ACE BRIEF FOR NEW AND EMERGING HEALTH TECHNOLOGIES

KardiaMobile for the Detection of Atrial Fibrillation

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Summary of Key Points

- Atrial fibrillation (AF) is the most common type of cardiac arrhythmia worldwide, with a local prevalence of 1.5% which is expected to rise with an ageing population.
- Current standards of AF detection by either 12-lead ECG following irregular pulse identified by manual pulse palpation, or by ambulatory AF detection (Holter and event monitors) following a negative electrocardiogram (ECG), are restricted by their limited time of rhythm surveillance.
- KardiaMobile (AliveCor, Inc.) is a portable ECG monitor available as a single- or six-lead device, which allows an ECG trace to be captured for an extended period and analysed by the KardiaAI algorithm for classification of possible AF.
- Based on the maturity of the evidence base, this brief focused on the single-lead KardiaMobile device (hereinafter referred to as KM) to detect AF in patients with suspected or known AF.
- In both populations of patients with suspected or known AF, KM was safe, acceptable, and had good diagnostic accuracy in AF detection (both sensitivity and specificity ≥92%) for both clinician or automated interpretation of KM-ECG trace, compared against standard care.
- Clinical utility and cost-effectiveness evidence generally favoured the use of KM in patients with suspected AF, especially those referred for ambulatory ECG monitoring.
    - In patients with suspected AF (e.g. undiagnosed palpitations) referred for ambulatory monitoring, KM significantly increased detection of AF by 10-fold (p=0.006), and earlier (9.9 vs. 48 days, p=0.004), than standard care at a reduced cost (by £13.22 [S$23] per person over two years compared to Holter monitor).
    - The use of KM as a single timepoint test in patient with suspected AF remains uncertain, although it could be cost-effective compared to 12-lead ECG in detecting AF (incremental cost-effectiveness ratio of £1,060 [S$1,824] per quality-adjusted life-year gained) despite limitations in the cost model.
    - In patients with known AF, limited evidence showed that KM increased detection of AF recurrence by 1.6- to 2.6-fold compared to standard care. However, evidence for other clinical outcomes remains limited. KM also incurred an additional cost of £85.91 (S$148) per person over 10 years to monitor for AF recurrence compared to Holter monitor.
- There is no evidence showing KM improved healthcare system benefits.
- Key limitations include the mixed populations of the diagnostic accuracy findings and a lack of direct evidence on the impact of KM on patient outcomes such as stroke incidence.
- The KM device costs S$137, while the Kardia app is free of cost.
- Key implementation considerations include the potential burden on local healthcare services resulting from an increased number of patients diagnosed with AF by KM, proper use of KM to minimise interference during ECG recording, accessibility, and cybersecurity concerns.

- In patients with suspected AF, the National Institute for Health and Care Excellence recommended the use of KM in those referred for ambulatory ECG monitoring while concluding insufficient evidence for its adoption as a single timepoint test.

I. Background

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia that arises from abnormal electrical activity within the atria of the heart.[1] It is characterised by an irregularly fast cardiac rhythm which may be paroxysmal (i.e. episodes are less than seven days) or persistent (i.e. episodes are more than seven days).[1] Due to irregular cardiac rhythm, blood flow in the heart becomes turbulent and increases the likelihood of a thrombus formation, which may dislodge and cause a stroke.[1] The accurate and timely detection of AF is important to enable prompt treatment and prevent such serious life-threatening complications.[2] Patients with AF may be asymptomatic or present symptoms such as chest pain, syncope, palpitations, dyspnoea on exertion or lower extremity swelling.[1]

Globally, the prevalence of AF is approximately 1%.[1] It has been estimated that between 2001 and 2050 the number of people with AF will double or triple.[1,3] In Singapore, the overall prevalence of AF was estimated to be 1.5% in 2008, increasing to 5.8% in adults above 80 years of age.[4] AF substantially impacts mortality and morbidity, with a two-fold increase in mortality and five-fold increase in the risk of stroke.[5] In addition, patients with AF are generally older and have a higher prevalence of comorbidities, all of which imposes a high burden on healthcare systems with increasing hospital cost and multiple admissions over the years.[6]

At present, traditional ambulatory rhythm monitoring devices for palpitations and AF such as Holter and event monitors, are restricted by their limited time for rhythm surveillance (up to 30 days) and lack of real-time data transmission.[7] This intermittent cardiac monitoring strategy is considered suboptimal, as it may not adequately capture sporadic episodes of arrhythmia.[7] Furthermore, in the primary care setting, people with intermittent AF that stops between manual pulse check and use of a 12-lead ECG may experience delayed diagnosis and treatment.[8] Together, this presents a clinical unmet need for monitoring devices that can capture abnormal heart rhythms over a long period of time, so to better inform clinical decisions, and for easy-to-use devices that can provide greater accuracy in detecting AF in primary care settings.[7]

II. Technology

KardiaMobile (AliveCor, Inc.) consists of the portable electrocardiogram (ECG) monitor, available as a single (KardiaMobile-1L) or six-lead (KardiaMobile-6L) device, and the Kardia mobile application that operates with a compatible smartphone or tablet for analysis of the ECG recording (Figure 1).[9] For an ECG recording to be captured by either device, two or more fingers of each hand are placed on each top surface electrode for 30 seconds. The KardiaMobile-6L device has an additional electrode on the bottom surface for contact with

the left knee or ankle.[9] The completed ECG recording can be wirelessly transferred to the Kardia mobile application for analysis by the KardiaAI algorithm. The ECG recording and results can be saved and emailed to healthcare professionals. Of note, the ECG recording interpreted by the algorithm does not provide a complete diagnosis and all interpretations should be reviewed by a medical professional for clinical decision-making.[10]

Figure 1. Illustration of the KardiaMobile system. Image adapted from https://store.kardia.com/products/kardiamobile

There are a number of arrythmia interpretations that can be made by the KardiaAI algorithm from the ECG traces, including AF, tachycardia, bradycardia, or unreadable if it cannot be interpreted due to interference.[11] Additional classifications (premature ventricular contractions, sinus rhythms with supraventricular ectopy and sinus rhythm with wide QRS) are available with a premium KardiaCare membership.[11] Also, compared to single-lead, the six-lead device can assess heart rhythm from multiple angles to detect other arrhythmias besides AF with the availability of a good ECG trace.[9]

The portability and ease-of-use of KardiaMobile gives patients the ability to monitor their ECG recordings for an extended period, at any time of the day. It also allows an ECG to be taken soon after an irregular pulse is detected, potentially increasing the likelihood of identifying paroxysmal AF episodes. Unlike conventional Holter or event monitors, KardiaMobile does not need to be fitted by trained healthcare professionals which means associated hospital appointments may be reduced.

III. Regulatory and Subsidy Status

The KardiaMobile system obtained regulatory clearance from the US Food and Drug Administration (FDA) in 2019 and 2021 for the single- and six-lead devices, respectively.[12,13] It is intended for use in adult patients with known or suspected heart conditions and health-conscious individuals.[12,13] Similarly, the KardiaAI software obtained FDA clearance in 2019.[14] The KardiaMobile system and the KardiaAI software were both granted the CE mark in 2018.[11]

IV. Stage of Development in Singapore

☒	Yet to emerge	☐	Established
☐	Investigational / Experimental (subject of clinical trials or deviate from standard practice and not routinely used)	☐	Established *but* modification in indication or technique

☐ Nearly established

☐ Established *but* should consider for reassessment (due to perceived no/low value)

V. Treatment Pathway

Based on the National Institute for Health and Care Excellence (NICE) guideline for the diagnosis and management of AF, individuals with suspected AF are first assessed for the presence of irregular pulse by manual pulse palpation.[15] Regardless of symptoms, if an irregular pulse is detected, a 12-lead ECG is then used to diagnose for AF.[15] For individuals with suspected paroxysmal AF undetected by 12-lead ECG, 24-hour ambulatory ECG monitoring, or longer term ambulatory monitors or event recorders, are recommended to be used depending on the interval of AF episodes.[15] Patients with previously diagnosed AF may also undergo ambulatory ECG monitoring for surveillance of AF recurrence.[11] Local clinicians shared that this pathway generally reflects local clinical practice, except that single-lead ECG traces of more than 30 seconds are commonly used to diagnose AF, especially with the increased use of ECG watches (Personal communication: Senior Consultant from National University Heart Centre Singapore, 21 July 2023).

KardiaMobile can be used either as a replacement or an add on to current standard of care, such as 12-lead ECG or ambulatory ECG monitoring, in the pathway to detect AF (see Figure A1 in Appendix A). Local clinicians shared that KardiaMobile may be used in the primary care or specialist outpatient setting.

