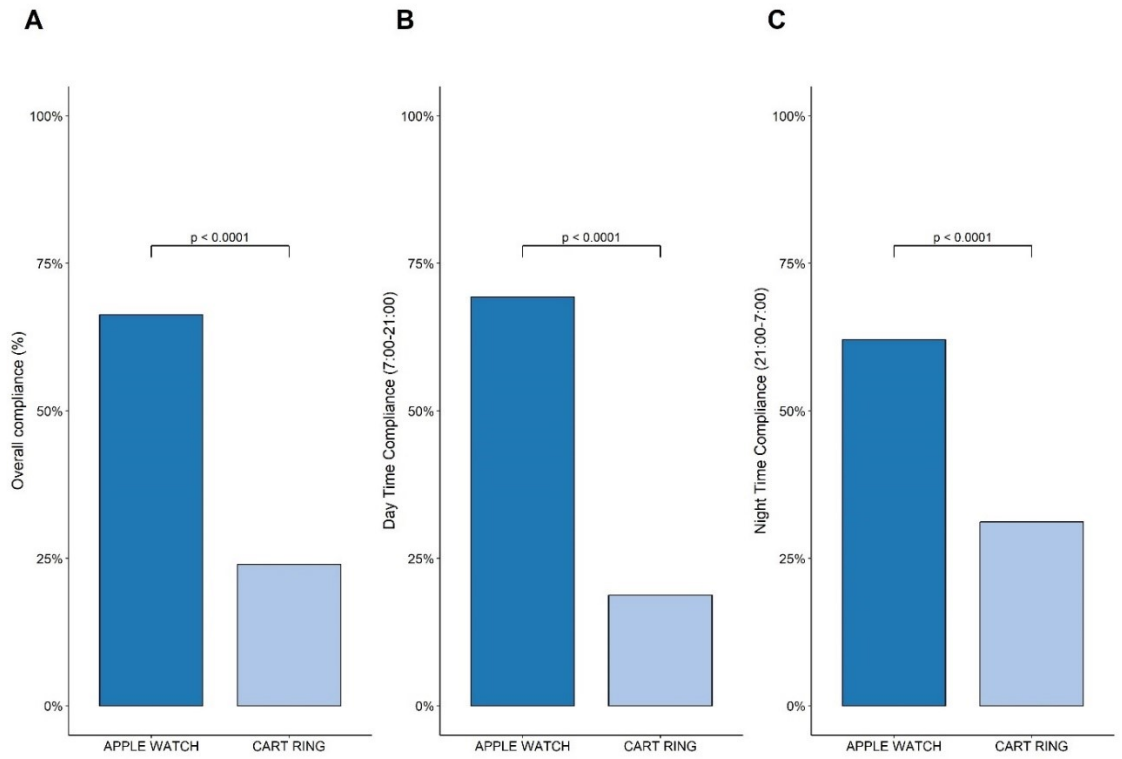

Figure 6-5 (A) *Overall adherence rates for the Apple Watch and CART Ring.* ***(B)*** *Adherence during daytime hours (7 am–9 pm).* ***(C)*** *Adherence during nighttime hours (9 pm–7 am). Reproduced with permission from Briosa e Gala et al.*[257]

6.5.3 Acknowledgement Rates and Responses Times

The acknowledgment rate of notifications varied between technologies. In Phase 1, the median time from ICM AF detection to SMS notification transmission was 2.4 hours, and 287 notifications (41.5%) were sent within 3 hours. Participants acknowledged 509 of 511 SMS notifications (99.6%) generated by the SMART-ALERT software, with a median response time of 4.5 minutes. The complete alert cycle comprising AF detection, notification, and acknowledgment, was achieved for 73.7% of episodes, with a median completion time of 4.2 hours (Figure 6-6, A-C).

In Phase 2, the Apple Watch cohort demonstrated a median notification time of 1.9 hours from AF onset. Participant engagement was lower than in Phase 1, with only 21 of 76 notifications (27.7%) acknowledged. As a result, 368 (94.6%) of 389 AF episodes that meet criteria for alert failed to complete the detection-notification-acknowledgement alert cycle. Among those episodes that did complete the cycle, the overall median time from AF onset to acknowledgment was 4.6 hours (Figure 6-6, D-F).

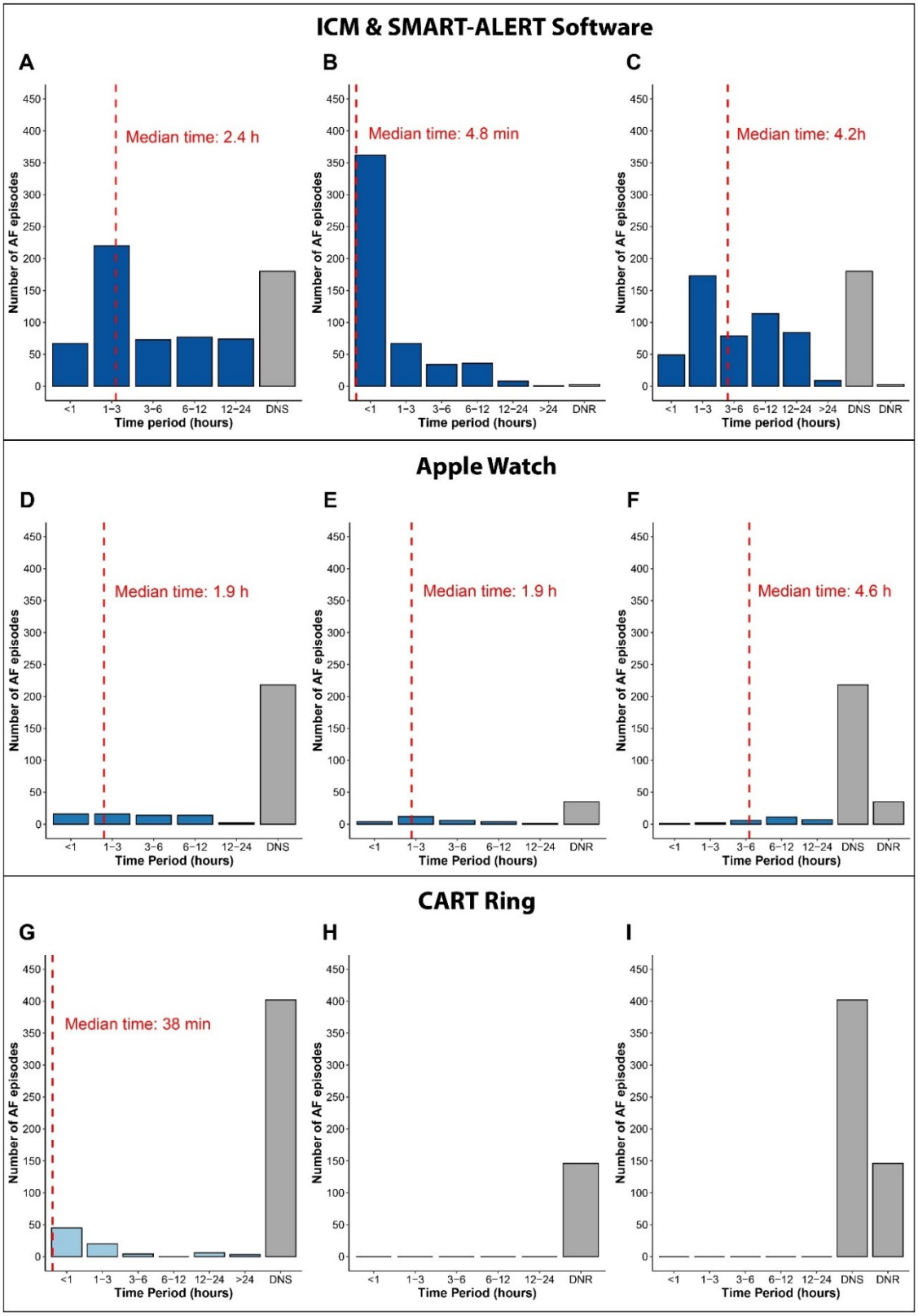

Figure 6-6.*Time intervals for AF detection, notification, and acknowledgement. Rows represent detection method:* ***ICM (SMART-ALERT)****,* ***Apple Watch****, and* ***CART Ring****. Columns represent: (1) Time from AF detection to notification, (2) Time from notification to participant acknowledgement, (3) Total time from AF onset to acknowledgement.* ***DNS*** *– did not send;* ***DNR*** *– did not reply. Reproduced with permission from Briosa e Gala et al.*[257]

The CART Ring cohort had a median notification time of 38 minutes; however, none of the 72 notifications sent (15.1% of total episodes) were acknowledged, resulting in no episodes completing the alert cycle (Figure 6-6, G-I). There were, however, acknowledgments for FP detections.

***Table 6-3**. Per-patient analysis of successful AF alerts sent by the SMART-ALERT software and AF notification by both wearable devices. Median and interquartile ranges for AF detection, acknowledgment and total times. Reproduced with permission from Briosa e Gala et al.[257]*

	Successful AF alerts (mean ± SD)	AF Detection to Notification (Median, Q1–Q3, min)	Notification to Acknowledgment (Median, Q1–Q3, min)	Total Time to Acknowledgment (Median, Q1–Q3, min)
ICM & SMART-ALERT software	65.7% ± 31.6%	107.3 (67.4-159.1)	1 (0.6-5.1)	126.1 (93.9-297)
Apple Watch	27.9% ± 27.6%	104.1 (57.8-186)	62 (60.6-309.8)	280 (258.9-323.7)
CART Ring	25% ± 33.5%	—	—	—

***ICM**, implantable cardiac monitor.*

6.5.4 Wearable Device Detection Rates by Episode Duration

Detection rates for AF episodes were analysed separately for periods when the Apple Watch (293 AF episodes) and the CART Ring (210 AF episodes) were worn (Table 6-4). The Apple Watch demonstrated a significant improvement in detection rates with longer episode durations, increasing from 6.4% for episodes lasting less than 3 hours to 58.7% for episodes exceeding 3 hours ($p < 0.01$).

***Table 6-4**. Detection rates of AF episodes for the Apple Watch and CART Ring according to episode duration. Reproduced with permission from Briosa e Gala et al.[257]*

Episode duration	Apple Watch		CART Ring	
	Episodes Detected	Detection Rate	Episodes Detected	Detection Rate
<1 hour	3/93	3.1%	28/89	31.5%
1-3 hours	8/86	9.3%	34/70	32.7%
3-6 hours	15/27	55.6%	5/11	45.45%
6-12 hours	18/32	56.25%	2/3	66.6%
12-24 hours	18/30	60%	1/1	100%
>24 hours	14/22	63.7%	—	—

In contrast, CART Ring detection was consistent across different episode durations with only a small increase for episodes longer than 3 hours. Therefore, its performance appears to be less dependent on episode duration.

6.5.5 Participants' Perspectives

A total of 30 out of 41 patients (73.2%) completed our questionnaire. Most participants (93.1%) reported no impact of AF alerts on daily activities, with 82.2% experiencing no change or reduced anxiety from monitoring (Appendix E, Figure S6-1). Three-quarters never had connectivity issues with the ICM app, and 81.9% acknowledged alerts "most of the time" or "always."

For wearable devices, 92.3% of Apple Watch users never had connection problems; however, only 55.2% felt very confident using the app and just 42.9% found it comfortable overnight. In contrast, 87.5% of CART Ring users wore their device overnight, but had a lower daily wear and nearly half experienced connectivity difficulties, with 20% reporting daily issues.

Participants expressed concerns that the apps drained the smartphones' battery and wearables had poor battery life (Appendix E, Table S6-2). When asked about 'pill-in-the-pocket' OAC, 86.7% (26/30) were willing to use an ICM-based system, compared to 68.8% (11/16) for the CART Ring and only 50% (7/14) for the Apple Watch (p=0.46).

6.6 Discussion

The SMART-ALERT study revealed a marked disparity between the SMART-ALERT/ICM system and wearable technology performance. The integration of the SMART-ALERT software with an ICM successfully triggered SMS notifications in 74% of eligible episodes, whilst wearable devices performed poorly, notifying participants of only 19.5% (Apple Watch) and 15.1% (CART Ring) of ICM-detected AF episodes.

