Screening people with diabetes for atrial fibrillation.

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This thesis is submitted for the degree of

Doctor of Philosophy

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Abstract

The aim of this thesis is to develop a comprehensive understanding around screening for atrial fibrillation [AF] in people with diabetes. Diabetes and AF are increasingly prevalent long-term conditions, and both increase morbidity and mortality. Stroke risk is higher in the presence of each of AF and diabetes, but considerably greater when they co-exist. Screening recommendations vary in terms of approach, method, and target groups. Screening studies to date have focused on high-risk, multi-morbid groups, but diabetes has not been the target population in its own right.

This thesis therefore comprises independent, yet related studies to build on existing evidence whilst adding insight into AF in the context of diabetes specifically, along with the interconnected complexities that encompass' AF screening. Firstly, a systematic review explores a novel approach to heart rhythm screening, by examining the feasibility, utility, and validity of a hand-held ECG recording device.

A trilogy of research studies then includes an AF screening study, whereby participants with diabetes are screened for AF, using the ECG device critiqued in the systematic review. This prevalence and predictors study aimed to determine if people with diabetes have a higher prevalence of AF than the general population. This was demonstrated, with a statistically significant difference between the prevalence of AF in the study population of people with diabetes as compared with the prevalence of AF in the general population without diabetes. Variables including age, sex, diabetes

duration, diabetes stability and screening location are explored, demonstrating increasing age as a significant predictor of the likelihood of an AF diagnosis (OR 1.089; 95% CI 1.025 – 1.158).

The second study sought to understand the impact of AF and then AF and diabetes in combination, on quality of life [QoL]. Participants accessed the 36-Item-Short-Form [SF-36] measurement tool via a nationwide heart rhythm website, revealing the AF and diabetes group to have a significantly poorer self-assessed QoL in five of the eight domains (Physical Functioning, Emotional Wellbeing, Energy and Fatigue, Social Functioning, Pain).

The third study sought to elucidate patients' views and understanding of AF and AF screening. Participants were recruited from the AF screening study if they had AF and were interviewed using a semi-structured approach. Understanding of AF was poor, highlighting the need for clear and concise information. Valuable information was obtained relating to screening preferences and location, convenience, personnel, and cost were important to patients when considering AF screening.

Together these studies have contributed to knowledge in this field through demonstration of the increased prevalence in the diabetes population and poorer QoL when both conditions exist. Through diagnosis, complications such as stroke can be minimised, and patient management directed to optimise health and reduce associated complications. In addition, patient feedback has elucidated support for AF screening, along with acceptance of the handheld ECG monitoring device as a feasible option for screening intervention. AF screening, therefore, in people with diabetes, is recommended to minimise the impact both increasingly prevalent conditions have on patients' health, morbidity and mortality, along with the wider social and economic impact.

Publications

Hall A, Mitchell A, Wood, L & Holland, C. (2020). Effectiveness of a single lead AliveCor® electrocardiogram application for the screening of atrial fibrillation. A systematic review. *Medicine, 99*(30), 1-19. https://doi.org/10.1097/MD.0000000000021388

Effectiveness of a single lead AliveCor® electrocardiogram application for the screening of atrial fibrillation (nih.gov)

Hall A, Mitchell A, Ashmore L & Holland C. (2021). Quality of life among people with atrial fibrillation with and without diabetes: a comparison study. *British Journal of Cardiology, 28*, 139-143. https://doi:10.5837/bjc.2021.042

Quality of life among people with atrial fibrillation with and without diabetes: a comparison study (bjcardio.co.uk)

Hall A, Mitchell A, Ashmore L & Holland C. (2022). Atrial fibrillation prevalence and predictors in patients with diabetes: a cross-sectional screening study. *British Journal of Cardiology, 29*, 21-25. https://doi:10.5387/bjc.2022.008.

Atrial fibrillation prevalence and predictors in patients with diabetes: a cross-sectional screening study (bjcardio.co.uk)

Hall A, Mitchell A, Ashmore L & Holland C. (2022). Should we be screening people with diabetes for atrial fibrillation? Exploring patients' views. *British Journal of Cardiology*, *29*, 145-9. https://doi:10.5837/bjc.2022.038

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The following publications are linked to this thesis by content relevance and written during the PhD programme.

Richardson E, Hall A & Mitchell A R. (2019). *Screening for Atrial Fibrillation and the Role of Digital Health Technologies*. In G Cismaru, & K. A. Chan (Eds.), Epidemiology and Treatment of Atrial Fibrillation. IntechOpen. https://doi.org/10.5772/intechopen.88660

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Hall A & Mitchell, A R. (2019). Should we be targeting people with diabetes when screening for atrial fibrillation? *British Journal of Cardiology, 26,* 48–9. https://doi:10.5837/bjc.2019.014

Presentations

Arrhythmia Alliance – Heart Rhythm Congress, Birmingham (virtual), October 2020. **Oral Presentation**. 'Undertaking Doctoral Research' (in Heart Rhythm Management).