VI. Summary of Evidence

This assessment was conducted based on the Population, Intervention, Comparator and Outcome (PICO) criteria for patients with suspected or known AF (Table 1). Literature searches were conducted in international health technology assessment (HTA) databases, Cochrane library, PubMed and Embase. Given the maturity of evidence, this brief focused on the single-lead KardiaMobile device (hereinafter referred to as KM) to detect AF.

A total of ten studies[9,16-24] were included in the key evidence base. Four studies from the key evidence base included patients with suspected AF – one HTA report from the National Institute for Health and Care Excellence (NICE; DG35, 2019),[23] two diagnostic accuracy studies[16,21] and one cohort study[19]. Two additional key studies reported on patients with known AF, including one randomised controlled trial (RCT)[20] and one cohort study[17]. A further four studies involved patients with either suspected or known AF, including one HTA report from NICE (MTG64, 2022)[9] and three diagnostic accuracy studies[18,22,24]. Of note, NICE MTG64[9] focused on the use of KM in patients with suspected or known AF referred for ambulatory ECG monitoring, while NICE DG35[23] evaluated single-lead ECG devices (including KM) as a single timepoint test to detect symptomatic AF in the primary care setting.

Two other studies were included as supplementary evidence including one post-hoc analysis[25] of a RCT and a cohort study[26] reporting on the clinical utility of KM. The study design and

characteristics of the key and supplementary evidence sources are presented in Tables B1 and B2 (Appendix B).

Table 1: Summary of PICO criteria

Population	Adults with suspected AF	Adults with known AF
Intervention	KardiaMobile	
Comparator	Current clinical pathway for AF detection, including 12-lead ECG and ambulatory ECG monitoring	Ambulatory ECG monitoring to detect AF recurrence
Outcome	Safety, clinical- and cost-effectiveness	
Abbreviations: AF, atrial fibrillation; ECG, electrocardiogram.		

Safety

KM was found to be generally safe with no major safety concerns. Among 27 studies included in NICE MTG64, three adverse events (AEs) were reported including high-pitched noise and impact of movement artefacts on the quality of ECG readings.[11] This same NICE assessment also reported eight AEs from the FDA Manufacturer and User Facility Device Experience (MAUDE) database, including misclassification of ECG readings and false positive reading.[11] Such risks may be mitigated with interpretation of ECG traces by a trained healthcare professional.[11] An updated search of the MAUDE database conducted in July 2023 did not identify any additional AE related to KM.

Effectiveness

A total of 10 studies[9,16-24] in the key evidence base reported on effectiveness of KM across the two intended populations. There is a greater availability of evidence for the use of KM in patients with suspected AF than known AF. Notably, NICE highlighted that the heterogeneity in the evidence base (e.g. population, usage frequency and comparators) reflects how KM would be used in a National Health Service (NHS) setting.[9,11]

Accuracy

Overall, KM demonstrated good diagnostic accuracy in the detection of AF in patients with suspected or known AF. In a heterogeneous population of patients with undiagnosed or known AF, clinician-interpreted KM-ECG trace demonstrated good sensitivity (92.8% to 100%) and specificity (94% to 100%) with reference to 12-lead ECG (see Table 2 and Table C1 in Appendix C).[16,18,22-24] Similarly, automated KM-ECG interpretation showed good sensitivity (92% to 100%) and specificity (92% to 98%) with reference to either clinician interpretation of KM-ECG trace or 12-lead ECG in a mixed population (see Table 2 and Table C2 in Appendix C).[9,21] It was acknowledged that the accuracy data reported in NICE MTG64 were based on a per ECG recording basis and may not represent the diagnostic accuracy of KM in diagnosing AF per patient.[9,11]

Table 2: Diagnostic accuracy of KM in detecting AF

Study (year)	Population (n)	Index test	Reference test	Sensitivity, % (95% CI)	Specificity, % (95% CI)
NICE DG35 (2019)[23]	Mixed population (n=484)[a]		12-lead ECG	94.0% (85.1% to 97.7%)[b]	96.8% (88.0% to 99.2%)[b]

Himmelreich et al. (2019)[16c]	Patients indicated for 12-lead ECG (n=214)	Clinician interpreted KM-ECG		100% (85.2% to 100%)	100% (98.1% to 100%)
Wegner et al. (2020)[24]	Patients from the EP ward (n=92)			100% (NR)	94% (NR)
Koltowski et al (2021)[18]	Patients with various cardiac conditions (n=99)			92.8% (NR)	100% (NR)
Mannhart et al. (2023)[22]	Patients presenting to a cardiology service, including those scheduled for arrhythmia treatment (n=201)			98% (89% to 100%)	98% (94% to 100%)
NICE MTG64 (2022)[9,11]	Mixed population (n=471)[d]	Algorithm interpreted KM-ECG	Clinician interpreted KM-ECG or 12-lead ECG	92% to 99% (NR)[e]	92% to 98% (NR)[e]
Leńska-Mieciek et al. (2022)[21]	Patients with acute ischemic stroke (n=50)		Clinician interpreted KM-ECG	100% (47.8% to 100%)	98.3% (97.2% to 99.0%)

[a] Include inpatients in a cardiology ward, cardiology clinical patients, people in tertiary care, people at a cardiology department and people attending an AF clinic who were known to have AF and people with unknown AF status.

[b] Pooled sensitivity and specificity from three studies.

[c] Includes the detection of AF or atrial flutter.

[d] Include patients with AF recurrence post-treatment, transient AF, known paroxysmal AF or a mixed population. Refer to Table C2 in Appendix C for more information.

[e] Diagnostic accuracy based on per ECG recording.

Abbreviations: AF, atrial fibrillation; CI, confidence interval; ECG, electrocardiogram; EP, electrophysiology; KM, KardiaMobile; NICE, National Institute for Health and Care Excellence; NR, not reported.

Clinical utility

Patients with suspected AF

In patients with suspected AF referred for ambulatory monitoring, NICE MTG64 concluded that KM detected more AF episodes compared to standard care (see Table C3 in Appendix C).[11] Based on two RCTs reviewed by NICE, KM significantly increased AF detection in patients with undiagnosed palpitations (10-fold, p=0.006) and stroke (p=0.024) compared to Holter monitor (Table 3).[11]

Table 3: Diagnostic yield of KM in patients with suspected AF referred for ambulatory ECG monitoring

Study (year)	Population (n)	Percentage of AF cases detected		Risk ratio (95% CI)	p-value
		KardiaMobile	Standard care		
Reed et al. (2019)	Undiagnosed palpitations (n=240)	6.5%	0%[a]	10.3 (95% CI, 1.3 to 78.5)	0.006
Koh et al. (2021)	Post-stroke or TIA (n=203)	9.5%	2.0%[b]	—	0.024

[a] Standard care depends on centre included: Holter (24-hour, 48-hour, 7+ days), subsequent ECG.

[b] Standard care involves additional round of Holter (24-hour).

Abbreviations: AF, atrial fibrillation; CI, confidence interval; TIA, transient ischemic attack.

Note: Table adapted from NICE MTG64[11].

Based on two comparative studies, NICE MTG64 found that KM detected AF earlier than standard care.[11] Compared to standard care, KM reduced time to AF detection in patients with undiagnosed palpitations (mean, 9.9 *vs.* 48 days, p=0.0004) and stroke (median, 3 *vs.* 7 days, p=0.02; see Table 4 and Table C4 in Appendix C).[9,11] In contrast, a recent study[19] found no difference in arrhythmia detection time between KM and implantable loop recorder in patients with adult congenital heart disease (ACHD). However, it should be noted that there were substantial between-group differences in patient characteristics (e.g. history of arrhythmia, severity of ACHD) and sample size.[19]

Table 4: Impact of KM on time to AF detection in patients with suspected AF referred for ambulatory ECG monitoring

Study (year); study design	Patient population (n)	Time to detection		p-value
		KardiaMobile	Standard care	
Reed et al. (2019); RCT	Undiagnosed palpitations (n=240)	9.9 days	48 days	0.0004
Yan et al. (2020); Observational study	Post-stroke or TIA (n=1079)	3 days (IQR, 2 to 6 days)	7 days (IQR, 6 to 10 days)	0.02

Abbreviations: AF, atrial fibrillation; ECG, electrocardiogram; IQR, interquartile range; KM, KardiaMobile; NR, not reported; TIA, transient ischemic attack.

Note: Table adapted from NICE MTG64[11].