The SMART-ALERT software's 74% notification rate should be interpreted with caution, as it reflects the intentional trade-offs in our decision tree: suppressing alerts beyond the first episode in a 24-hours period and those uploaded more than 24 hours after onset. This design was suited to our high-burden AF cohort (4,080 AF episodes in 31 patients) as a more aggressive notification algorithm would risk notification fatigue and affect patient engagement. SMS failures were primarily due to connectivity issues that led to delays in uploading episodes within a 24-h period, not software performance. Of the 26% (180/691) of eligible AF episodes that did not trigger SMS alerts, it was estimated that 44% (80/180) in 23 patients were due to failure to upload an AF episode to CareLink within 24 hours (Appendix E, Figure S6-4). Episodes uploaded

depend on three factors: Bluetooth® connectivity, the MyCareLink Heart smartphone app running in the background, and an active internet connection. If the app was closed, participants were only reminded to reopen the app after four consecutive days of data transmission failure. The SMART-ALERT software successfully alerted other participants during the same period, which is highly suggestive that these failures to send alerts stemmed from app connectivity challenges with the LINQ II ICM (Appendix, Figure S6-5).

Wearable devices tested showed a marked disparity between their real-world performance in ambulatory irregular rhythm monitoring and previous validation studies of spot-check ECGs, which reported high sensitivity (>90%).[96,301,311] The testing environment was biased towards showing positive performance metrics by including only AF and sinus rhythm, testing in optimal conditions with patients at rest, and optimising device position.

The comparison of devices using intermittent heart rhythm sampling (Apple Watch and CART Ring) against continuous monitoring systems (ICMs) introduces an inherent detection bias. The Apple Watch's low AF notification rate of 19.5% likely stemmed from the well-document limitations of PPG monitoring during daily activities, which include motion artefacts, variable skin contact, and intermittent sampling. Importantly, detection remained low at 25.5% even when worn. This suggests technical shortcoming rather than simple non-wear time.

Apple Watch performance improved with longer episodes (9.3% for 1–3-hours vs 63.7% for >24 hours), which suggests that the current algorithm characteristic favours longer episodes, and that the inherent sampling frequency yields a systematic bias against detection of shorter episodes. The CART Rings' irregular rhythm notifications were poor, failing to detect close to two-thirds of AF episodes and, more alarming, generating 74% FP notifications.

The suboptimal performance of wearable PPG-based AF detection has been repeatedly shown in ambulatory studies. Wasserlauf *et al.*, reported that only half of AF episodes occurred while smartwatches were worn, with a patient-level sensitivity for these episodes of 72% against ICMs and cardiac implantable electronic devices.[265] Moreover, nighttime episodes were not included as it was accepted that the battery life would precluded monitoring overnight. Similarly, episode level detection with the Apple Watch was only 21.4% when compared to a 24-hour Holter monitor.[312] The Fitbit Heart Study showed similar limitations with participant-level and episode-level sensitivities of 70.9% and 67.6%, respectively, using a 7-day Holter as reference.[296] The Verily wrist-worn device has a different approach and samples heart rate at all levels of activity

but only analyses adequate-quality PPG tracings. The overall sensitivity in ambulatory patients was 75.5%, increasing to 96.1% when poor-quality samples (22.8%) were excluded.[313]

These results indicate a sobering reality: despite considerable advancements in consumer wearable technologies, substantial barriers remain in using these tools as reliable clinical monitoring systems. While spot-check ECGs are useful for AF screening, PPG-based monitoring capabilities face fundamental limitations in both sampling frequency and signal quality, falling short for continuous monitoring in ambulatory patients.

The median delay from AF episode detection to SMS notification was longer for the ICM and SMART-ALERT software (2.6 hours) than with the wearable devices (1.9 hours for the Apple Watch and 38 minutes for the CART Ring). This mostly reflects the design of each monitoring system. The ICM typically uploads episodes after termination, so that a final duration can be assigned. For long or ongoing episodes, transmission can be postponed until termination or occur without a duration field. For uploads to occur the smartphone app must be running with an internet connection. The SMART-ALERT software was programmed to check episode start time and ascertain whether 30 minutes had elapsed, even in the absence of a duration being given. The software reviews all CareLink transmissions every 5 minutes, and SMS notifications were sent within seconds of an appropriate event. Wearables, by contrast, have integrated apps and, therefore, once AF is detected an alert can be quickly sent directly to the smartphone.

There was a striking difference in acknowledgment rates: 99.6% for SMS notifications versus 27.7% for Apple Watch and zero for CART Ring. The reasons for this discrepancy were likely multifactorial. SMS messages are prioritised by smartphone operating systems and are harder to ignore or miss than app-based notifications, which may be muted or lost amongst other notifications, limiting their visibility. A few participants acknowledged CART Ring notifications from FP episodes, while others used SL-ECGs to document acknowledgment instead of adhering to study protocol and sending SMS messages to the research team. SMS alerts during Phase 1 sent by the SMART-ALERT explicitly requested an acknowledgment. This clear instruction may also have translated to more consistent replies across participants.

Participants wearing the Apple Watch had a mean daily wear time of 16 hours, compared to 5.7 hours for the CART Ring, but device malfunction must be taken into account when interpreting these differences in wear time. Non-adherence had an impact on AF detection performance, with the Apple Watch missing 24.6% of AF episodes due to non-wear, while the CART Ring missed 55.7% of episodes. These adherence challenges align with previous wearable devices

studies.[314,315] For example, a study using the Oura Ring found wear times ranging from 15 to 19 hours across 30-day periods, with users attributing non-adherence to battery limitations, discomfort, and inconvenience.[316] It is important to consider how adherence changes over time. In their study of smartwatch users, Ding *et al.* reported that adherence dropped from 73% to 63% at the end of the first month, with fewer than half of participants wearing the watch for at least five hours.[317]

The SMART-ALERT has important implications for a 'pill-in-the-pocket' OAC strategy. The meta-analysis described in Chapter 3 highlighted that manual adjudication of all AF ICM episodes was not only resource-intensive but also led to unacceptable delays in starting OAC. Integrating the SMART-ALERT software with an ICM resulted in near real-time automated patient notifications, with a 74% success rate within 24 hours of AF episodes. Moreover, the ICM data showed high PPV for AF, in line with Mittal *et al.* who reported a 91.3% PPV for AF episodes longer than 30 minutes in 1,049 patients with the Reveal LINQ ICM.[262]

Despite a low risk of FP, possibly leading to inappropriate initiation of OAC in about 1 in 20 patients, closed-loop systems with direct patient alerts could significantly reduce delays in OAC initiation. To ensure safety, the clinical team would subsequently adjudicate all alerts. In the case of FP episodes, the team would contact the patient and advise them to stop OAC. In practice, this would result in only a few days of inappropriate OAC in individuals who would otherwise be on lifelong OAC according to the current guidelines.

Patient perspectives also support exploring ICM-based approaches for pill-in-the-pocket OAC. In our previous survey of 321 AF patients conducted in collaboration with the AF Association, 54% expressed willingness to use ICM-guided OAC if proven to be as safe as continuous OAC, whilst only 48% would consider using a wearable device.[318] This preference was confirmed in our post-study questionnaires, with 86.7% of participants preferring the use of an ICM, in contrast to 68.8% for the CART Ring and 50% for the Apple Watch (Appendix E, Figure S6-1, Table S6-2).

Building on the findings from this study, we have refined the SMART-ALERT software. The latest iteration improves connectivity by including SMS reminders to participants if no data uploads occur within a 24-hour rolling window and alerts the researchers during scheduled CareLink maintenance which may require manual restart of the software. Testing of the improved SMART-ALERT system has shown a 100% success rate for eligible episodes. These improvements have informed the design of the ongoing RESPOND-AF study (NCT06922695), which is a single centre study evaluating a real-world 'pill-in-the-pocket' OAC pathway guided by the SMART-ALERT platform and is currently recruiting.

Intermittent use, low detection rates, and unreliable notifications with wearable devices are particularly problematic for a 'pill-in-the-pocket' OAC strategy; it can result in failed AF detection, delayed OAC, and increased stroke risk.

Innovations should focus on three key areas. First, improving adherence requires optimising battery life to reduce the frequency of charging and implementing design improvements to boost comfort. Second, increasing PPG sampling frequency, including during periods of activity. To mitigate the likely reduced quality of PPG tracings, artificial intelligence (AI)-based algorithms can compensate by improving the signal-to-noise ratio, filtering artefacts, and overall enhancing arrhythmia detection.[319,320] Finally, shifting analysis from device to cloud-based systems with larger processing power and with continuous updates to AI training sets as new patterns emerge.

6.6.1 Limitations

This study has several limitations. The small sample size and relatively brief follow-up time limit generalisability of our findings, particularly for populations with different AF burdens and characteristics. Heterogeneity among participants' knowledge and familiarity with wearable technology together with compliance with study protocols are important sources of potential bias in the evaluation of such devices. Technical issues with the CART Ring, such as frequent device malfunction necessitating replacement, also add complexity to interpretation of adherence and overall utility as a monitoring device. All AF episodes stored on the LINQ II ICMs were included in our analysis, but there is still a possibility of ascertainment bias. The LINQ II ICM is reported to have a sensitivity for AF episodes longer than 30 seconds of >98%, but it will at times miss AF episodes. As such, it is conceivable that a small number of true-AF episodes went undetected and were excluded from analysis, which may impact comparison with the wearable devices. However, given that we set a cutoff of more than 30 minutes, the likelihood and importance of any such bias are expected to be negligible.

Finally, another important limitation is the deliberate design of our software to censor notifications uploaded to CareLink more than 24 hours after initiation, which may have underestimated the software's notification performance in patients with low AF burden, such as those eligible for a 'pill-in-the-pocket' strategy. Larger studies with longer follow-up periods are needed to validate these results and determine the feasibility of wearable devices in AF screening, monitoring and OAC management.

6.7 Conclusion

The SMART-ALERT study showed a stark contrast between ICM-based and wearable device real-time AF notifications. The integration of the SMART-ALERT software with the ICM showed promising efficacy in AF notifications (74% success rate) within 24 hours, but it had important connectivity problems: 44% of missed notifications occurred due to data transmission failure between ICM and CareLink platform. Despite this, there was strong participant engagement with 99.6% of alerts acknowledged.

The current generation of wearable devices tested, the Apple Watch and the CART Ring, showed poor AF detection rates in ambulatory patients (19.5% for the Apple Watch and 15.1% for CART Rings). Adherence was suboptimal and AF notifications were frequently missed. Although these digital health technologies are non-invasive and potentially scalable, our findings highlight that significant technical hurdles must be overcome before they can support time-sensitive AF management strategies.

The SMART-ALERT study offers important proof-of-concept data for the integration of the SMART-ALERT software to support future trials, and it is an important stepping stone in the development of monitoring tools that can deliver reliable real-time direct-to-patient notifications.

7 Conclusion

7.1 Introduction

AF is the most common sustained cardiac arrhythmia with rising incidence in the Western World and it is increasingly viewed as a growing epidemic.[1-3] AF-related strokes are responsible for approximately a quarter of all strokes.[8-10] Stroke prevention with OAC is one of the few interventions in AF management that offers a prognostic benefit.[1, 9] There has been a concerted effort by International Cardiology Societies to standardise the approach to stroke prevention and educate both physicians and patients.[1,2]

As outlined in the literature review (Chapter 1) there is growing evidence suggesting that thromboembolic risk is dynamic and influenced by AF episodes and overall burden.[179,310] However, current risk scores used to guide OAC decisions do not include these AF patterns.[1,2] Instead, they only use co-morbidities and are binary: once an individual meets a certain risk threshold, they are committed to lifelong OAC regardless of AF burden.

The hypothesis of this thesis is that if devices can capture real-time AF episodes with high accuracy, patients are reliably notified and engaged in a timely manner in response to these alerts, then these devices could be used to guide a 'pill-in-the-pocket' OAC strategy. This alternative approach of targeting only high-risk periods would represent a paradigm shift in current OAC strategies, potentially reducing bleeding and healthcare costs, whilst having comparable stroke prevention benefit. This change would have far-reaching implications in how AF is managed.

This final chapter brings together the findings from four complementary studies that investigated whether novel technologies (ICMs integrated with a bespoke software, and wearable devices) can support a pill-in-the-pocket OAC strategy. These four studies were designed with a sequential approach to address critical questions: beginning by appraising the existing literature for studies exploring rhythm-guided 'pill-in-the-pocket' OAC, followed by determining the diagnostic performance of ICMs (Confirm Rx and LINQ II ICMs) and wearable devices (Apple Watch and CART Ring), and finally testing the feasibility of 'real-time' AF detection, notification, and patient interaction. Therefore, each chapter adds a different piece of the puzzle by exploring the evidence behind 'pill-in-the-pocket' OAC, diagnostic accuracy and detection reliability of the study devices, user behaviours and engagement, and clinical integration. Collectively, these studies lay the technical and conceptual foundation for a robust platform to deliver rhythm-guided patient-centred 'pill-in-the-pocket' OAC.