3-Minute Thesis, Lancaster University, Lancaster (virtual), March 2021. Received 'Highly commended' award.

Arrhythmia Alliance - Heart Rhythm Congress, Birmingham (virtual), October 2021. **Oral Abstract**. 'Should we be screening people with diabetes for atrial fibrillation?'

Arrhythmia Alliance – Heart Rhythm Congress, Birmingham, (prepared for July 2022). **Oral Presentation**. 'Outcomes from my PhD in Health Research. Should we be screening people with diabetes for atrial fibrillation?'

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Abbreviations.

ABC Pathway	A – avoid stroke (with anticoagulation), B – better symptom management, C – cardiovascular and comorbidity risk optimisation
ABC	Atrial fibrillation, Blood pressure, Cholesterol. PHE Campaign for cardiovascular disease prevention
ADDQoL	Audit of Diabetes Dependent Quality of Life
ACE	Angiotensin Converting Enzyme
ADS	Appraisal of Diabetes Scale
AF	Atrial Fibrillation
AF6	Atrial Fibrillation 6 (a QoL questionnaire)
AFEQT	Atrial Fibrillation Effect on QualiTy of Life Survey
AFNET	AF Network
AFQLQ	Atrial Fibrillation Quality of Life Questionnaire
AF-QoL	Atrial Fibrillation Quality of Life
AFSS	Atrial Fibrillation Severity Scale
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
ARB	Angiotensin Receptor Blocker
ARIC	Atherosclerosis Risk in Communities
ATT19	The Diabetes Integration Scale-19
ATT39	The Diabetes Integration Scale-39
BHRS	British Heart Rhythm Association
BMI	Body Mass Index

BP	Blood Pressure
CCS-SAF	Canadian Cardiovascular Society Severity of Atrial Fibrillation Scale
CE	Common (or Current) Era
CHA_2DS_2-VASc	Stroke / Thromboembolic risk assessment in the context of atrial fibrillation. **C**ongestive Heart Failure / left ventricular systolic dysfunction, **H**ypertension (treated or consistently above 140/90mmHg), **A**ge >75 years, **D**iabetes Mellitus, **S**troke / trans-ischaemic attack, **V**ascular disease (e.g., peripheral artery disease, myocardial infarction, aortic plaque), **A**ge 65-74 years, **S**ex category (female)
CIED	Cardiac Implantable Electronic Device
COPD	Chronic Obstructive Pulmonary Disease
DCCT	The Diabetes Control and Complications Trial
df	Degrees of Freedom
DHP-1	Diabetes Health Profile
DPP-4	Dipeptidyl Peptidase-4 inhibitors
DQoL	Diabetes Quality of Life (QoL questionnaire)
DSQOLS	The Diabetes-Specific Quality of Life Scale
DQLCTQ	The Diabetes Quality of Life Clinical Trial Questionnaire
ERIC	Education Resources Information Centre
eTHoS	E-Theses Online Service
ECG	Electrocardiogram
EHRA	European Heart Rhythm Association

EQ-5D	Quality of Life Measurement Instrument developed by the EuroQol group with 5 dimensions
ESC	European Society of Cardiology
EuroQol	The EuroQol Group
F	F test (statistical test that uses the F-distribution)
FDA	Food and Drug Administration
FRACTAL	The Fibrillation Registry Assessing Costs, Therapies, Adverse Events and Lifestyle Study
GP	General Practitioner
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
GLP-1	Glucagon-Like Peptide
HbA1C	Haemoglobin A1C (glycated haemoglobin)
HGV	Heavy Goods Vehicle
HM	Holter Monitor
ILR	Implantable Loop Recorder
INR	International Normalised Ratio
mHealth	Mobile Health
mSToPS	mHealth Screening to Prevent Strokes Trial
MANOVA	Multivariate analysis of variance
MeSH	Medical Subject Headings
MOS	Medical Outcomes Survey
MMAT	Mixed Methods Appraisal Tool
MMR	Mixed Methods Research

NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NNS	Numbers Needed to Screen
NOMED-AF	NOninvasive Monitoring for Early Detection of Atrial Fibrillation
NSC	National Screening Committee
NVivo	Qualitative data management program (play on words from 'in vivo', developed from Computer Assisted Qualitative Data Analysis Software). NVivo has its roots in the NUD*IST program, developed for qualitative data management
OSA	Obstructive Sleep Apnoea
P	p value, or probability value
PHE	Public Health England
PICO	P - Population/Patient/Problem, I - Intervention, C - Comparison, O - Outcome
PPG	Photoplethysmography
SAFE	The Screening for Atrial Fibrillation with Electrocardiography Study
SD	Standard Deviation
SF-12	12-Item Short Form Health Survey
SF-36	36-Item Short Form Health Survey
SGLT-2	Sodium-Glucose Co-Transporter -2
SPSS	Statistical Package for the Social Science
TIA	Trans-ischaemic Attack
QoL	Quality of Life
QLAF	Quality of Life in Atrial Fibrillation Questionnaire

QSD	The Questionnaire on Stress in Patients with Diabetes
QSD-R	The Questionnaire on Stress in Patients with Diabetes – Revised
RAS	Renin-angiotensin system
RR	Risk Reduction
UK	United Kingdom
VALUE	The Valsartan Antihypertensive Long-term Use Evaluation
WHO	World Health Organisation
X^2	Chi-squared test

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Declaration

I declare that the work presented in this thesis is, to the best of my knowledge and belief, original and my own work. The material has not been submitted either in whole or in part, for a degree at this or any other university. This thesis does not exceed the maximum permitted word length of 80,000 words including appendices and footnotes, excluding the bibliography. An estimate of the word count is 80,846.

Angela Jane Moss Hall

Statement of Authorship and certification from supplementary authors.

AUTHORSHIP STATEMENT

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All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication before its appearance in the *Hong Kong Journal of Occupational Therapy*.

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Preface.

About the author. Nursing clinical and academic path.

As a registered nurse for twenty-three years, cardiology has always been the area of greatest interest. During my early career, the hospital in Jersey did not have dedicated cardiology nurses or indeed a cardiology unit. A move to London was therefore orchestrated and five years were spent gaining invaluable cardiology speciality experience and training (along with the opportunities and never to be forgotten years of fun!). Qualifications were gained in cardio-respiratory nursing, critical care, advanced life support, mentorship, supervision, and leadership. A return to Jersey then resulted in eight years working within the Intensive Care Unit, the latter four years as the ward Sister. Opportunities throughout the interim years in Intensive Care were however, not wasted. The implementation of evidence-based initiatives led to advances in local delivery of critical care, such as role advancements for health care assistants, mentorship programmes for junior colleagues, shifts with daily care procedures to more research-based practices and development of risk assessments for critical care, ventilated and multi-organ supported patients.

The acute side of cardiology however, remained a passion. A dynamic and extremely supportive Cardiologist was appointed, who was instrumental in establishing nurse specialty roles. This opportunity was relished, and my role as the Arrhythmia Nurse Specialist began. Since appointment, nurse-led clinics, streamlining of patient care, reductions in waiting times, nurse-delivered procedures and direct patient links were developed, leading to modelling of best practice in Jersey. Theatre usage was re-designed, having seen a lack of efficiency through ways of working. Documentation was amended with dedicated nurse assessment, less theatre cancellations, cost savings and the all-important single-point-of-care for patients introduced. New drugs were researched and obtained, following the production of in-depth reports, presented to senior medical and pharmaceutical boards. This led to new protocols and ways patients with arrhythmias were managed. Many patients no longer needed to travel to England, for stressful and potentially life-changing outcomes. Bed usage in hospital was slashed and patients discharged home sooner, made possible through

nurse-led diagnosis, investigation requests and analysis, prescription, overall management, and follow-up. Much of this work has been shared nationally with regards to service design.

Some of this work resulted in national recognition with awards relating to innovation and improvements in cardiac care. Perhaps the most overwhelming was the accolade received from the Royal College of Nursing, as the Nurse of the Year, in 2018. This was an unforgettable experience which saw all-deserving, inspiring and nurses receive recognition through sharing of best practice across the country, leading to further motivation and encouragement for all involved. This also solidified a considerable amount of ongoing work with the field of arrhythmia management and allowed for wider networking and learning from others, with regards to AF care and research.