To add, a real-world study suggested that KM could potentially impact clinical decision-making, as 7.2% of symptomatic patients referred for ambulatory KM monitoring were prescribed anti-arrhythmic or anticoagulant therapy.[26]

There is limited evidence on the clinical utility of KM as a single timepoint test for patients with suspected AF. Unpublished evidence reported in NICE DG35 suggested that a significant proportion (69.9%) of people with newly diagnosed AF had used KM, however NICE concluded that this benefit remained unclear with respect to standard care.[8] Another study also included in NICE DG35 found that clinical management changed in five out of six people following AF detection by KM.[8]

Patients with known AF

KM was found to improve detection of AF recurrence in patients with AF. Compared to standard care, three studies reviewed in NICE MTG64 reported that KM significantly improved AF detection in patients with a history of AF by 1.6- to 2.6-fold (Table 5).[11] In particular, NICE highlighted that AF detection is influenced by the frequency and duration of KM use, which should be advised by the managing healthcare professionals.[11] Similar findings were observed in a post-hoc study of the iHEART RCT, where frequent KM users with a history of AF were 23% more likely to report premature atrial contractions (rhythm abnormality associated with AF) than infrequent users (p=0.002; see Figure C1 in Appendix C).[25]

Table 5: Diagnostic yield of KM in patients with known AF

Study (year)	Population (n)	Percentage of AF cases detected		HR (95% CI)	p-value
		KardiaMobile	Standard care		
Hickey et al. (2017); Case-control	AF recurrence after treatment (n=46)	60.9%	30.4%[a]	2.55 (95% CI, 1.0 to 6.11)	0.04

Goldenthal et al. (2019); RCT	AF recurrence after treatment (n=238)	50.4%	41.5%[b]	1.56 (95% CI, 1.06 to 2.3)	0.024
Hermans et al. (2021); Dx accuracy	AF recurrence after treatment (n=115)	25.2%	14.8%[c]	—	<0.001

[a] Standard care involves usual cardiac medical care (no daily ECG self-monitoring).

[b] Standard care not defined.

[c] Standard care refers to Holter (min 24-hour), repeated at 3, 6 and 12 months.

Abbreviations: AF, atrial fibrillation; CI, confidence interval; Dx, diagnostic; HR, hazard ratio; KM, KardiaMobile.

Note: Table adapted from NICE MTG64[11].

However, evidence to determine the impact of KM on time to detection, clinical decision and quality-of-life (QoL) in patients with known AF was limited. One RCT reviewed in NICE MTG64 reported that KM detected cardiac arrhythmia recurrence earlier than standard care, although this was not quantified (see Table C4 in Appendix C).[11] Another study (n=29) included in NICE MTG64 reported a change in clinical management in 9 out of 12 patients with potential AF detected by KM.[11] Moreover, two RCTs demonstrated that KM improved AF-related QoL scores in patients with a history of AF compared to baseline, although its impact on QoL may be confounded by other concurrent interventions (see Table C5 in Appendix C).[9,11]

To highlight, across both populations of patients with suspected or known AF, the findings of clinical utility had a greater applicability when KM was used in patients referred for ambulatory ECG monitoring than as a single timepoint test. NICE MTG64 concluded that among patients with suspected or known AF referred for ambulatory monitoring, KM detected significantly more people with AF than Holter monitor.[11] In contrast, NICE DG35 cautioned the applicability of its finding for symptomatic patients with suspected AF undergoing single timepoint testing with KM as the evidence comprised people who were asymptomatic for AF, although many had a history of AF.[8]

Patient acceptance

Aside from clinical utility, KM was well-accepted by patients. Nine studies reviewed in NICE MTG64 consistently reported a high level of patient acceptance.[11] Across these studies, most people (87% to 100%) found KM easy to use and reduced anxiety (see Tables C6 and C7 in Appendix C).[11] Similar findings were reported in NICE DG35, where KM was well-accepted by patients and general practitioners.[8] However, a small proportion of people (6.1%) surveyed by NICE reported difficulty in transferring ECG trace to healthcare professionals.[11]

Healthcare system benefit

There is no evidence suggesting additional healthcare system benefit of KM compared to standard care. In patients with suspected or known AF referred for ambulatory monitoring, NICE MTG64 and two other studies found no between-group differences in outpatient appointments, GP attendances, hospital admissions and number of ECGs performed (see Table C8 in Appendix C).[11,17,20] Two studies reported significantly reduced ECG monitors required with KM over standard care, while inconsistent findings were reported for ED attendance.[11,17,20] These equivocal findings were highlighted by NICE, who concluded that system-level benefits of KM were not proven.[11]

Cost-effectiveness

Patients with suspected AF

Overall, compared to standard care, KM was found to be either cost saving or cost-effective in patients with suspected AF. In people presenting with undiagnosed palpitations referred for ambulatory monitoring, NICE's cost model showed that KM led to cost savings of £13.22 (S$23)[a] per person over two years for the detection of AF compared to Holter monitor (Table 6).[9] The cost savings were driven by the reduction in diagnostic cost as cost of KM is lower than that of Holter monitor.[9] Findings from the cost model are consistent with other published economic analyses reviewed by NICE, where cost savings were reported largely due to reduced healthcare appointments (see Table C9 in Appendix C).[9,11]

As a single timepoint test in patients with suspected AF, NICE DG35 reported that KM appeared to be cost-effective over standard care with an incremental cost-effectiveness ratio (ICER) of £1,060 (S$1,824)[a] per quality-adjusted life-year (QALY) gained (Table 6).[23] However, NICE considered that the model's cost-effectiveness finding was inconclusive due to limitations in the diagnostic accuracy estimates used, uncertainty that the model captured all AEs induced by anticoagulants used in clinical practice, and sensitivity of the model towards the prevalence of paroxysmal AF.[8]

Patients with known AF

When compared to Holter monitor, KM was likely cost-incurring by £85.91 (S$148)[a] per patient over 10 years when used to monitor for AF recurrence post-treatment in a population with low risk of stroke (Table 6).[9] This was driven by an increased anticoagulant use for stroke prevention although NICE cautioned the applicability of this finding due to the complex and varied clinical management strategies for AF recurrence stemming from patients' comorbidities and their medical history.[9]

Table 6: Summary of economic modelling for KM *vs.* standard care

Study	Economic model	Population	Comparison arms	Time horizon	Outcome
Patients with suspected AF					
NICE MTG64 (2022)[9]	CMA	Patients presenting with undiagnosed palpitations	KM *vs.* Holter monitor	2 years	Cost savings of £13.22 per person
NICE DG35 (2019)[23]	CEA	Patients presenting in primary care with signs and symptoms of AF and who have an irregular pulse	KM *vs.* 12-lead ECG	30 years	ICER of £1,060 per QALY gained
Patients with known AF					
NICE MTG64 (2022)[9]	CMA	Patients with AF recurrence at one year post-treatment and in those referred for repeat testing in the low risk stroke group (CHA_2DS_2-VASc=1)	KM *vs.* Holter monitor	10 years	Cost incurring by £85.91 per person
Abbreviations: AF, atrial fibrillation; CEA, cost-effectiveness analysis; CMA, cost-minimalisation analysis; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 and					

[a] Based on the Monetary Authority of Singapore exchange rate as of 15 August 2023: £1=S$1.7208. Figures were rounded to the nearest dollar.

sex category (female); ICER, incremental cost-effectiveness ratio; KM, KardiaMobile; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life-year.

Ongoing trials

As identified from the ScanMedicine database (NIHR Innovation Observatory), there are five ongoing trials investigating the use of KM for patients with suspected AF and two trials for patients with known AF (Table 7). Of these, six are RCTs to determine the resource utilisation, diagnostic yield and health outcomes of KM compared to standard care.

Table 7: Summary of ongoing trials

Study (Trial ID)	Estimated enrolment	Brief description	Estimated completion date
Patients with suspected AF			
WAHOO (ACTRN12619000793112)	80	A RCT to determine the diagnostic yield of KM for heart rhythm disorders compared to Holter in patients with undiagnosed palpitations.	Not reported
CATCH-AF (NCT04302311)	220	A RCT to investigate if the KM monitoring device is a superior strategy for diagnosing AF compared to normal ambulatory monitoring in patients with symptoms of AF.	July 2023
CANDLE-AF (KCT0005592)	200	A RCT to compare the detection rate of AF with KM monitoring three times a day and 72 hours of single-lead ECG patch monitoring compared with the conventional Holter test in patients with acute ischemic stroke.	November 2025
Monitor-ACS (NCT03940066)	169	A RCT to evaluate the efficacy of monitoring with Biomonitor-2 and KM after discharge of patients with high-risk acute coronary syndrome.	June 2023
SPOT AF (ACTRN12616001293459)	300	A single-arm study to compare the number of stroke sufferers with previously undiagnosed intermittent AF that are detected by KM to 12-lead ECG and 24 to 48 hours of Holter monitoring or cardiac telemetry.	Not reported
Patients with known AF			
KardiaMobile ECG Monitoring Effects on Health Care Utilization and Patient Experience with AF (NCT05407415)	100	A RCT to determine healthcare utilisation and patient's satisfaction with KM compared to routine standard of care in patients with AF.	December 2023
AFibLITT_R (NCT04076020)	264	A RCT to evaluate the effect of the use of relational agent[a] and KM compared to usual care daily for 120 days on health outcomes in people with AF.	August 2023

[a] Smartphone-based intervention that simulates conversation and provides coaching, guidance, and assistance with chronic disease self-management.