7.2 Original Contributions

7.2.1 Systematic Review and Meta-analysis of 'Pill-in-the-Pocket' OAC

The systematic review and meta-analysis presented in Chapter 3 critically summarised the existing literature on rhythm-guided OAC for stroke prevention in AF.[254] It provided the first structured appraisal and meta-analysis of the evidence.

The review included 8 studies with a total of 711 patients. The pooled annualised event rates demonstrated a low thromboembolic event rate of 0.5 events per 100 patient-years (95% CI 0.2–2.1), which is not dissimilar to patients on continuous OAC with similar stroke risk profile (mean CHA_2DS_2-VASc score of 2.2).[146,165] The major bleeding rate was low at 2.4 per 100 patient-years (95% CI 1.3-4.0) .

Chapter 3 also identified several key limitations of existing evidence for 'pill-in-the-pocket' OAC. Most studies were small feasibility or pilot studies without a comparator arm (continuous OAC) enrolling a heterogeneous patient population. The thresholds used to initiate and discontinue OAC were varied and used ICM, CIEDs, single-spot ECGs, or pulse-checks to inform these decisions. The criteria to start OAC ranged from 1 to >6 hours of AF burden, and while some studies advocated for a four-week period of OAC after an AF episode, others limited OAC to just a few days or a week. These important limitations precluded strong conclusions regarding the non-inferiority of rhythm-guided OAC compared to the current practice of continuous OAC.

Nonetheless, this review identified key workflow limitations of existing studies that would hinder the clinical implementation of a 'pill-in-the-pocket' OAC approach. In six studies with continuous rhythm monitoring, AF episodes were transmitted, at best, only once every 24 hours, required manual adjudication by the research team, and patients were contacted if OAC was indicated. This was a resource-intensive process which is not easily scalable and likely led to considerable delays between AF detection and OAC initiation. Only three studies used patient-initiated OAC, and none reported the mean time from AF detection to OAC initiation. This is a critical barrier to an effective 'pill-in-the-pocket' OAC strategy, which is based on the theoretical benefit of targeted OAC during high-risk periods and requires timely initiation of OAC to prevent thrombus formation.

These findings established the rationale for my subsequent studies (Chapter 4-6), especially the need to develop and test a closed-loop system that reliably and accurately detected AF, obviating the need for adjudication, and with direct-to-patient alerts. It directly informed the development of the SMART-ALERT software and study design in Chapter 6.

7.2.2 UK Confirm Rx Study

The UK Confirm Rx study presented in Chapter 4 was the first comprehensive investigation of the diagnostic performance of the Confirm Rx ICM for detecting AF episodes of different durations and across various implant indications.[255] The Confirm Rx ICM gained CE-marking and FDA approval based on the DETECT-AF study which tested its previous iteration, the SJM Confirm, against a 48-hour Holter monitor in 79 patients.[47] However, it only had a limited number of patients, it investigated relatively short AF episodes (>2 minutes) and had a short duration of monitoring. The new Confirm Rx ICM not only had a smaller design, different implant technique, but also included a new and improved algorithms (SharpSense) that reportedly enhanced AF detection, but without any independent validation studies.

The UK Confirm Rx study included 232 participants with over 16,000 AF episodes and demonstrated an overall episode-level PPV of 75% for AF episodes lasting ≥6 minutes. The patient-level PPV was slightly lower at 66.9%. The main finding was that the diagnostic performance improved with longer AF episodes: for AF episodes ≥1 hour, the PPV was 88%; for episodes ≥6 hours, it increased to 98%; and for episodes lasting longer than 24 hours, the PPV was 100%.

Several other important observations emerged from this study. First, atrial and ventricular ectopy accounted for over half of FP detections. Second, AF performance was significantly worse during tachycardic episodes (52% FP). Third, the estimated AF burden precision was high at 93.3%. Lastly, women had significantly lower R-wave amplitudes than men and a lower PPV, and making this the first study to describe sex-based differences in Confirm Rx detection performance. The sex-based differences represent a previously unrecognised and clinically relevant finding which suggests that device settings or different implant techniques may be needed to improve signal quality in women.

These findings have important implications for any platform using an ICM to deliver direct patient notifications following AF episodes without manual adjudication. Both the TACTIC-AF and REACT.COM studies used an AF ≥1 hour as the cut-off that would trigger OAC.[68,199] If Confirm Rx ICMs were used in this context, approximately one in eight patients would receive an inappropriate AF alert. However, using a higher threshold of ≥6 hours would approximately halve this number to 1 in 33 patients, thus demonstrating that a closed-loop system with direct notification without adjudication is feasible and would likely lead to short times from AF detection to start of OAC.

Despite these strengths, the Confirm Rx ICM was not used in the SMART-ALERT study in Chapter 6 due to a critical limitation in its connectivity. Although it was the first ICM to communicate directly with a smartphone app, it only provides real-time upload to the remote monitoring platform when patients manually activated a symptom recording. Automated detections are transmitted only once every 24 hours.

Efforts to collaborate with the manufacturer to overcome the connectivity challenges and optimise the device were ultimately unsuccessful. It would have involved redesigning the architecture of their smartphone app and remote monitoring platform, which was not feasible within my timelines. Therefore, I used the Medtronic LINQ II ICM, which was released in 2021, and offered a greater potential for real-time notifications as it also communicated with a smartphone app. Nonetheless, the findings from the UK Confirm Rx established the diagnostic performance benchmark for implantable monitors with increased PPV for longer AF episodes and directly informed the design of the SMART-ALERT feasibility study.

7.2.3 WEAR-TECH ECG Study

Chapter 5 outlines the WEAR-TECH ECG study which was a prospective multicentre study comparing the diagnostic performance of the SL-ECGs from the Apple Watch and the CART Ring compared to a 12-lead ECG.[256] It explored the real-world diagnostic performance by including patients with a broad range of cardiac rhythms, who are often excluded from validation studies.

It enrolled 483 patients and analysed 2,398 SL-ECG recordings across three UK centres. The study revealed important differences in performance between both devices.

In the 'worst-case' analysis, the CART Ring outperformed the Apple Watch for automated AF detection for both sensitivity (84.6% vs 69.1%) and specificity (89.9% vs 72.6%). This study identified an important limitation of the Apple Watch with approximately one in five SL-ECGs being unclassified. Yet, physician interpretation significantly improved diagnostic performance of both devices in detecting sinus rhythm and AF. The WEAR-TECH ECG study was the first to explore atrial arrhythmia (AF, AT and flutter) detection showing that both automated detection and physician interpretation fell short with a high number of false-negative detections as ATs were frequently misclassified as sinus rhythm.

By including different cardiac rhythms beyond AF and restricting the number of attempts, the WEAR-TECH ECG study highlighted key methodological limitations, which often overestimate validation studies sponsored by manufacturers, thus offering more clinically relevant performance metrics. It also argued for more robust standards when evaluating novel

technologies before they are integrated into routine care or are used to guide clinical decisions. Most studies thus far have only included patients in sinus rhythm and AF, and this binary choice favours automated AF detection and does not reflect the spectrum of rhythms seen in daily practice.

From a broader perspective, these data also suggested that, although the devices tested have potential, automated AF detection is still suboptimal and should be included in a hybrid model integrating physician adjudication.

From a 'pill-in-the-pocket' OAC perspective, a spot-check ECG could, in theory, be used as a second-step confirmation of AF before taking OAC, but the low sensitivity of the Apple Watch and high number of unclassified ECGs questioned its value in this approach. Nonetheless, SL-ECGs can offer rhythm documentation for physician adjudication at a later stage.

AF notifications from the Apple Watch and CART Ring rely solely on PPG signals, yet neither device displays these data, therefore precluding adjudication of PPG signals. As a result, physicians cannot verify whether an AF notification was appropriate. This limitation underscored the value of evaluating the Apple Watch and CART Ring AF notifications against an ICM, as undertaken in Chapter 6.

7.2.4 SMART-ALERT Study

The SMART-ALERT study presented in Chapter 6 was a prospective single-centre feasibility study designed to investigate the performance of three automated AF detection and notification systems (ICM integrated with the SMART-ALERT, Apple Watch, and CART Ring).[257] It was designed to address a critical gap identified in previous chapters, which highlighted the need for 'real-time' closed-loop alert systems during AF episodes to support a 'pill-in-the-pocket' OAC.

The innovative aspect of this study included the development and integration of the SMART-ALERT cloud-based software with the LINQ II ICM and Carelink remote monitoring platform, which directly addressed the workflow limitations identified in the systematic review (Chapter 3). This system achieved a 74% notification success rate (within 24 hours), with 99.6% of alerts acknowledged and a median acknowledgment time of just 4.5 minutes. It demonstrated the feasibility of an ICM-based closed-loop AF notification system, but identified several important technical limitations that required optimisation, such as connectivity checks between the ICM and its smartphone app.

In contrast, the Apple Watch only detected 19.5% of AF episodes and the CART Ring 15.1%. Adherence was an important barrier to effective monitoring: the CART Ring was not worn during

55.7% of AF episodes and the Apple Watch during 24.6%. Another clinically relevant finding was that SMS alerts were very effective (99.6% acknowledgment rate), whilst the pop-up notifications had a very low response rate, presumably as they compete with other app notifications and are easily missed.

This study provided the first comprehensive comparison of intermittent rhythm monitoring with wearables versus continuous monitoring from an ICM-based notification system assessing 'real-time' AF detection and notifications. It clearly demonstrated that wearable technologies, although promising, have important limitations with regards to adherence and diagnostic accuracy in ambulatory patients. Importantly, the SMART-ALERT software bridged the gap between ICMs, which are very accurate monitoring tools, but do not provide direct patient feedback.

7.3 Strengths and Limitations

This thesis benefits from several methodological strengths. Each study built upon the findings of the previous one with a logical progression from systematic review with appraisal of the evidence to validation and feasibility testing. The studies presented in Chapters 4-6 draw on data collected from a diverse group of patients with AF. WEAR-TECH ECG and UK Confirm studies were multicentre studies which strengthens their findings.

Wearable devices were evaluated in a head-to-head comparison, and all ECGs were adjudicated by two cardiologists blinded to the participants' data. Moreover, the wearable devices were tested in a rigorous testing environment designed to determine their diagnostic performance in clinically relevant contexts: (1) SL-ECGs for various cardiac rhythms and (2) AF notifications in ambulatory patients, using an ICM as the gold standard.

The development and integration of the SMART-ALERT bespoke software platform represents a significant translational contribution to the field, bridging the gap between continuous monitoring with highly sensitive devices to direct-to-patient notification.

Lastly, I collected participants' feedback to better understand their experiences and preferences, recognising that human factors are essential in guiding a successful clinical implementation (Appendix E, Figure S6-1, Table S6-1).

However, there were several methodological limitations that must also be acknowledged. This thesis investigated the feasibility of monitoring technologies, but the safety and efficacy of a 'pill-in-the-pocket' OAC still needs to be demonstrated in prospective studies.

There continues to be uncertainty in the AF episode duration or daily burden that requires OAC and for how long it should be taken. The studies presented in Chapters 4-6 had short follow-up periods, which is particularly important when evaluating long-term trends in user behaviours and adherence with wearable devices and study protocols that require prompt replies to SMS or app notifications. As a result, the patterns observed may not reflect long-term trends in patient engagement.

It is also important to acknowledge that the high rate of technological change means that these findings only apply to the current generation of devices and not to newer iterations which have since been released and may have improved algorithms. The SMART-ALERT study was tested in participants with high-AF burden, as PPV is influenced by AF prevalence, the results may differ in individuals with infrequent AF episodes who are the ideal candidates for 'pill-in-the-pocket' OAC. Finally, participants in the studies were generally motivated volunteers who might not represent the broader AF population's activity and adherence.

7.4 Future Directions

This thesis demonstrated that integrating the SMART-ALERT system with an ICM for 'real-time' AF detection and notification is technically feasible. In contrast, it identified important technological barriers with the wearable technology tested, Apple Watch and CART Ring, which limit their use in their current form.

One of the main findings of the SMART-ALERT study was that 26% of eligible AF episodes did not trigger an SMS as these episodes were not uploaded to CareLink remote monitoring platform within a 24-hour period. 'Pill-in-the-pocket' OAC relies on correctly identifying AF and timely initiation of OAC, making delays of 24 hours for episode upload particularly problematic.

I have identified and addressed the two main factors that contribute to these delays. First, data uploads to CareLink only take place when the MyCareLink app is open and running in the background. If the app is closed, it will only alert participants after four days of inactivity, reminding them to open the app. The SMART-ALERT software now issues an automatic SMS reminder to participants if no data upload occurs within a 24-hour period and continues to issue reminders at 24-hour intervals. This update should prompt participants to keep their MyCarelink app running, resulting in more reliable transmissions without data loss.

Second, when the CareLink website is undergoing maintenance, the SMART-ALERT software cannot access it, resulting in an SMS failure. Occasionally, this led to an error within the code which required a manual restart of the programme. The updated version addresses these

limitations and improves reliability during CareLink maintenance or Chrome Browser updates by adding an automatic restart process that attempts to reconnect repeatedly. There is also now a 'watcher' program that runs alongside which logs all the events to try and understand the sources of software failure. This 'watcher' program adds another layer of safety, by triggering an automatic email to the research team if the SMART-ALERT is not running. This should prompt a review and manual restart if required. This newer iteration of the software with these changes has been prospectively tested in a small pilot cohort, achieving a 100% SMS delivery success rate.

Future research in wearable devices should focus on two critical aspects. First, adherence needs to be optimised; wearable devices cannot detect arrhythmias if they are not being worn. This requires longer battery life, faster charging cycles and improved comfort. Second, when the devices are being worn, they must have improved PPG sampling frequency to avoid missing AF episodes. To prevent FP detection, manufacturers should make use of improved sensor electrodes, signal processing and use of machine learning so that signals can also be collected and analysed during periods of activity and not only at rest.

This thesis set out to investigate and develop a robust platform to support a 'pill-in-the-pocket' OAC strategy that would deliver automated 'real-time' alerts, obviating the need for adjudication and thus reducing the time from detection to OAC initiation. However, critical questions remain unanswered and are fundamental for a safe implementation of this strategy. Further research is required to better define the AF episode duration threshold that warrants OAC, and for how long OAC should be continued once initiated. These studies must leverage data from devices with continuous rhythm monitoring, either from CIEDs and ICMs, and establish AF episode duration or burden in individuals not on OAC who experienced thromboembolic events. Moreover, other risk factors, such as AF pattern, recurrence rate, symptom burden, and biomarkers should be explored to refine risk stratification profiles and personalise treatment algorithms to better inform a 'pill-in-the-pocket' OAC. Finally, a health economic evaluation is needed to determine the cost-effectiveness of 'pill-in-the-pocket' OAC strategy. This analysis should consider the device costs against the reduction of OAC use, potential savings from fewer bleeding complications and impact on quality-of-life.

My work is being directly translated into clinical practice with a newer iteration of the SMART-ALERT algorithm currently being tested in the RESPOND-AF study (NCT06922695). This study builds on the foundations laid by this thesis, and it is prospectively evaluating the SMART-ALERT software in guiding real-time automated AF alerts to inform OAC decisions. RESPOND-AF is

single-arm ‘pill-in-the-pocket’ OAC study supported by Medtronic, which will provide important technical support to optimise the connectivity issues identified in the SMART-ALERT study, further developing a robust platform that can integrate seamlessly with CareLink remote monitoring platform. Its results will inform the design of a randomised controlled non-inferiority trial comparing rhythm-guided, ‘pill-in-the-pocket’ OAC with the SMART-ALERT software to continuous lifelong OAC.

7.5 Conclusion

This thesis systematically investigated whether current monitoring technologies could be used to deliver a ‘pill-in-the-pocket’ OAC. Through four complementary studies, I have established that the integration of the SMART-ALERT software with the LINQ II ICM offers a promising platform for ‘real-time’ AF notification which can be used in future studies comparing rhythm-guided OAC versus standard care. In contrast, current wearable technologies have significant limitations in diagnostic performance, adherence, and notifications for this specific clinical context.

The refinement and direct translation of the SMART-ALERT software into the RESPOND-AF study demonstrates the impact and relevance of my research. As monitoring technologies continue to evolve and so does our understanding of the relationship between AF patterns and thromboembolic risk. Future studies on rhythm-guided 'pill-in-the-pocket' OAC may demonstrate that this approach is as safe and effective as continuous lifelong OAC. This would expand the options for both patients and clinicians, leading to a paradigm shift in stroke prevention.

8 Appendix A

SMART-ALERT Code Snippets

This appendix contains selected code excerpts from the SMART-ALERT software developed in collaboration with BrainLogic and refined during the course of this research work. The aim of the software was the enable seamless integration with the CareLink remote monitoring platform, enabling 'real-time' automated AF notifications to participants.

These snippets represent the latest version of the SMART-ALERT software. The code was written in C# using the .NET framework to interact with CareLink via a Chrome Internet Browser. It can also access third-party communication services (SMS and email), and store local data. The sections below highlight the main code logic responsible for episode evaluation, patient notifications, inbound SMS processing, and scheduled monitoring tasks.

Table S2-1. *AF Episode Eligibility Logic (ApprovalToSendSms.cs)*

```
using System;
using System.Linq;
using System.Threading.Tasks;
using Microsoft.Extensions.Configuration;
using OCS.BusinessLogic.Interfaces;
using OCS.DataServices.Interfaces;
using OCS.Entities;

namespace OCS.BusinessLogic
{
    public class ApprovalToSendSms : IApprovalToSendSms
    {
        private readonly IDataServiceEpisodes _dataServiceEpisodes;
        private readonly IDataServiceSmsHistory _dataServiceSmsHistory;
        private readonly IConfiguration _configuration;

        public ApprovalToSendSms(IDataServiceEpisodes dataServiceEpisodes,
            IDataServiceSmsHistory dataServiceSmsHistory,
            IConfiguration configuration)
        {
            _dataServiceEpisodes = dataServiceEpisodes;
            _dataServiceSmsHistory = dataServiceSmsHistory;
            _configuration = configuration;
        }

        public async Task<SmsApproval> Execute(ulong id)
        {
            SmsApproval result = new()
            {
                Confirmed = false,
                ErrorMessage = $"Unknown Error."
            };

            var episode = await _dataServiceEpisodes.Get(id);

            if (episode is null || episode.Id == 0)
            {
                result.ErrorMessage = $"Unable to find the Episode in the
database.";

                return result;
            }
```

Table S2-2. *AF Event Processing and SMS Logic (ProcessAFEvent.cs)*

```
using System;
using System.Threading.Tasks;
using BrainLogic.Email.Interfaces;
using BrainLogic.SMS.Twilio.Interfaces;
using BrainLogic.SMS.Twilio.Interfaces.Models;
using Microsoft.Extensions.Configuration;
using OCS.BusinessLogic.Interfaces;
using OCS.DataServices.Interfaces;
using OCS.Entities;
using OpenQA.Selenium;
using OpenQA.Selenium.Support.UI;

namespace OCS.BusinessLogic
{
    public class ProcessAFEvent : IProcessAFEvent
    {
        private readonly ISmsSender _smsSender;
        private readonly IEmailSender _emailSender;
        private readonly IConfiguration _configuration;
        private readonly IPhoneNumberTools _phoneNumberTools;
        private readonly IDataServiceEpisodes _dataServiceEpisodes;
        private readonly IDataServiceSmsHistory _dataServiceSmsHistory;
        private readonly IApprovalToSendSms _approvalToSendSms;
        private IWebDriver _driver;
        private WebDriverWait _webDriverWait;

        public ProcessAFEvent(ISmsSender smsSender,
            IEmailSender emailSender,
            IConfiguration configuration,
            IPhoneNumberTools phoneNumberTools,
            IDataServiceEpisodes dataServiceEpisodes,
            IDataServiceSmsHistory dataServiceSmsHistory,
            IApprovalToSendSms approvalToSendSms)
        {
            _smsSender = smsSender;
            _emailSender = emailSender;
            _configuration = configuration;
            _phoneNumberTools = phoneNumberTools;
            _dataServiceEpisodes = dataServiceEpisodes;
            _dataServiceSmsHistory = dataServiceSmsHistory;
            _approvalToSendSms = approvalToSendSms;
        }
```

Table S2-3. Handling Patient SMS Acknowledgment (ProcessIncomingSms.cs)

```
using System;
using System.Linq;
using System.Threading.Tasks;
using OCS.BusinessLogic.Interfaces;
using OCS.DataServices.Interfaces;
using OCS.Entities;
using Twilio.AspNet.Common;

namespace OCS.BusinessLogic
{
    public class ProcessIncomingSms : IProcessIncomingSms
    {
        private readonly IDataServiceSmsHistory _dataServiceSmsHistory;
        private readonly IDataServiceEpisodes _dataServiceEpisodes;
        private readonly IPhoneNumberTools _phoneNumberTools;

        public ProcessIncomingSms(IDataServiceSmsHistory dataServiceSmsHistory,
            IDataServiceEpisodes dataServiceEpisodes,
            IPhoneNumberTools phoneNumberTools)
        {
            _dataServiceSmsHistory = dataServiceSmsHistory;
            _dataServiceEpisodes = dataServiceEpisodes;
            _phoneNumberTools = phoneNumberTools;
        }

        public async Task<string> Execute(SmsRequest incomingMessage)
        {
            string result = null;

            if (incomingMessage is null)
            {
                return $"Incoming Message is null.";
            }

            string from = _phoneNumberTools.Clean(incomingMessage.From);

            var episodes = await
_dataServiceEpisodes.GetByPrimaryPhoneNumber(from);

            var lastUnConfirmedEpisode = episodes.Where(x => x.SmsSent != null &&
x.SmsConfirmed == null).OrderBy(x => x.EpisodeNumber).LastOrDefault();
```

Table S2-4. Follow-Up SMS Scheduler (SendFollowUpSms.cs)

```
using BrainLogic.SMS.Twilio.Interfaces.Models;
using Microsoft.Extensions.Configuration;
using OCS.BusinessLogic.Interfaces;
using OCS.DataServices.Interfaces;
using OCS.Entities;
using System;
using System.Collections.Generic;
using System.Linq;
using System.Text;
using System.Threading.Tasks;
using BrainLogic.Email.Interfaces;
using BrainLogic.SMS.Twilio.Interfaces;

namespace OCS.BusinessLogic
{
    public class SendFollowUpSms : ISendFollowUpSms
    {
        private readonly IDataServiceEpisodes _dataServiceEpisodes;
        private readonly IDataServiceSmsHistory _dataServiceSmsHistory;
        private readonly IConfiguration _configuration;
        private readonly IEmailSender _emailSender;
        private readonly ISmsSender _smsSender;
        private readonly IPhoneNumberTools _phoneNumberTools;

        public bool HasError { get; set; }

        public string ErrorMessage { get; set; }

        public SendFollowUpSms(IDataServiceEpisodes dataServiceEpisodes,
            IDataServiceSmsHistory dataServiceSmsHistory,
            IConfiguration configuration,
            IEmailSender emailSender,
            ISmsSender smsSender,
            IPhoneNumberTools phoneNumberTools)
        {
            _dataServiceEpisodes = dataServiceEpisodes;
            _dataServiceSmsHistory = dataServiceSmsHistory;
            _configuration = configuration;
            _emailSender = emailSender;
            _smsSender = smsSender;
            _phoneNumberTools = phoneNumberTools;
        }
```

Table S2-5. *ChromeDriver Compatibility Check (CheckChromeVersion.cs)*

```
using System;
using System.Diagnostics;
using System.Threading.Tasks;
using BrainLogic.Email.Interfaces;
using Microsoft.Win32;
using OCS.BusinessLogic.Interfaces;
using OpenQA.Selenium;
using OpenQA.Selenium.Chrome;

namespace OCS.BusinessLogic
{
    public class CheckChromeVersion : ICheckChromeVersion
    {
        private IWebDriver _driver;
        private readonly IEmailSender _emailSender;

        public CheckChromeVersion(IEmailSender emailSender)
        {
            _emailSender = emailSender;
        }

        public async Task Execute()
        {
            string fileVersion = "";
            int majorFileVersionn = int.MaxValue;

            var chromeDriverService = ChromeDriverService.CreateDefaultService();
            chromeDriverService.HideCommandPromptWindow = true;
            chromeDriverService.SuppressInitialDiagnosticInformation = true;

            _driver = new ChromeDriver(chromeDriverService);

            ICapabilities capabilities = ((ChromeDriver)_driver).Capabilities;

            var browserVersion =
capabilities.GetCapability("browserVersion").ToString();

            Debug.WriteLine($"ChromeDriver browserVersion: {browserVersion}");

            int.TryParse(browserVersion?.Substring(0, browserVersion.IndexOf('.')),
out var majorChromeDriverBrowserVersion);
```