Abbreviations: AF, atrial fibrillation; ECG, electrocardiogram; KM, KardiaMobile; RCT, randomised controlled trial.

Summary

Based on the evidence, KM was found to be safe and acceptable. It showed good diagnostic accuracy in detecting AF in patients with suspected or known AF, with both automated or clinician-interpreted KM-ECG trace demonstrating sensitivity and specificity above 92%. Further, the evidence on clinical utility and cost-effectiveness generally favoured the use of KM in patients with suspected AF, especially those referred for ambulatory ECG monitoring

where AF detection improved by 10-fold (p=0.006), and at an earlier time point (9.9 vs. 48 days, p=0.004), compared to standard care. Use of KM also resulted in a reduced cost of £13.22 (S$23) per person over two years compared to Holter monitor. In contrast, the clinical utility of KM as a single timepoint test in patients with suspected AF remains limited, although it appeared to be cost-effective over 12-lead ECG in detecting AF (ICER of £1,060 [S$1,824] per QALY gained) despite limitations in the cost model.

In patients with known AF, KM significantly improved detection of AF recurrence by 1.6- to 2.6-fold with limited evidence on its impact on time to detection, clinical management and other patient outcomes. In addition, healthcare system benefits of KM across patients with suspected or known AF were not proved. Moreover, KM was found to incur additional cost of £85.91 (S$148) per person over 10 years to monitor for AF recurrence.

It is worth to exercise caution in interpreting these findings, as the evidence supporting diagnostic accuracy was generated in a mixed population with various conditions including AF. Also, there is a paucity of direct evidence on the impact of KM on patient outcomes after AF diagnosis, such as stroke incidence.

VII. Estimated Costs

NICE reported KM to cost £82.50 (S$137)[a] with the Kardia app free of cost.[9] As listed on the company's website, the premium KardiaCare membership costs US$99 (S$134)[b] annually.[27]

VIII. Implementation Considerations

Implementation of KM into local clinical practice requires several considerations. As highlighted by NICE, the widespread use of KM in the UK NHS without careful patient selection may strain local healthcare services.[9] This was similarly raised by a local clinician, who noted that KM may lead to unnecessary healthcare utilisation as patients seek medical attention for unreadable or poorly recorded ECGs classified as abnormal. In particular, NICE shared that patients with suspected paroxysmal AF represent the most relevant clinical cases for the use of KM.[9] Thus, it is important that the prescription of KM involves careful patient selection guided by clinical judgement and individual circumstances.[9] Some key factors include risk of developing AF, age, comorbidities, and the availability of primary and secondary care resource to interpret ECG traces.[9] However, this is further complicated by the availability of KM 'off-the-shelf' to consumers.

It is also worth noting that the use of KM requires training of patients or their caregivers. To minimise unreadable recordings, training is important to reduce any interference during recording of ECG traces. Further, the technology may not be easily accessible to older people, who are at the greatest risk of AF, as the use of KM requires an internet connection and email address to create an account.[11] It should also be noted that KM may not be used in certain

[b] Based on the Monetary Authority of Singapore exchange rate as of 15 August 2023: US$1=S$1.3562. Figures were rounded to the nearest dollar.

group of individuals, such as those with hand tremors, disabilities or conditions affecting manual dexterity, who may not be able to record an ECG with the device.

The involvement of the Kardia mobile application to store and transmit ECG recordings may also pose data and privacy risk. Proper information governance and cybersecurity frameworks should be in place to ensure data protection and compliance of the device with local legislation and policies. In the UK, the company has fulfilled the Digital Technology Assessment Criteria framework that ensure digital health technologies fulfil requirements such as clinical safety, data protection, technical assurance, interoperability and usability for use in the NHS.[9]

IX. Concurrent Developments

Similar to KM, various handheld ECG monitors are in ongoing development (Table 8). Other mobile ambulatory ECG devices, that are patch-based and involve smartwatches are also being developed (see Table D1 in Appendix D). Of note, a local clinician shared that the main competitors for KM would be watch-based ECG devices (Personal communication: Senior Consultant from National University Heart Centre Singapore, 6 September 2023). Additionally, there are indications that AliveCor is developing a 12-lead KM device.[28,29] The company has also commercialised the single-lead KardiaMobile card, which is a credit-card-sized personal ECG similar to KM.[30]

Table 8: Concurrent development of handheld ambulatory ECG devices

Technology (Manufacturer)	Brief description	Status
ECG Check (Cardiac Designs)	The ECG Check can record, store, and send single-lead ECG tracings. It works in tandem with the ECG Check smartphone application, and also displays ECG tracings and uses an algorithm to detect the presence of normal sinus rhythm and abnormal rhythms.	FDA cleared and CE marked
Coala Heart Monitor (Coala Life)	The Coala Heart Monitor is a portable device that is securely connected to the patient's smartphone via Bluetooth. Patients start their monitor measurement by holding the device against their chest for thirty seconds, followed by a thumb ECG for increased detection accuracy.	
Portable EKG Monitor (EMAY)	Stand-alone personal EKG heart monitor that works independently without the need of a smartphone. Designed with real-time display of ECG trace, and built-in memory to store up to 100 readings.	FDA cleared
MyDiagnostick (MyDiagnostick Medical B.V.)	A single-lead ECG device that can produce and interpret an ECG trace.	CE marked
imPulse (Plessey Semiconductors Ltd)	A single lead ECG device, which is provided with downloadable software for data analysis (imPulse Viewer).	
Zenicor-ECG (Zenicor Medical Systems AB)	The technology comprises a single lead ECG device and an online system for analysis and storage.	

Abbreviations: CE, Conformitè Europëenne; ECG, electrocardiogram; FDA, US Food and Drug Administration.

Note: The list of concurrently developed technologies is not intended to be an exhaustive or comprehensive list, but rather represents the information available at the time of report development.

X. Additional Information

The use of single-lead ECG traces for the diagnosis of AF has been endorsed by some international clinical practice guidelines. The European Society of Cardiology has recommended the use of 12-lead ECG recording, or a single-lead ECG tracing of at least 30 seconds for the diagnosis of AF.[31] Similarly, both single-lead or 12-lead ECG are recommended for AF diagnosis by the Asia Pacific Heart Rhythm Society guideline on AF screening.[32]

Particularly for KM, the Scottish Health Technologies Group (SHTG)[33] and NICE[9] recommended its use in patients with suspected AF referred for ambulatory ECG monitoring (Table 9). As mentioned in Section VIII, among the diverse range of population groups reported in the evidence base, NICE considered that KM was clinically most relevant in symptomatic people with suspected paroxysmal AF.[9] In symptomatic patients with suspected AF, NICE concluded there was insufficient evidence for the routine adoption of KM to detect AF when used as a single timepoint test, and that further research is required.[23]

In addition, experts consulted by SHTG shared that KM has the potential to empower patients, allowing them to monitor their symptoms with minimal disruption to their daily lives.[33]

Table 9: Guideline recommendations for the adoption of KardiaMobile

Guideline	Recommendation
Patients with suspected AF referred for ambulatory ECG monitoring	
NICE MTG64 (2022)[9]	KardiaMobile is recommended as an option for detecting AF for people with suspected paroxysmal AF, who present with symptoms such as palpitations and are referred for ambulatory ECG monitoring by a clinician.
SHTG Adaptation (2022)[33]	Single-lead KardiaMobile is recommended as an option for detecting AF for people with suspected paroxysmal AF, who present with symptoms such as palpitations and are referred for ambulatory ECG monitoring by a clinician.
Patients with suspected AF referred for 12-lead ECG	
NICE DG35 (2019)[23]	There is not enough evidence to recommend the routine adoption of lead-I ECG devices (imPulse, KardiaMobile, MyDiagnostick and Zenicor-ECG) to detect AF when used for single time point testing in primary care for people with signs or symptoms of the condition and an irregular pulse.
Abbreviations: AF, atrial fibrillation; ECG, electrocardiogram; NICE, National Institute for Health and Care Excellence; SHTG, Scottish Health Technologies Group.	