Table S2-6. *Periodic CareLink Data Scraper (FetchPatientAlerts.cs)*

```
using System;
using System.Collections.Generic;
using System.IO;
using System.Linq;
using System.Threading.Tasks;
using System.Timers;
using BrainLogic.Email.Interfaces;
using Microsoft.Extensions.Configuration;
using OCS.BusinessLogic.Interfaces;
using OCS.BusinessLogic.Screens;
using OCS.DataServices.Interfaces;
using OCS.Domain.Models;
using OCS.Entities;
using OCS.Parsers.Interfaces;
using OpenQA.Selenium;
using OpenQA.Selenium.Chrome;
using OpenQA.Selenium.Support.UI;
using SeleniumExtras.WaitHelpers;
using Twilio.TwiML.Messaging;
using Timer = System.Timers.Timer;

namespace OCS.BusinessLogic
{
    public class FetchPatientAlerts : IFetchPatientAlerts
    {
        private Timer _timer;
        private readonly IParseManageMyPatientsTable _parseManageMyPatientsTable;
        //private readonly IParseTransmissionsTable _parseTransmissionsTable;
        private readonly IParseEpisodesTable _parseEpisodesTable;
        private readonly IEmailSender _emailSender;
        private readonly IConfiguration _configuration;
        private readonly IProcessAFEvent _processAFEvent;
        private readonly IPhoneNumberTools _phoneNumberTools;
        private readonly IDataServiceHeartbeat _dataServiceHeartbeat;
        private readonly ISendFollowUpSms _sendFollowUpSms;
        private IWebDriver _driver;
        private WebDriverWait _webDriverWait;

        private string _username;
        private string _password;
        private bool _debug;

        public FetchPatientAlerts(IParseManageMyPatientsTable
parseManageMyPatientsTable,
            IParseEpisodesTable parseEpisodesTable,
            IEmailSender emailSender,
            IConfiguration configuration,
            IProcessAFEvent processAFEvent,
            IPhoneNumberTools phoneNumberTools,
            IDataServiceHeartbeat dataServiceHeartbeat,
            ISendFollowUpSms sendFollowUpSms)
        {
            _parseManageMyPatientsTable = parseManageMyPatientsTable;
            _parseEpisodesTable = parseEpisodesTable;
            _emailSender = emailSender;
```

```
            _configuration = configuration;
            _processAFEvent = processAFEvent;
            _phoneNumberTools = phoneNumberTools;
            _dataServiceHeartbeat = dataServiceHeartbeat;
            _sendFollowUpSms = sendFollowUpSms;
```

9 Appendix B

Systematic Review and Meta-analysis of 'Pill-in-the-Pocket' OAC supplementary material

This appendix contains supplementary figures and tables that provide additional information to support the findings presented in *Chapter 3.*

Table S3-1. *Embase search strategy (1974 to 29th of July 2022).*

	Searches	Results
1	ATRIAL FIBRILLATION	91145
2	ATRIAL FLUTTER	11199
3	“atrial fibrillation” “.ab, kw.ti	152656
4	“atrial flutter” “.ab, kw.ti	10755
5	“atrial arrhythmia” “.ab,kw,ti	7039
6	“atrial tachyarrhythmia” “.ab, kw.ti	2928
7	“atrial tachycardia” “.ab, kw.ti	7316
8	AF.ab, kw.ti	91611
9	AFibab, kw.ti	1623
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	216984
11	ANTICOAGULANTS/ad	3817
12	ANTICOAGULANTS /tu	55560
13	“VitaminK”/ai	14878
14	Warfarin/	100863
15	Dabigatran/	17034
16	Rivorixaban/	23937
17	Apixaban/	17034
18	Edoxaban/	6574
19	Warfarin.ab, kw.ti	44699
20	dabigatran a,tib, kw.ti	11335
21	Rivaroxaban.ab, kw.ti	11885
22	apixaban.ab, kw.ti	9663
23	edoxaban.ab, kw.ti	3372
24	“vitamin K antagonist” “.ab,kw.ti	12694
25	“nonvitamin K antagonist” “.ab,kw.ti	196
26	(NOAC* or DOAC*) ab,kw.ti	13043
27	“Novel oral anticoagul” “.ab,kw.ti	2696
28	“New oral anticoagul” “.ab,kw.ti	3337

29	“direct oral anticoagul” “.ab,kw.ti	8909
30	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29	183784
31	STROKE/	181202
32	THROBOEMBOLISM/	72822
33	“stroke*” “ab,kw,ti.	473565
34	“thromboemboli*”.ab,kw,ti.	110392
35	31 or 32 or 33 or 34	642091
36	TIME FACTORS/	38319
37	(needed or required or target* or tailor* or guide* or detect* or reinitial*).ab,ti.	8417167
38	(infrequent* or intermittent* or noncontinuous or nonpermanent or “non continuous” or “non permanent”).ab,ti	219977
39	36 or 37 or 38	8603144
40	ANTICOAGULANT AGENT	55560
41	“VITAMIN K”	14878
42	30 or 40 or 41	183784
43	10 and 35 and 39 and 42	8487
44	(study or trial).ti.	2257992
45	FOLLOW-UP STUDIES	1406557
46	44 OR 45	3438882
47	43 AND 46	2146
48	limit 43 to (clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial)	1549
49	47 or 48	3080
50	Limit 49 to conference abstracts	1197
51	49 and 50	1883

Table S3-2. *Medline search strategy (January 2004 to July 2022).*

	Searches	Results
1	ATRIAL FIBRILLATION	66738
2	ATRIAL FLUTTER	6231
3	“atrial fibrillation” “.ab, kw.ti	85504
4	“atrial flutter” “.ab, kw.ti	6558
5	“atrial arrhythmia” “.ab,kw,ti	4033
6	“atrial tachyarrhythmia” “.ab, kw.ti	1839
7	“atrial tachycardia” “.ab, kw.ti	4398
8	AF.ab, kw.ti	48611
9	AFibab, kw.ti	420
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	121462
11	ANTICOAGULANTS/ad	18808
12	ANTICOAGULANTS /tu	44107
13	“VitaminK”/ai	3085
14	Warfarin/	20981
15	Dabigatran/	3701
16	Rivorixaban/	4354
17	Apixaban/	0
18	Edoxaban/	0
19	Warfarin.ab, kw.ti	26714
20	dabigatran a,tib, kw.ti	5629
21	Rivaroxaban.ab, kw.ti	6754
22	apixaban.ab, kw.ti	4498
23	edoxaban.ab, kw.ti	1841
24	“vitamin K antagonist” “.ab,kw.ti	7469
25	“nonvitamin K antagonist” “.ab,kw.ti	145
26	(NOAC* or DOAC*) ab,kw.ti	6423
27	“Novel oral anticoagul” “.ab,kw.ti	1450
28	“New oral anticoagul” “.ab,kw.ti	1758

29	“direct oral anticoagul” “.ab,kw.ti	5135
30	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29	87438
31	STROKE/	123047
32	THROBOEMBOLISM/	25202
33	“stroke*” “ab,kw,ti.	2961145
34	“thromboemboli*”.ab,kw,ti.	71962
35	31 or 32 or 33 or 34	383150
36	TIME FACTORS/	1227861
37	(needed or required or target* or tailor* or guide* or detect* or reinitial*).ab,ti.	6402678
38	(infrequent* or intermittent* or noncontinuous or nonpermanent or “non continuous” or “non permanent”).ab,ti	159084
39	36 or 37 or 38	7501861
40	10 and 30 and 35 and 39	4890
41	(study or trial).ti.	1855338
42	FOLLOW-UP STUDIES/	686601
43	41 or 42	2430672
44	40 and 43	1053
45	Limit 40 to (clinical trial, all or clinical trial or comparative studies controlled clinical trial or mutlicenter study or randomised controlled trial	1189
46	44 or 45	1671

Table S3-3.Baseline characteristics of patients on 'pill-in-the-pocket' OAC. *Reproduced with permission from Briosa e Gala et al.*[254]

	Zuern et al (n = 65)	Mascare-nhas et al (n = 70)	REACT.COM (n = 59)	iCARE-AF (n=29)	TACTIC[168] (n = 48)	Zado et al (n = 99)	Mascare-nhas et al (n=145)	Prothineni et al (n=196)
Age[a]	63±10	73.3±11.7	66.8±7.7	65.5±12.2	71.3±10	64±8	77.3±10.3	64.7±11.3
Male	44 (68%)	37(53%)	44 (75%)	5 (17.2%)	31(65.%)	83 (84%)	73 (49.2%)	131 (66.85%)
AF/Flutter	65 (100%)	70 (100%)	59 (100%)	29 (100%)	48 (100%)	99 (100%)	145 (100%)	196 (100%)
Paroxysmal AF	39 (60%)	-	45(76%)	29(100%)	38 (79%)	72 (73%)	145 (100%)	97 (49.5%)
Persistent AF	30 (40%)	-	14(24%)	-	10 (21%)	28 (27%)	-	99 (50.5%)
AF ablation	65 (100%)	-	41(70%)	10(17%)	-	99 (100%)	-	196 (100%)
$CHADS_2$[a]	1.9	2.93	1.3	1.6	1.7	1.6	-	-
CHA_2DS_2-VAS[a]	2.8	2.93	2.4	2.5	-	1.9	2.9	2.2
HASBLED[a]	2.3	3.13	-	1.9	-	-	3.1	-
HTN	-	63(90%)	55 (93%)	26(90%)	37 (77%)	85 (86%)	140 (86%)	103 (50.6%)
DM	-	17(24.3%)	13 (22%)	10(34%)	10 (21%)	15 (15%)	50 (34.4%)	25 (12.8%)
IHD	20(31%)	24(34.3%)	-	7(24.1%)	-	-	122(85.5%)	36 (18.4%)
Stroke/TIA	0	0	0	0	0	3 (3%)	0	16 (8.1%)
CCF	-	-	2 (3%)	2(6.9%)	0	3 (3%)	-	32 (16.3%)
EF (%)	-	61.5	-	-	58.4	-	51	-
VKA	37(57%)	-	0	-	0	0	44(30%)	32 (16.3%)
DOAC	28(33%)	-	59 (100%)	29(100%)	48 (100%)	99 (100%)	44 (30%)	164 (83.7%)
AAD	19(29%)	70(100%)	20 (34%)	16 (55.2%)	22 (46%)	145	-	177 (90.3%)
Antiplatelet	-	-	-	15(51.7%)	-	-	16 (11%)	-

***AF**, atrial fibrillation. **AAD**, antiarrhythmic drugs. **CCF**, congestive cardiac failure. **DM**, diabetes mellitus. **DOAC**, direct oral anticoagulants. **EF**, ejection fraction. **IHD**, ischaemic heart disease. **TIA**, transient ischaemic attack. **VKA**, vitamin K antagonists. Values are given as mean±SD or n and percentages. [a] Me*

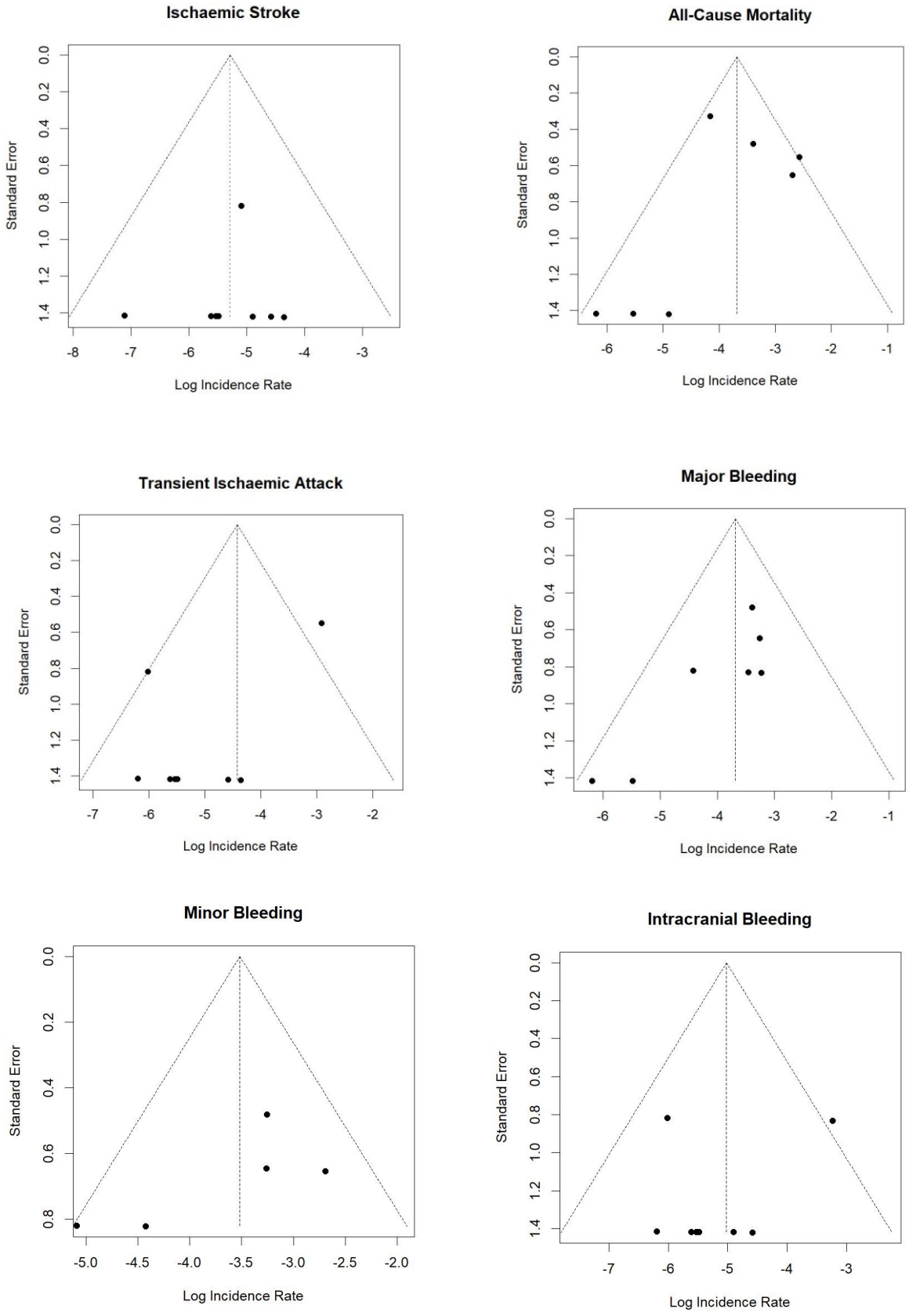

Figure S3-1. *Funnel Plots assessing publication bias. Reproduced with permission from Briosa e Gala et al.*[254]