References

1. Nesheiwat Z, Goyal A, Jagtap M. Atrial Fibrillation. StatPearls: StatPearls Publishing LLC.; 2023. PMID: 30252328

2. Seitanidis P, Gialelis J, Papaconstantinou G. Identifying heart arrhythmias through multi-level algorithmic processing of ECG on edge devices. *Procedia Computer Science*. 2022;203:699-706. doi: 10.1016/j.procs.2022.07.104.

3. Go AS, Hylek EM, Phillips KA, et al. Prevalence of Diagnosed Atrial Fibrillation in Adults: National Implications for Rhythm Management and Stroke Prevention: the AnTicoagulation and Risk Factors In Atrial Fibrillation (ATRIA) Study. *JAMA*. 2001;285(18):2370-5. doi: 10.1001/jama.285.18.2370.

4. Yap KB, Ng TP, Ong HY. Low prevalence of atrial fibrillation in community-dwelling Chinese aged 55 years or older in Singapore: a population-based study. *J Electrocardiol*. 2008;41(2):94-8. doi: 10.1016/j.jelectrocard.2007.03.012.

5. Chia PL. Stroke prevention in atrial fibrillation: the Singapore story. *Singapore Med J*. 2020;61(12):617-8. doi: 10.11622/smedj.2020175.

6. Kang HM, Ng SJ, Yap S, et al. Outcomes of Patients Presenting with Primary or Secondary Atrial Fibrillation with Rapid Ventricular Rate to the Emergency Department. *Ann Acad Med Singap*. 2018;47(11):438-44. https://pubmed.ncbi.nlm.nih.gov/30578422/

7. Baman JR, Mathew DT, Jiang M, et al. Mobile Health for Arrhythmia Diagnosis and Management. *J Gen Intern Med*. 2022;37(1):188-97. doi: 10.1007/s11606-021-07007-w.

8. National Institute for Health and Care Excellence. *Lead-I ECG devices for detecting symptomatic atrial fibrillation using single time point testing in primary care: overview*. London: NICE; 2019. [Accessed July 9, 2023]. https://www.nice.org.uk/guidance/dg35/documents/overview

9. National Institute for Health and Care Excellence. *KardiaMobile for detecting atrial fibrillation*. London: NICE; 2022. [Accessed July 26, 2023]. https://www.nice.org.uk/guidance/mtg64

10. AliveCor Inc. *Instructions for Use (KardiaMobile)* [Internet]. United States: AliveCor; 2021. [Assessed July 20, 2023]. https://alivecor.zendesk.com/hc/en-us/articles/1500000462022-User-Manuals.

11. National Institute for Health and Care Excellence. *KardiaMobile for detecting atrial fibrillation: supporting documentation*. London: NICE; 2021. [Accessed July 26, 2023]. https://www.nice.org.uk/guidance/mtg64/history

12. 510(k) Premarket Notification. K182396. United States: US Food and Drug Administration April 12, 2019. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K182396

13. 510(k) Premarket Notification. K210753. United States: US Food and Drug Administration June 30, 2021. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K210753

14. 510(k) Premarket Notification. K181823. United States: US Food and Drug Administration March 11, 2019. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K181823

15. National Institute for Health and Care Excellence. *Atrial fibrillation: diagnosis and management*. London: NICE; 2021. [Accessed July 10, 2023]. https://www.nice.org.uk/guidance/ng196

16. Himmelreich JCL, Karregat EPM, Lucassen WAM, et al. Diagnostic Accuracy of a Smartphone-Operated, Single-Lead Electrocardiography Device for Detection of Rhythm and Conduction Abnormalities in Primary Care. *Ann Fam Med*. 2019;17(5):403-11. doi: 10.1370/afm.2438.

17. Junarta J, O'Neill P, Dikdan SJ, et al. Mobile electrocardiographic devices and healthcare utilization in post-atrial fibrillation ablation patients. *J Electrocardiol*. 2023;80:139-42. doi: 10.1016/j.jelectrocard.2023.06.004.

18. Koltowski L, Balsam P, Glowczynska R, et al. Kardia Mobile applicability in clinical practice: A comparison of Kardia Mobile and standard 12-lead electrocardiogram records in 100 consecutive patients of a tertiary cardiovascular care center. *Cardiol J*. 2021;28(4):543-8. doi: 10.5603/CJ.a2019.0001.

19. Koole MA, Kauw D, Kooiman KM, et al. An implantable loop recorder or smartphone based single-lead electrocardiogram to detect arrhythmia in adults with congenital heart disease? *Front Cardiovasc Med*. 2022;9:1099014. doi: 10.3389/fcvm.2022.1099014.

20. Lambert CT, Patel D, Bumgarner JM, et al. Atrial fibrillation future clinic. Novel platform to integrate smart device electrocardiogram into clinical practice. *Cardiovasc Digit Health J*. 2021;2(2):92-100. doi: 10.1016/j.cvdhj.2021.02.002.

21. Leńska-Mieciek M, Kuls-Oszmaniec A, Dociak N, et al. Mobile Single-Lead Electrocardiogram Technology for Atrial Fibrillation Detection in Acute Ischemic Stroke Patients. *J Clin Med*. 2022;11(3):665. doi: 10.3390/jcm11030665.

22. Mannhart D, Lischer M, Knecht S, et al. Clinical Validation of 5 Direct-to-Consumer Wearable Smart Devices to Detect Atrial Fibrillation: BASEL Wearable Study. *JACC Clin Electrophysiol*. 2023;9(2):232-42. doi: 10.1016/j.jacep.2022.09.011.

23. National Institute for Health and Care Excellence. *Lead-I ECG devices for detecting symptomatic atrial fibrillation using single time point testing in primary care*. London: NICE; 2019. [Accessed July 9, 2023]. https://www.nice.org.uk/guidance/dg35

24. Wegner FK, Kochhäuser S, Ellermann C, et al. Prospective blinded Evaluation of the smartphone-based AliveCor Kardia ECG monitor for Atrial Fibrillation detection: The PEAK-AF study. *Eur J Intern Med*. 2020;73:72-5. doi: 10.1016/j.ejim.2019.11.018.

25. Masterson Creber RM, Reading Turchioe M, Biviano A, et al. Cardiac symptom burden and arrhythmia recurrence drives digital health use: results from the iHEART randomized controlled trial. *Eur J Cardiovasc Nurs*. 2022;21(2):107-15. doi: 10.1093/eurjcn/zvab009.

26. Cullen J, Reed MJ, Muir A, et al. Experience of a smartphone ambulatory ECG clinic for emergency department patients with palpitation: a single-centre cohort study. *Eur J Emerg Med*. 2021;28(6):463-8. doi: 10.1097/mej.0000000000000859.

27. AliveCor Inc. *KARDIACARE™* [Internet]. United States: AliveCor; 2022. [Assessed August 16, 2023]. https://store.kardia.com/products/kardiacare.

28. ClinicalTrials.gov. *Identifier: NCT05053243, Clinical Validation of the AliveCor Kardia 12L and 6L Devices* [Internet]. Bethesda, MD: National Library of Medicine; 2000. [Assessed August 10, 2023]. https://clinicaltrials.gov/study/NCT05053243.

29. ClinicalTrials.gov. *Identifier: NCT05617001, Clinical Validation and Safety of the AC 12L ECG System Against a Standard of Care 12-Lead ECG (AC 12L ECG)* [Internet]. Bethesda, MD: National Library of Medicine; 2020. [Assessed August 10, 2023]. https://clinicaltrials.gov/study/NCT05617001.

30. AliveCor Inc. *KardiaMobile® Card* [Internet]. United States: AliveCor; 2022. [Assessed September 10, 2023]. https://store.kardia.com/products/kardiamobile-card.

31. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021;42(5):373-498. doi: 10.1093/eurheartj/ehaa612.

32. Chan N-Y, Orchard J, Agbayani M-J, et al. 2021 Asia Pacific Heart Rhythm Society (APHRS) practice guidance on atrial fibrillation screening. *Journal of Arrhythmia*. 2022;38(1):31-49. doi: 10.1002/joa3.12669.

33. Scottish Health Technologies Group. *KardiaMobile® for detecting atrial fibrillation* [Internet]. Scotland: SHTG; 2022. [Assessed August 1, 2023]. https://shtg.scot/our-advice/kardiamobile-for-detecting-atrial-fibrillation/.

Appendix

Appendix A: Place of KardiaMobile (KM) in the diagnostic pathway of AF

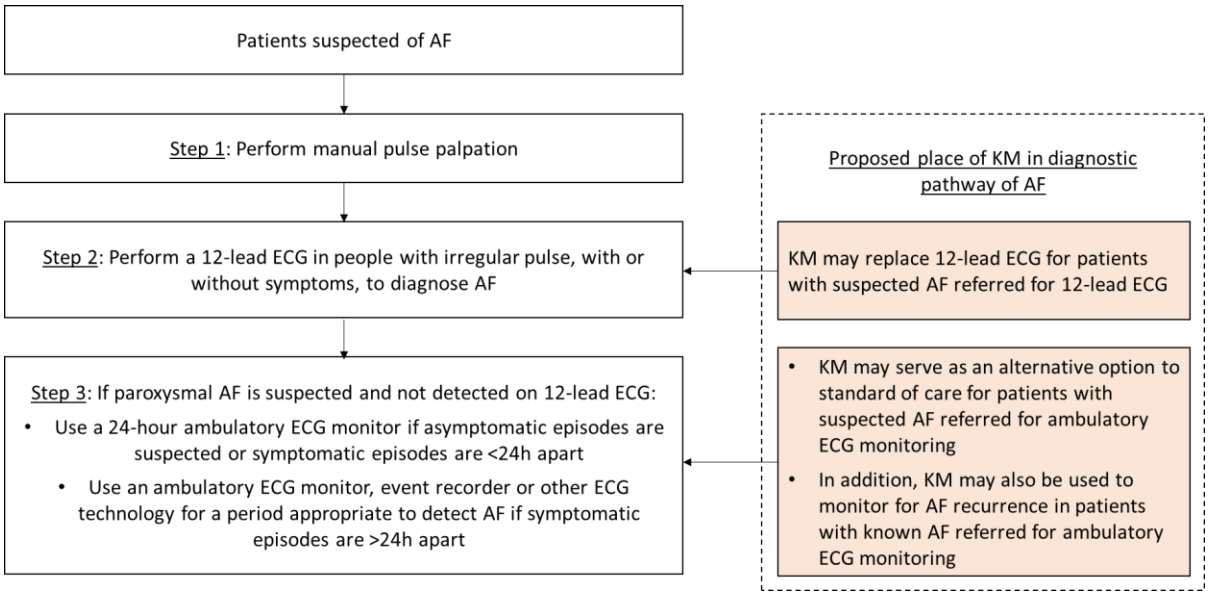

Figure A1: Proposed place of KardiaMobile in relation to the diagnostic pathway for atrial fibrillation. Abbreviations: AF, atrial fibrillation; ECG, electrocardiogram.

Appendix B: Studies included and study design

Table B1: List of included studies

Type of study	Key evidence base			Supplementary evidence base		
	Patients with suspected AF	Patients with known AF	Patients with suspected or known AF	Patients with suspected AF	Patients with known AF	Patients with suspected or known AF
Health technology assessment report	1	—	1	—	—	—
Randomised controlled trial	—	1	—	—	—	—
Diagnostic accuracy study	2	—	3	—	—	—
Cohort study	1	1	—	1	—	—
Single-arm study	—	—	—	—	1	—

Note:

1. Inclusion criteria
   a. Studies that fulfil the PICO criteria listed in Table 1.
2. Exclusion criteria
   a. Studies only available in the abstract form.

Table B2: Characteristic of included studies

Study	Scope	Study design	Number of studies /patients	Population	Intervention	Comparator or reference test
Key evidence						
Himmelreich et al. (2019)[16]	Patients with suspected AF	Diagnostic accuracy study	214 patients	Patients aged 18 years or older who were assigned to 12L-ECG for any nonacute indication as ordered by the local primary care physician in 1 of 10 participating general practices across the Netherlands	Single-lead KM-ECG interpreted by device algorithm and clinicians	Reference test: 12-lead ECG
NICE DG35 (2019)[23]	Patients with suspected AF	HTA	5 studies[a]	Mixed population[b]	Single-lead KM-ECG interpreted by device	Comparator: Manual pulse palpation followed by a 12-lead ECG

					algorithm or clinicians	in primary or secondary care before starting anticoagulation therapy. Note: 12-lead ECG is the reference standard for assessing diagnostic accuracy.
Wegner et al. (2020)[24]	Patients with suspected or known AF	Diagnostic accuracy study	99 patients	Inpatients from the electrophysiology ward in a large tertiary-care university hospital	Single-lead KM-ECG and novel parasternal lead interpreted by device algorithm and clinicians	Reference test: 12-lead ECG
Koltowski et al. (2021)[18]	Patients with suspected or known AF, or other cardiac conditions	Diagnostic accuracy study	100 patients	Patients admitted to hospital elective diagnostic and treatment procedures for various cardiac conditions (arrhythmias, conduction disorders, stable coronary disease, hypertension and others)	Single-lead KM-ECG interpreted by clinicians	12-lead ECG
Lambert et al. (2021)[20]	Patients with known AF	Open label RCT	100 patients	Patients presenting 3 to 4 months after early successful AF ablation	Single-lead KM device and enrolled in the Kardia Pro platform	Comparator: Standard-of-care, where patients were followed clinically based on symptoms and were not provided with a cardiac monitor at the time of randomization

Leńska-Mieciek et al. (2022)[21]	Patients with suspected AF	Diagnostic accuracy study	50 patients	Patients with acute ischemic stroke	Single-lead KM-ECG interpreted by device algorithm	Reference test: Single-lead KM-ECG interpreted by clinicians
NICE MTG64 (2022)[9]	Patients with suspected or known AF	HTA	32 studies	Adults (18 years or older) with known or suspected atrial fibrillation are referred for ambulatory ECG monitoring by a clinician in primary, secondary, or tertiary care	Single-lead KM	Comparator: Current pathway for AF detection, which includes ECG (a 12-lead ECG, performed and interpreted by a trained healthcare professional, is the reference standard for assessing diagnostic accuracy) and ambulatory monitoring (Holter or event monitoring).
Junarta et al. (2023)[17]	Patients with known AF	Cohort study	184 patients	Patients with paroxysmal or persistent AF presenting for their first AF ablation	Single-lead KM users	Comparator: Non-KM users
Koole et al. (2023)[19]	Patients with suspected AF	Cohort study	116 patients	Patients with adult congenital heart disease with palpitations within the last 3 years	Single-lead KM-ECG interpreted by specialised nurses	Comparator: Implantable loop recorder
Mannhart et al. (2023)[22]	Patients with suspected or known AF, or other cardiac conditions	Diagnostic accuracy study	201 patients	Patients presenting to a cardiology service at a tertiary referral center, including patients scheduled for catheter ablation procedures,	Apple Watch 6, AliveCor KardiaMobile or KardiaMo-bile 6L, Fitbit Sense, Samsung Galaxy Watch 3, and Withings Scanwatch ECG	12-lead ECG

				electric cardioversions, pacemaker or implantable cardioverter-defibrillator		
Supplementary evidence						
Cullen et al. (2021)[26]	Patients with suspected AF	Cohort study	290 patients	Patients (over 16 years) presenting consecutively to ED with palpitation or pre-syncope, whose ECG was normal, had a compatible device and where an underlying cardiac dysrhythmia was possible	Single-lead KM interpreted by clinicians	—
Masterson Creber et al. (2022)[25]	Patients with known AF	Post-hoc analysis of RCT	105 patients	Patients ≥18 years of age with documented AF and at least one AF-related risk factor, who were undergoing either direct current cardioversion or radiofrequency ablation as treatment to restore normal sinus rhythm	KM and behavioural altering messages	

[a] Number of diagnostic accuracy studies pertaining to KardiaMobile.

[b] Include inpatients in a cardiology ward, cardiology clinical patients, people in tertiary care, people at a cardiology department and people attending an AF clinic who were known to have AF and people with unknown AF status.

Abbreviations: AF, atrial fibrillation; ECG, electrocardiogram; ED, emergency department; HTA, health technology assessment; KM, KardiaMobile; RCT, randomised controlled trial.

Appendix C: List of supplementary tables and figure

Table C1: Diagnostic accuracy of KM as a single timepoint test in patients with suspected AF

Study (year)	Population (n)	Interpretation of KM-ECG	Reference test	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV	NPV
Himmelreich et al. (2019)[16a]	Patients indicated for 12-lead ECG (n=214)	HCP		100% (85.2% to 100%)	100% (98.1% to 100%)	100%	100%
		Algorithm		87% (66.4% to 97.2%)	97.9% (94.7% to 99.4%)	83.3% (65.2% to 93%)	98.4% (95.6% to 99.4%)
NICE DG35 (2019)[23]	Mixed population (n=484)[b]	HCP	12-lead ECG	94.0% (85.1% to 97.7%)[c]	96.8% (88.0% to 99.2%)[c]	—	—
	Mixed population (n=469)[b]	Algorithm		88.0% (32.3% to 99.1%)[d]	97.2% (95.1% to 98.5%)[d]	—	—
Wegner et al. (2020)[24b]	Patients from the EP ward (n=92)	HCP		100% (NR)	94% (NR)	—	—
		Algorithm		70% (NR)	69% (NR)	—	—
Koltowski et al (2021)[18]	Patients with various cardiac conditions (n=99)	HCP		92.8% (NR)	100% (NR)	—	—
Mannhart et al. (2023)[22]	Patients presenting to a cardiology service, including those scheduled for arrhythmia treatment (n=201)	HCP		98% (89% to 100%)	98% (94% to 100%)	96% (86% to 100%)	99% (95% to 100%)
		Algorithm		95% (83% to 99%)	96% (90% to 99%)	93% (90% to 98%)	98% (92% to 100%)

[a] Includes the detection of AF or Afl.