***Table S3-4**. Adverse events in patient taking 'pill-in-the-pocket' OAC. Reproduced with permission from Briosa e Gala et al.*[254]

	Zuern et al[62] (n = 65)	Mascarenhas et al[60] (n =70)	REACT.COM[61] (n = 59)	iCare-AF[82] (n = 29)	TACTIC[168] (n = 48)	Zado et al[222] (n = 99)	Mascarenhas et al[198] (2019) (n =145)	Pothineni et al[199] (n=196)	Total (n=711)
Death	0	4 (6%)	0	3 (10.3%)	2 (4.2%)	0	9 (6.2%)	NR	18± (3.4%)
Ischaemic stroke	0	0	0	0	0	1 (1%)	0	0	1(0.14%)
TIA	0	0	3	0	0	0	1	0	4(0.56%)
Systemic embolism	0	NR	0	0	0	0	NR	0	0
Intracranial bleeding	0	0	0	0	1	0	1	0	2 (0.28%)
Major Bleeding	1 (1.5%)	4 (6%)	2 (3.4%)	1 (3.4%)	1 (2.1%)	0	NR	0	9* (1.6%)
Minor Bleeding	1 (1.5%)	NR	3 (5.1%)	NR	2 (4.2%)	1 (1%)	NR	4 (2.0%)	11* (1.5%)
Total Bleeding	2 (3%)	NR	5 (8.5%)	NR	3 (6.3%)	1 (1%)	12 (8.2%)	4(2.0%)	27 (3.8%)

TIA, transient ischaemic attack. NR, not reported.
Values percentages as number and percentages
*Excluding Mascarenhas et al (2019) ± Excluding Prothineni et al

10 Appendix C

UK Confirm Rx Study supplementary material

This appendix contains supplementary figures and tables that provide additional information to support the findings presented in *Chapter 4.*

Table S4-1. *Diagnostic performance of AF detection algorithm for episodes of different durations and according to implant indication. Reproduced with permission from Briosa e Gala et al.*[255]

Indication	Episode duration	Number of AF episodes detected	Number of True AF episodes	PPV
Palpitations (n=36)	>6 minutes	2695	1,516	56.3%
	>10 minutes	1765	946	53.6%
	>30 minutes	656	338	51.5%
	>1h	322	196	60.9%
	>3h	67	51	76.1%
	>6h	21	20	95.2%
	>12h	8	8	100%
	>24h	6	6	100%
AF Management (n=6)	>6 minutes	155	148	95.5%
	>10 minutes	131	126	96.2%
	>30 minutes	97	95	97.9%
	>1h	73	73	100%
	>3h	49	49	100%
	>6h	37	37	100%
	>12h	24	24	100%
	>24h	3	3	100%
Syncope (n=151)	>6 minutes	10529	8573	81.4%
	>10 minutes	6817	5714	83.8%
	>30 minutes	2498	2221	88.9%
	>1h	1417	1286	90.8%
	>3h	649	612	94.3%
	>6h	404	391	96.5%
	>12h	256	255	99.6%
	> 24h	133	133	100%
Suspected AF (n=15)	>6 minutes	1387	614	44.3%
	>10 minutes	946	447	47.3%
	>30 minutes	359	231	64.3%
	>1h	161	138	85.7%
	>3h	36	33	91.7%
	>6h	15	13	86.7%
	>12h	9	7	77.8%
	>24h	-	-	-
Other (n=24)	>6 minutes	1464	1320	90.2%
	>10 minutes	1148	1156	92.1%
	>30 minutes	658	633	96.2%
	>1h	468	455	97.2%
	>3h	272	270	99.3%
	>6h	144	144	100%
	>12h	18	17	94.4%
	>24h	13	13	100%

AF, *atrial fibrillation.* ***PPV,*** *positive predictive value.*

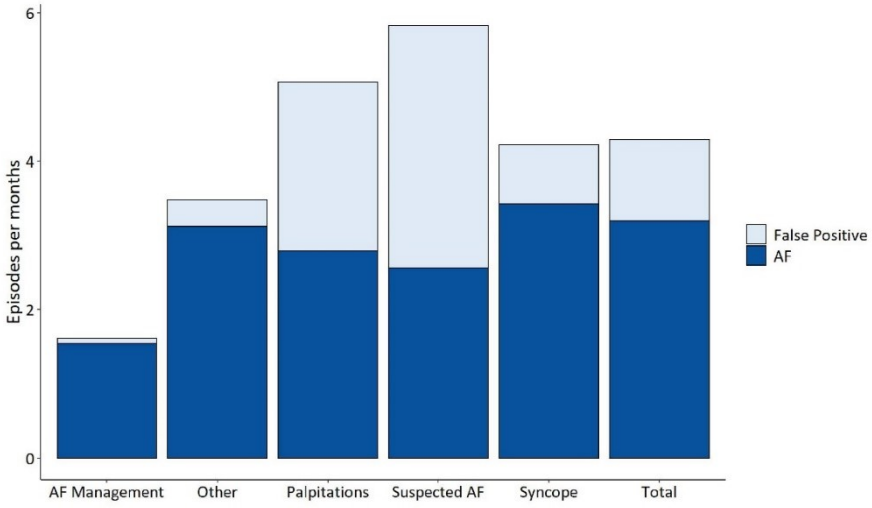

Figure S4-1. *Number of Confirm Rx episode AF recordings per patient month for different implant indications. Reproduced with permission from Briosa e Gala et al.*[255]

Table S4-2.*Summary of number of patients and episodes based on R-wave amplitude. Reproduced with permission from Briosa e Gala et al.*[255]

R-wave categories (mV)	Number of patients	Number of AF episodes detected	Number of True-AF episodes
0-0.19	20	1952	1038
0.2-0.39	49	3757	2136
0.4-0.59	63	4235	3589
0.6-0.79	29	1631	1290
0.8-0.99	19	2440	2131
1.0-1.19	19	498	443
1.2-1.39	1	162	162
1.4-1.59	0	0	0
1.6-1.79	0	0	0
1.8-1.99	0	0	0
>2	1	2	2

Table S4-3. *FP detections according to implant indications. Reproduced with permission from Briosa e Gala et al.*[255]

	Palpitations	**AF Management**	**Syncope**	**Suspected AF**	**Others**	**p-value**[1]
False-positive	1187 (44%)	7 (4.5%)	1964 (19%)	774 (56%)	146 (10%)	<0.001
True-AF	1516 (56%)	148 (95.5%)	8573 (81%)	614 (44%)	1320 (90)%	<0.01

[1]Chi-square test of independence

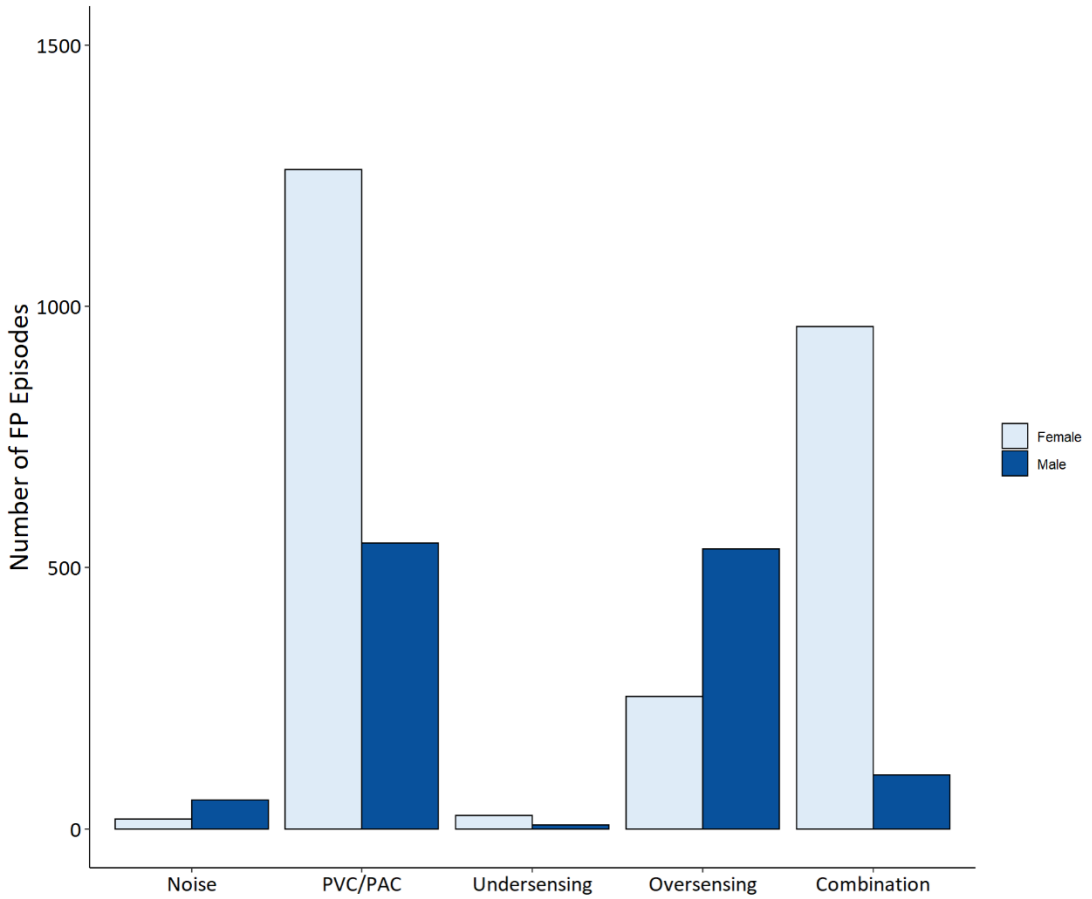

Figure S4-2. *Distribution of types of FP detections according to gender. Reproduced with permission from Briosa e Gala et al.*[255]