[b] Include inpatients in a cardiology ward, cardiology clinical patients, people in tertiary care, people at a cardiology department and people attending an AF clinic who were known to have AF and people with unknown AF status.

[c] Pooled sensitivity and specificity from three studies.

[d] Pooled sensitivity and specificity from two studies.

Abbreviations: Afl, atrial flutter; CI, confidence interval; ECG, electrocardiogram; HCP, healthcare professional; KM, KardiaMobile; NICE, National Institute for Health and Care Excellence; NR, not reported.

Table C2: Diagnostic accuracy of KM in patients with suspected or known AF referred for ambulatory ECG monitoring as reported in the supporting document for NICE MTG64 (2022)[11].

Study (year)	Population (n)	Index test	Reference test	Sensitivity (95% CI)	Specificity (95% CI)

William et al. (2018)	AF recurrence post-treatment (n=52)	Kardia app interpretation	12-lead ECG	96.6% (NR)	94.1% (NR)
Lowres et al. (2016)	Transient AF (n=42)		Clinical interpretation of KM ECG	94.6% (85.1% to 98.9%)	92.9% (92.0% to 93.8%)
Javed et al. (2019)	Known paroxysmal AF (n=29)			99% (NR)	98% (NR)
Selder et al. (2019)	Mixed population (n=233)[a]			92% (NR)	95% (NR)
Hermans et al. (2021)	AF recurrence post-treatment (n=115)			95.3% (NR)	97.5% (NR)

[a] Includes patients presenting with paroxysmal AF, palpitations of unknown origin or near-collapse who were selected by cardiologists of the clinic to participate in the program, although indications for inclusion in the program was left at the discretion of the physician.

Abbreviations: AF, atrial fibrillation; CI, confidence interval; ECG, electrocardiogram; KM, KardiaMobile; NR, not reported.

Table C3: Diagnostic yield of KM in patients with suspected or known AF referred for ambulatory ECG monitoring

Study (year); study design	Patient population (N)	Definition of standard care	Percentage of AF cases detected		RR/HR, (95% CI)	p-value
			KM arm	Standard care arm		
Patients with suspected AF						
Narashimha et al. (2018); Diagnostic accuracy	Undiagnosed palpitations (n=33)	External loop recorder (14-30 days)	18.2%	12.1%	—	—
Reed et al. (2019); RCT	Undiagnosed palpitations (n=240)	Depends on centre included: Holter (24-hour, 48-hour, 7+ days), subsequent ECG	6.5%	0%	RR, 10.3 (95% CI, 1.3 to 78.5)	0.006
Yan et al. (2020); Observational study	Post-stroke or TIA (n=1079)	Holter (24-hour)	8.8%	NR	—	—
Koh et al. (2021); RCT	Post-stroke or TIA (n=203)	Additional round of Holter (24-hour)	9.5%	2.0%	—	0.024
Patients with known AF						
Hickey et al. (2017); Case-control	AF recurrence after treatment (n=46)	Usual cardiac medical care (no daily ECG self-monitoring)	60.9%	30.4%	HR, 2.55 (95% CI, 1.0 to 6.11)	0.04

Goldenthal et al. (2019); RCT	AF recurrence after treatment (n=238)	Not defined	50.4%	41.5%	HR, 1.56 (95% CI, 1.06 to 2.3)	0.024
Hermans et al. (2021); Diagnostic accuracy	AF recurrence after treatment (n=115)	Holter (min 24-hour), repeated at 3, 6 and 12 months	25.2%	14.8%	—	<0.001

Abbreviations: AF, atrial fibrillation; CI, confidence interval; ECG, electrocardiogram; HR, hazard ratio; KM, KardiaMobile; RR, risk ratio; TIA, transient ischemic attack.

Note: Table adapted from the supporting document of NICE MTG64 (2022)[11].

Table C4: Time to AF detection in patients with suspected or known AF referred for ambulatory ECG monitoring

Study (year); study design	Patient population (N)	Time to detection		p-value
		KardiaMobile	Standard care	
Patients with suspected AF				
Dimarco et al. (2018); Observational study	Undiagnosed palpitations (n=148)	Median 12 days (range, 1 to 66 days)	—	—
Reed et al. (2019); RCT	Undiagnosed palpitations (n=240)	9.9 days	48 days	0.0004
Yan et al. (2020); Observational study	Post-stroke or TIA (n=1079)	3 days (IQR, 2 to 6 days)	7 days (IQR, 6 to 10 days)	0.02
Patients with known AF				
Goldenthal et al. (2019); RCT	AF recurrence after treatment (n=238)	NR[a]	NR[a]	—
Lowres et al. (2020); Observational study	New onset transient AF (n=29)	Median, 6 days (range, 2 to 23 days)	—	—

[a] Goldenthal et al. (2019) reported that cardiac arrhythmia recurrence was detected earlier with KardiaMobile than standard care, although this was not quantified.

Abbreviations: AF, atrial fibrillation; ECG, electrocardiogram; IQR, interquartile range; NR, not reported; TIA, transient ischemic attack.

Note: Table adapted from the supporting document of NICE MTG64 (2022)[11].

Table C5: Impact of KM on quality-of-life in patients with suspected or known AF referred for ambulatory ECG monitoring

Study (year); study design	Population (N)	Intervention arm	Control arm	QoL outcomes
Patients with known AF				
Smith et al. (2016); cohort study [abstract]	Patients with paroxysmal AF and rhythm control management (n=17)	KM	—	At 3-month follow-up compared to baseline: • No significant difference in QoL as assessed by SF-36 and AFEQT
Hickey et al. (2017); case-control[a]	Adults aged 21 years or older with a documented history	KM	—	At 6-month follow-up compared to baseline:

	of AF, scheduled to undergo a cardioversion ablation or medical management aimed at maintaining a normal sinus rhythm (n=13)			● Significant increase in physical component summary scores (50.3 to 55.9, p=0.02) ● No significant increase in mental component summary scores (47.5 to 51.7, p=NR)
Caceres et al. (2020); RCT	Adults aged 18 years and over, undergoing catheter radiofrequency ablation or direct current cardioversion. All had history of documented AF and at least one AF risk factor (n=238)	KM, text messages and standard care	Standard care	At 6-month follow-up compared to baseline: ● Both arms had improved AFEQT and AF symptom severity scores ● Global AFEQT scores improved significantly in the intervention (18.5±25.5) and control arm (11.2±18.5; p<0.05) ● No significant difference in HRQoL, QALY or AF symptom severity between arms
Guhl et al. (2020); RCT	Patients aged 18 years or older, history of chronic AF, prescribed oral anticoagulation for stroke prevention secondary to AF, English speaking sufficient to use a smartphone-based relational agent (n=120)	KM and relational agent	Standard care	At 30-days follow-up compared to baseline: ● There was a significantly higher improvement in total AFEQT score (adjusted MD 4.5; 95% CI, 0.6 to 8.3; p=0.03) and AFEQT daily activity sub-scores (adjusted MD 7.1; 95% CI, 1.8 to 2.4; p=0.009) in the intervention

				compared to control arm
Mixed population				
Praus et al. (2021); observational study	Adult patients who had two or more AF-related emergency department or urgent care visits in last 12 months, needed rate control medication titration, or needed monitoring of AF reoccurrence after re-establishing sinus rhythm (n=43)	KM and NowClinic (telehealth platform)	—	Assessed QoL using the Hospital Anxiety and Depression Scale pre- and post-intervention, with no paired analysis reported

[a] QoL only assessed in the intervention arm.

Abbreviations: AF, atrial fibrillation; AFEQT, atrial fibrillation effect on quality-of-life; CI, confidence interval; HRQoL, health-related quality-of-life; KM, KardiaMobile; MD, mean difference; NR, not reported; QALY, quality-adjusted life year; QoL, quality-of-life; RCT, randomised controlled trial.

Note: Table adapted from the supporting document of NICE MTG64 (2022)[11].