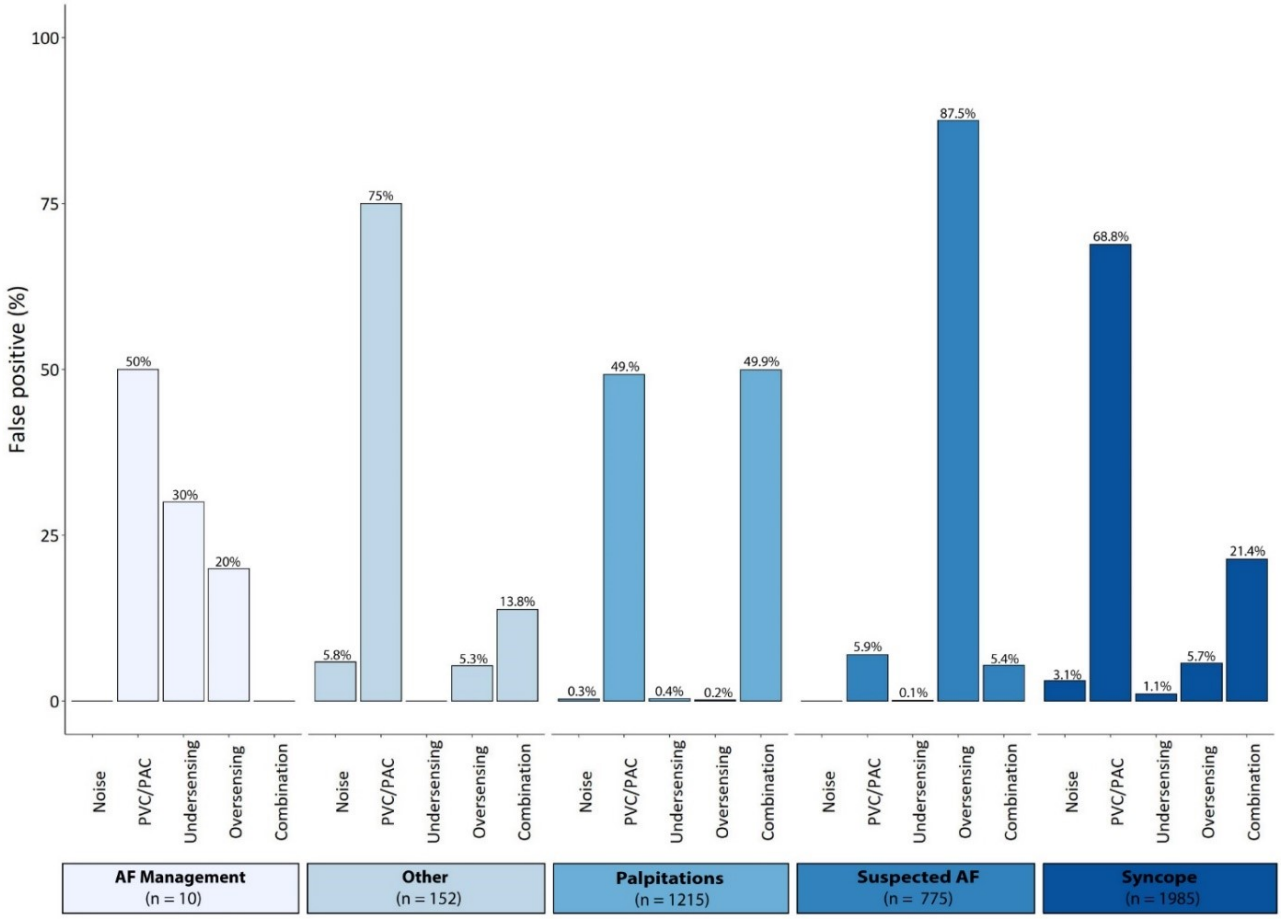

Figure S4-3. *FP detections according to implant indications. Reproduced with permission from Briosa e Gala et al.*[255]

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11 Appendix D

WEAR-TECH ECG Study supplementary material

This appendix contains supplementary figures and tables that provide additional information to support the findings presented in *Chapter 5.*

Table S5-1. *Diagnostic performance of the automatic detection and physician-interpretation of SL-ECGs for atrial arrhythmias using the 12-lead ECGs as gold standard. Reproduced with permission from Briosa e Gala et al.*[256]

Device	Atrial arrhythmia detection	N	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Apple Watch	Algorithm (all ECGs)	483	59.3 (53.0-65.2)	79.2 (73.6-83.8)	74.2 (67.6-79.9)	65.7 (60.1-71.0)
	Algorithm (unclassified excluded)	386	75.8 (69.2-81.3)	96.9 (93.5-98.6)	96.0 (91.5-98.2)	80.5 (75.0-85.1)
	Physician (all ECGs)	483	96.2 (92.9-98.0)	96.8 (93.7-98.3)	96.6 (93.4-98.3)	96.4 (93.2-98.1)
CART ring	Algorithm (all SL-ECG)	483	75.3 (69.5-80.3)	93.8 (89.9-96.2))	92.4 (87.9-95.4)	78.9 (73.8-83.3)
	Algorithm (unclassified excluded)	474	77.2 (71.5-82.1)	94.9 (91.4-97.1)	93.8 (89.6-96.4)	80.6 (75.6-84.9)
	Physician (all SL-ECG)	483	90.8 (86.5-93.9)	96.7 (93.6-98.3)	96.5 (93.2-98.2)	91.4 (87.4-94.3)

CI*, Confidence Intervals.* ***ECG****, electrocardiogram.* ***NPV****, negative predictive value.* ***PPV****, positive predictive value.* ***SL-ECG****, single-lead electrocardiogram.*

Table S5-2. *Diagnostic performance of physician interpretation of SL-ECGs for other cardiac rhythm using the 12-lead ECG as gold standard. Reproduced with permission from Briosa e Gala et al.*[256]

Device	Rhythm	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Apple Watch	Atrial Fibrillation	95.4 (91.4-97.5)	89.6 (85.6-92.6)	86.0 (80.8 - 90.0)	96.6 (93.7 - 98.2)
	Sinus Rhythm	92.1 (87.6-95.0)	93.3 (89.6-95.7)	91.6 (87.2-94.6)	93.6 (90.0-96.0)
	Atrial Flutter/Tachycardia	37.5 (25.2-51.6)	99.5 (98.3-99.9)	90.0 (69.9-97.2)	93.5 (90.9-95.4
	Sinus rhythm with ectopy	58.8 (36.0-78.4)	97.4 (95.5-98.5)	45.5 (26.9-65.3)	98.5 (96.9-99.3)
	AF with complete heart block	50 (9.5-90.5)	100 (99.2- 100)	100 (20.7-100)	99.8 (98.9-100)
	Complete heart block	20 (3.6- 62.4)	100 (99.2- 100)	100 (20.7-100)	99.2 (97.9-99.7)
	Ventricular tachycardia	0 (0-79.3)	100 (99.2- 100)	—	99.8 (98.9-100)
	Junctional rhythm	0 (0-79.3)	100 (99.2- 100)	—	99.8 (98.9-100)
CART Ring	Atrial Fibrillation	94.3 (90.1-96.8)	88.9 (84.8-92.0)	85.1 (79.7- 89.3)	95.9 (92.8- 97.7)
	Sinus Rhythm	87.3 (82.2-91.2)	92.1 (88.2-94.8)	89.9 (85.0-93.3)	90.1 (85.9-93.2)
	Atrial Flutter/Tachycardia	22.9 (13.3-36.5)	99.5 (98.3-99.9)	84.6 (57.8-95.7)	92.1 (89.3-94.2)
	Sinus rhythm with ectopy	52.9 (31.0-73.8)	95.9 (93.7-97.4)	32.1 (17.9-50.7)	98.2 (96.5-99.1)
	AF with complete heart block	0 (0-65.8)	100 (99.2-100)	—	99.6 (98.5-99.9)
	Complete heart block	0 (0.0-43.4)	100 (99.2-100)	—	99.0 (97.6-99.6)
	Ventricular tachycardia	0 (0-79.3)	100 (99-100)	—	99.8 (98.9-100)
	Junctional rhythm	0 (0-79.3)	100 (99-100)	—	0 (0-79.3)

AF*, Atrial fibrillation.* ***CI****, Confidence Intervals.* ***ECG****, Electrocardiogram.* ***PPV****, Positive predictive value.* ***NPV****, Negative predictive value.* ***SL-ECG****, Single-lead electrocardiogram.*

Table S5-3. *Proportion of correct rhythm identification of SL-ECGs from the Apple Watch and CART Ring, stratified by diagnostic SL-ECGs' quality rated by adjudicators (high, intermediate, uninterpretable). Reproduced with permission from Briosa e Gala et al.*[256]

Method	Apple Watch	CART Ring	P-value
Automated detection			
• High	292/381(76.6%)	348/386 (90.2%)	< 0.001
• Intermediate	46/89 (51.7%)	68/78 (87.2%)	< 0.001
• Uninterpretable	0/7	8/17 (47.1%)	0.03
Physician Interpretation			
• High	351/381 (86.1%)	350/386 (90.7%)	0.47
• Intermediate	77/89 (86.5%)	72/78 (92.6%)	0.23
• Uninterpretable	0/7	0/17	—

12 Appendix E

SMART-ALERT Study supplementary material

This appendix contains supplementary figures and tables that provide additional information to support the findings presented in *Chapter 6.*

Table S6-1. *Daily wear time of the Apple Watch and CART Ring. Reproduced with permission from Briosa e Gala et al.*[257]

	Apple Watch	**CART Ring**	**p-value**
Daily Wear Time (min)	954 ± 401	344 ± 478	<0.001
Daytime Wear (min)	582 ± 219	157 ± 233	<0.001
Nighttime Wear (min)	372 ± 246	187 ± 264	<0.001

Values represent mean ± SD; p-values are measured using the Wilcoxon ranked-sum test.

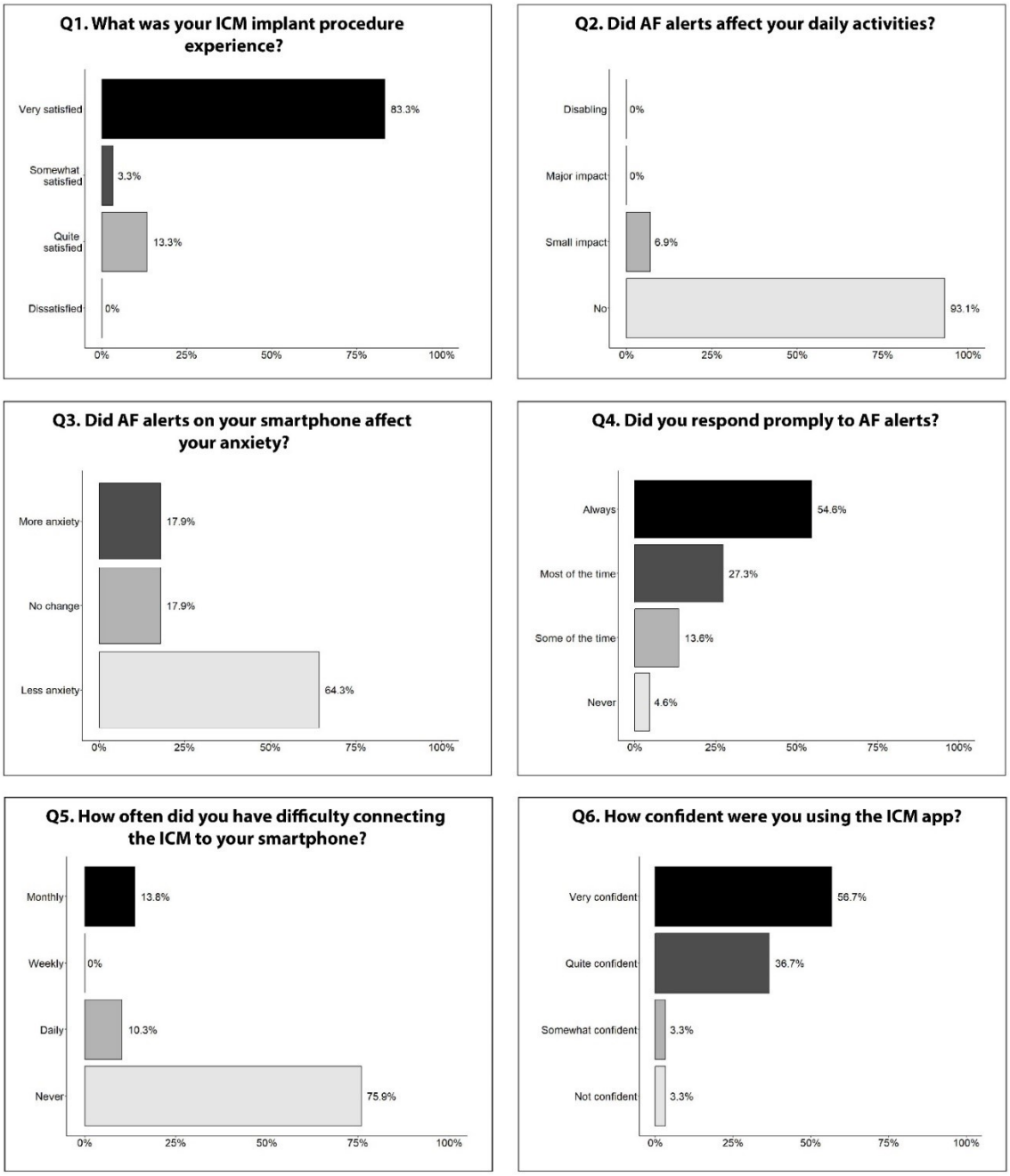

Figure S6-1. *SMART-ALERT Questionnaire Answers (Part A). A total of 30 of 39 patients completed the questionnaire. Responses are shown for the first six questions pertaining to the ICM.*