Table C6: Summary of studies reporting on the ease of use of KM

Study	Outcome
Lowres et al. (2016)	95% found KM easy to use. Only two participants reported they needed a familiarisation period. Shorter training was required for patients of higher education level and previous smartphone experience.
Hickey et al. (2017)	During six months no patient had reported trouble using device.
Reading et al. (2017)	52% of subjects needed frequent reminders (more than three) to transmit their ECG daily over the six-month monitoring period per protocol.
Narasimha et al. (2018)	Patients reported (via questionnaire) that KM was significantly easier to use than external loop recorder. Confirmed by higher compliance in KM arm.
William et al. (2018)	93.6% found KM easy to use.
Reed et al. (2019)	87% found KM easy to use.
Turchioe et al. (2019)	Patients found the device easy to use and gave highest scores (on 5-point Likert scale) for device portability.
Lowres et al. (2020)	All patients reported that KM was easy to use and that the time taken to record the ECG was not onerous.
Hermans et al. (2021)	More patients found long-term intermittent KM use more convenient than short-term continuous Holter monitoring.

Abbreviations: ECG, electrocardiogram; KM, KardiaMobile.

Note: Table adapted from the supporting document for NICE MTG64 (2022)[11].

Table C7: Summary of studies reporting on patient satisfaction of KM

Study	Outcome
Hickey et al. (2017)	92% of patients thought the device was beneficial.
William et al. (2018)	KM reduced anxiety.
Reed et al. (2019)	56% of patients agreed or strongly agreed that KM would be useful in diagnosing the cause of their symptoms.

Frey et al. (2020)	Patients felt reassured on the absence of cardiac rhythm disturbance using KM.
Lowres et al. (2020)	69% (11/16) of patients felt a sense of security from being able to self-monitor at home.
Praus et al. (2021)	KM reduced anxiety.
Abbreviations: ECG, electrocardiogram; KM, KardiaMobile. Note: Table adapted from the supporting document for NICE MTG64 (2022)[11].	

Table C8: Summary of healthcare system benefits of KM in patients with known or suspected AF referred for ambulatory ECG monitoring

Studies	Population (N)	Healthcare resource usage (KM *vs.* standard care)					
		Outpatient appointment	GP attendance	Hospital admission	ECGs performed	ED attendance	Additional ECG monitors
Included in NICE MTG64[11]							
Hickey et al. (2017)	Patients with AF undergoing ablation (n=46)	NR	NR	↔	NR	NR	NR
Goldenthal et al. (2019)	Patients with AF undergoing ablation (n=238)	NR	NR	↔	NR	↔	NR
Reed et al. (2019)	Undiagnosed symptomatic patients (n=240)	↔	↔	↔	↔	↑ (9.7% *vs.* 2.6%; p=0.031)	NR
Additional studies							
Lambert et al. (2021)[20]	Patients with AF undergoing ablation (n=100)	↔	NR	↔	NR	↔	↓ (5.9% *vs.* 27.1%; p=0.004)
Junarta et al. (2023)[17]	Patients with AF undergoing ablation (n=184)	↔	NR	↔	NR	↔	↓ (7 *vs.* 22; MD, -0.12; p=0.04)
Note: '↔' denotes no significant difference, '↑' denotes an increase and '↓' denotes a decrease in healthcare utilisation. Abbreviations: ECG, electrocardiogram; ED, emergency department; GP, general practitioner; KM, KardiaMobile; MD, mean difference; NICE, National Institute for Health and Care Excellence; NR, not reported; RCT, randomised controlled trial.							

Table C9: Economic evidence reviewed by NICE for KM in patients with suspected AF

Study	Economic model	Population	Time horizon	Outcome
YHEC (2018); UK	Economic impact evaluation	Modelling of a typical AF diagnostic pathway	1 year	KM saved £968 per patient by avoiding diagnostics and referrals to secondary care

Reed et al. (2019); UK	Costing analysis added to an RCT	Patients presenting with an episode of palpitations or pre-syncope with undiagnosed ECG rhythm after ED assessment	90 days	Cost per symptomatic rhythm diagnosed was £921 less per patient in the intervention (KM + SOC) group (£474; n=69) compared with the control (SOC) group (£1,395; n=11)
Abbreviations: AF, atrial fibrillation; ECG, Electrocardiogram; ED, emergency department; KM, KardiaMobile; NICE, National Institute for Health and Care Excellence; SOC, standard of care; YHEC, York Health Economics Consortium. Note: Table adapted from the supporting document of NICE MTG64 (2022)[11].				

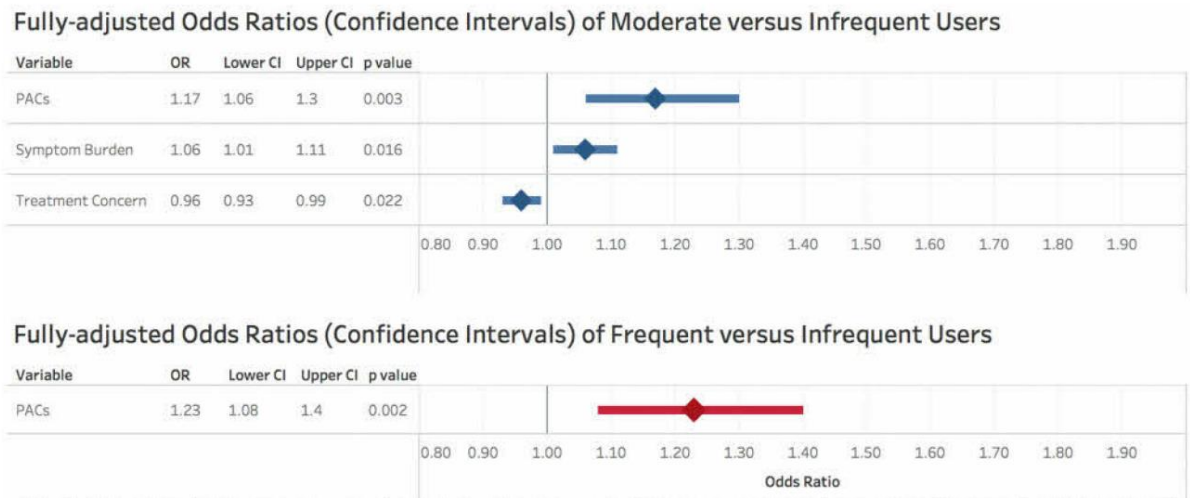

Figure C1: Likelihood of events between users with varying usage frequency of KardiaMobile. Multinomial logistic regression model examining the relationship between baseline characteristics and KardiaMobile use (comparing frequent and moderate to infrequent users). Abbreviation: PAC: premature atrial contraction. Figure adapted from Masterson Creber et al. (2022)[25].

Appendix D: Ongoing developments of mobile ECG devices

Table D1: Concurrent development of patch- and smartwatch-based ambulatory ECG devices

Technology (Manufacturer)	Brief description	Status
Patch		
Zio patch (iRhythm Technologies, Inc.)	Zio AT and Zio XT are single-use heart rate monitors that captures beat-to-beat cardiac rhythm for up to 14 days.	FDA cleared and CE marked
Carnation Ambulatory Monitor (Bardy Diagnostics, Inc.)	The CAM patch is designed to be placed along the sternum to optimize P-wave signal capture, improve ECG resolution, and provide more information about heart rhythm that may help lead to more clinically actionable diagnoses.	
Mobile Cardiac Outpatient Telemetry Patch System (BioTel Heart)	BioTel Heart's MCOT Patch is a convenient heart monitor that detects and transmits abnormal heart rhythms wirelessly.	FDA cleared
Smartwatch		
Apple Watch Series 4 (Apple Inc.)	Apple Watch Series 4 and later has an electrical heart rate sensor that, along with the ECG app, allows you to take an ECG.	FDA cleared and CE marked
Samsung Galaxy Watch (Samsung)	The ECG App uses the Galaxy watch to record and analyse your heart rhythm for the presence of AF.	
Fitbit smartwatch (Fitbit)	Fitbit's ECG app records those electrical signals and looks for signs of AF.	
Garmin ECG (Garmin)	An ECG app that allows users to record their heart rhythm and check for signs of AF.	FDA cleared
HUAWEI ECG App (Huawei)	An app that allows medical-grade ECG reading of their heart, allowing people to conveniently monitor their cardiac rhythm and proactively address potential heart health risks.	CE marked

Abbreviations: AF, atrial fibrillation; CAM, Carnation Ambulatory Monitor; CE, Conformité Européene; ECG, electrocardiogram; FDA, US Food and Drug Administration; MCOT, Mobile Cardiac Outpatient Telemetry.

Note: The list of concurrently developed technologies is not intended to be an exhaustive or comprehensive list, but rather represents the information available at the time of report development.