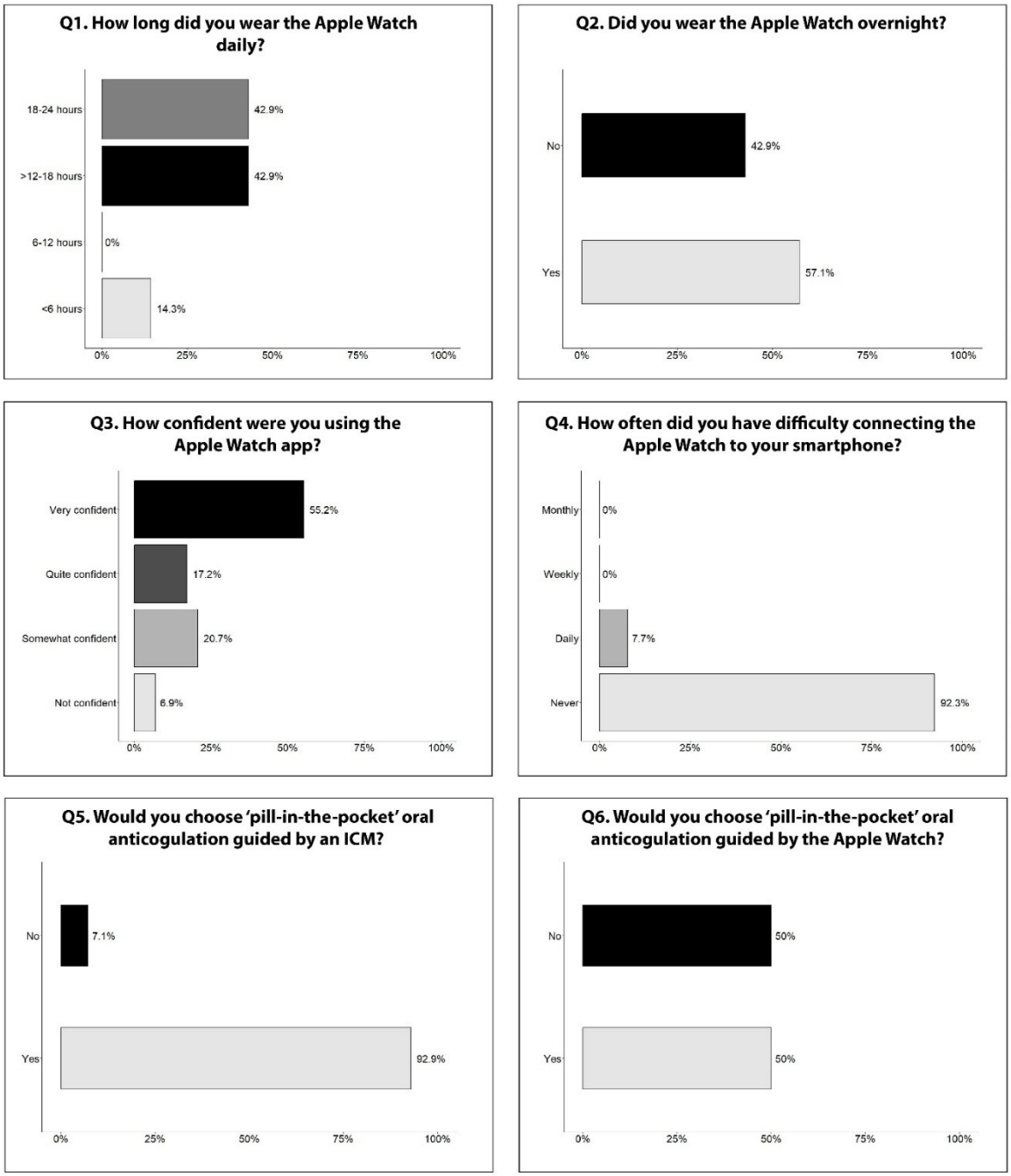

Figure S6-2. *SMART-ALERT Questionnaire Answers (Part B). A total of 14 of 20 patients allocated the Apple Watch completed the part B of the questionnaire.*

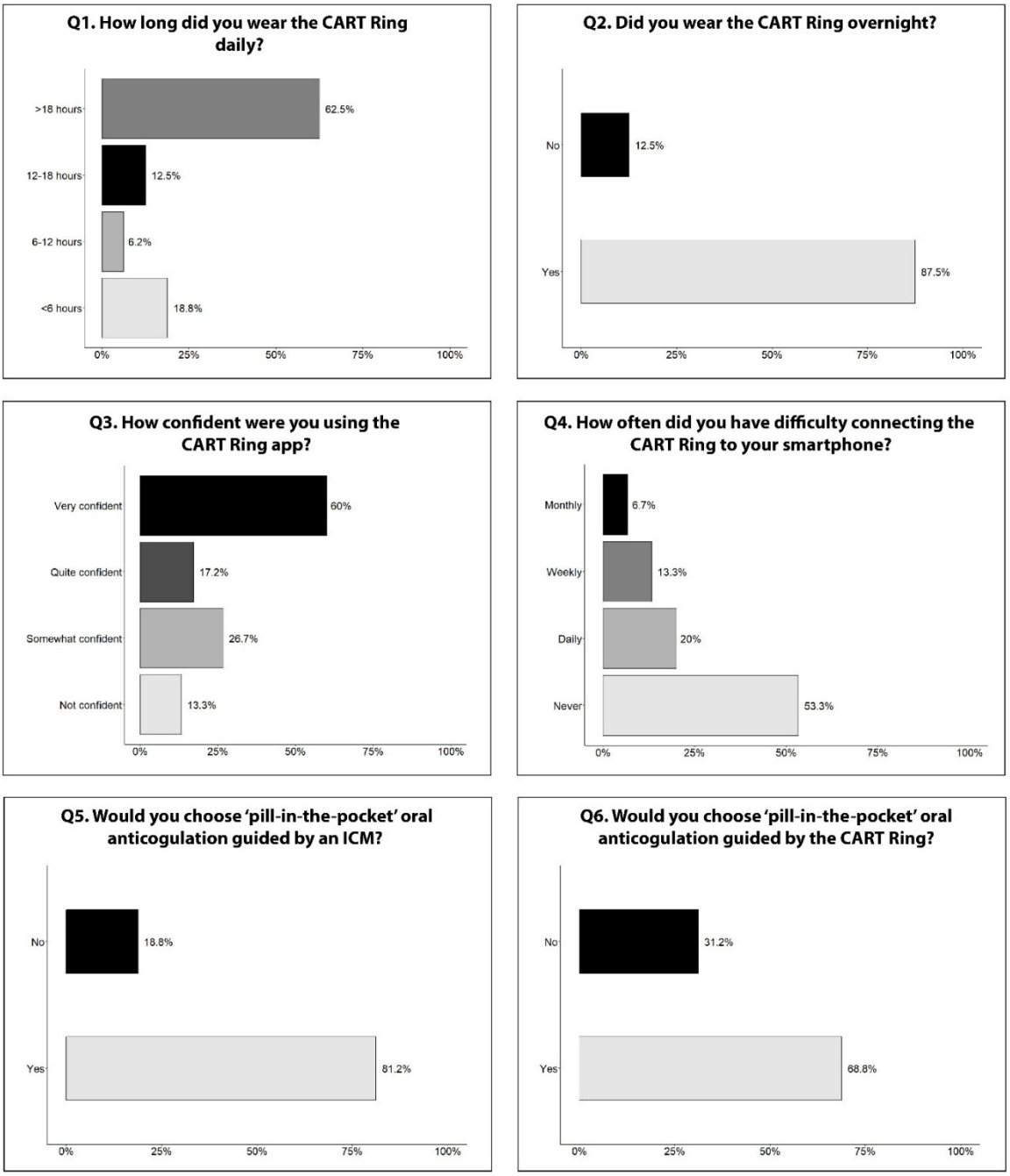

***Figure S6-3**. SMART-ALERT Questionnaire Answers (Part C). A total of 16 of 20 patients allocated the CART Ring completed the part C of the questionnaire.*

Table S6-2. *Summary of participants' feedback on the study devices in the SMART-ALERT Study. Reproduced with permission from Briosa e Gala et al.*[257]

Study devices	Top theme	Representative comments	Other feedback
ICM	Reliability, reassurance	"ICM works well"	"ICM and phone app impressive"; "Improved quality of life"; "Having a an ICM was reassuring"
Apple Watch	Comfort, good connectivity, missed alerts	"Forgot to wear"; "Not comfortable during sleep"	"Could not wear with some clothes"; "Too intrusive"; "Had no alerts"; "Did not detect AF episodes"; "Would depend on accuracy for pill-in-pocket strategy"
CART Ring	App connectivity, poor, battery life, discomfort	"App lost connection most days"	"Poor battery life"; "Too cumbersome"; "Used a lot of phone battery"; "App did not connect well"; "Too heavy"; "Stopped working after 2 months"

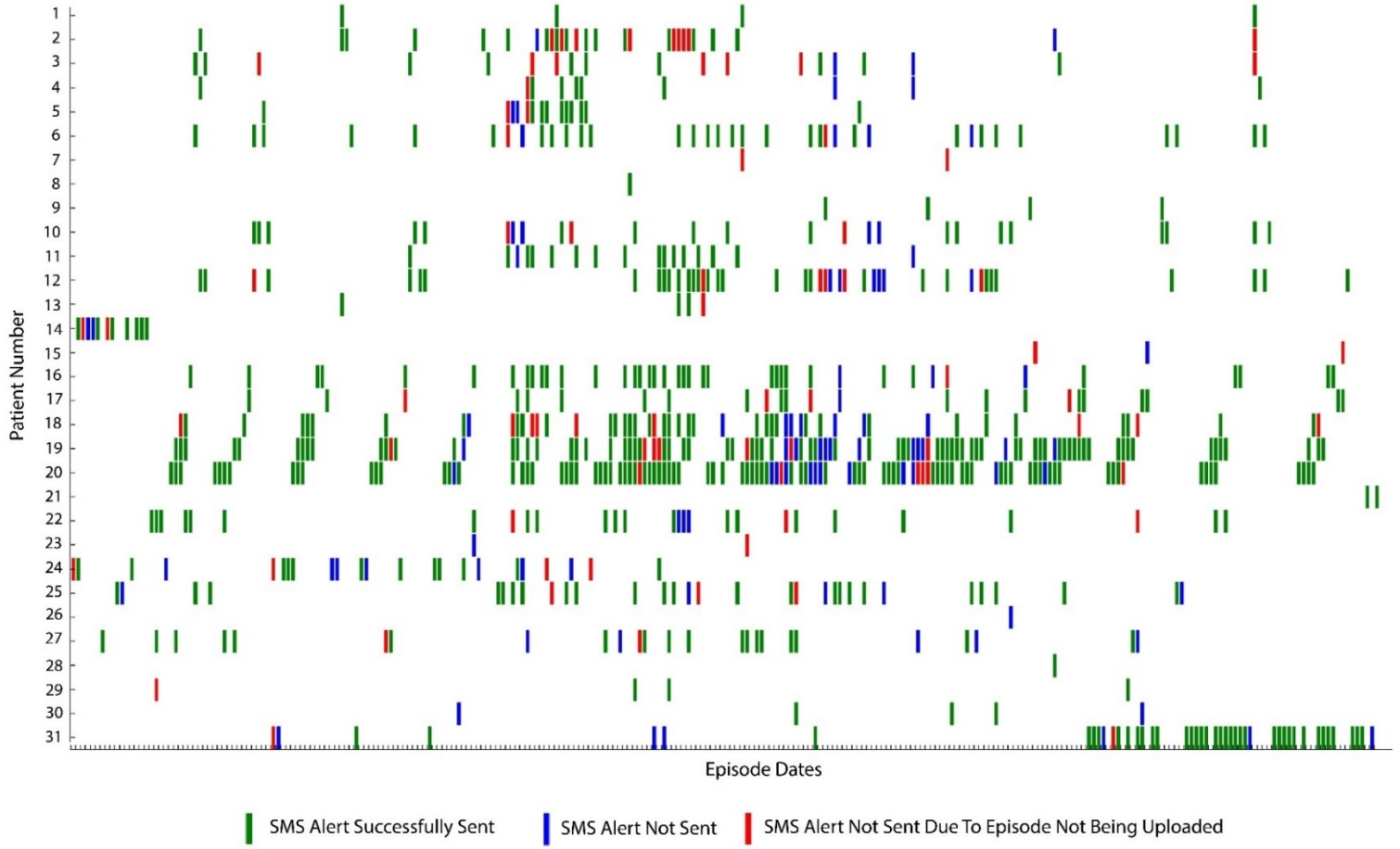

Figure S6-4. *Distribution of SMS alert statuses across episodes during phase 1: green bars indicate successfully sent alerts, blue bars represent alerts not sent, and red bars denote alerts not sent due to episodes not being uploaded.*

13 References

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