Improving and enhancing patient care was then, and remains, the fundamental reason for self-determination within my chosen speciality. Strengthening this through evidenced-based practice, research, and opportunities to develop academically alongside the clinical journey, have included many challenges. A Masters in Advanced Practice including a non-medical prescribing qualification, assisted with furthering skills and practice within academia, whilst applying knowledge to practice. The research module and dissertation paved the way to the devisal of the research proposal for this PhD. Unanswered questions around AF screening in high-risk populations, resulted in queries that the author felt were important to address. It was therefore, through clinical practice and daily care of patients with AF, that led to this interest. The impact of AF on physical, psychological, and societal health is significant and as the specialist nurse managing the care of these patients, often without medical input, targeting and structuring care to optimise their holistic health, has direct relevance. The link specifically with diabetes came under enquiry through what appeared to be an increase in presentation of both chronic conditions in co-existence, and the desire to explore this beyond what first appeared a coincidence. This was strengthened by uncovering divergent theories relating to AF and diabetes, the mechanisms and pathophysiology behind this. Research whereby this was explored either as a primary objective or secondary consideration, revealed varying outcomes from different study designs, often lacking consistency and reliability. Similarly,

prevalence data of AF in people with diabetes was not obtainable, and these gaps, therefore, contributed to the development of research presented within this thesis.

Furthermore, this interest was propelled through work undertaken as a nurse representative with the British Heart Rhythm Society, a national group of doctors, physiologists and two nurses, who meet six times a year to discuss matters of national relevance around arrhythmia management. This includes policy and guideline writing, considerations around curriculum, and workforce, for example. As part of my role here, national guidance was written regarding heart monitoring, and this along with debate around national AF screening recommendations, made a significant contribution to my onward academic path and chosen research focus.

It was therefore, considered entirely appropriate to enter this field and intensity of study, to give the dedication to this sub-specialism of cardiology and to enhance and develop understanding around the extremely detrimental effects these conditions have. Patients with AF are encountered daily, and in various settings. The role as a nurse specialist is exciting and varied, with some days spent reviewing ward-based patients during different phases of stability, other days running the nurse-led AF clinic and other times guiding the Emergency Department or GPs on the appropriate patient management. One day a week is spent performing electrical cardioversion, a procedure aimed at restoring a normal heart rhythm, from AF. These experiences have contributed to the awareness and relevance of research within this patient group, the multi-faceted issues surrounding heart rhythm management, and the mechanisms underpinning this. The love and passion for my job means this interest has not diminished along this journey and continues to have direct bearing on my daily practice.

The constant evolution of arrhythmia management, findings from my research and developments within my clinical role, have resulted in personally set objectives, whereby links within primary care and public health are being strengthened. These objectives encompass an enhanced focus on AF detection, methods and approaches along with screening tools, stroke risk reduction and management. The hope is then to feed this work into the national committees, along with shared working with interdisciplinary networks. Furthermore, within my objectives, is the desire to drive

forward my ever-increasing passion for research development and progression, within nursing, locally. So much of this doctorate programme has presented new challenges and learning, some of which should perhaps be introduced much earlier in nurse training. As nursing roles continue to evolve, with many boundaries blurred with our medical colleagues, principles of research should be equally shared. Whilst not all nurses will consider this path, the foundations of research practice offer invaluable grounding for reading and comprehending published research, along with enabling nurses to feel more comfortable with audit, data collecting and project design, which may lead to formal research. As nurses, we are in an ideal environment to engage as primary researchers or work within a research team, alongside our clinical nursing or as a direct adjunct within our careers. All around me, there is an abundance of opportunities where research could be instigated, but many nurses are unfamiliar and lack confidence to proceed in this way. Environments within healthcare from outpatient clinics, to nursing home care, communication delivery, patient experiences, advanced practice roles, prescribing practice, and the essential basics of nursing care, offer such opportunities. This personal academic journey, therefore, has led to a drive towards increasing research awareness across the local nursing workforce. This was recently expressed through presentation delivery at the local Nursing Forum and has also led to joining forces with the research forum for the British Association of Nurses in Cardiovascular Care.

The opportunities nursing has provided me both clinically and academically, has resulted in this being the ideal career. Through this path, the sub-specialism of arrhythmia management has enabled me to truly focus on a rapidly developing and dynamic area. The research undertaken and presented in this thesis, has opened many more opportunities for enquiry, providing a platform for ongoing and progressive research.

Geographical location for these studies.

Two of the research studies within this thesis were undertaken in Jersey, Channel Islands (the AF screening study, *Study 2, Chapter 4*, and the patient interviews, *Study 4, Chapter 6*). Jersey is the largest of the Channel Islands and is set in the Bay of St Malo, nineteen miles off the coast of Normandy, France and eighty-five miles south of the English coast. Jersey is a self-governing state and an English Crown Dependency. The island is approximately nine miles by five miles and the latest census describes a population of 103,267 (Government of Jersey, 2021a). The life expectancy of island residents is higher than all English regions at 81.4 years for men and 85.2 years for women (Government of Jersey, 2022). This reveals a gradual increase since the beginning of the decade.

Causes of death in Jersey are led by cancers (30% of island deaths) and then cardiovascular system disease, including stroke (27% of island deaths) (States of Jersey, 2017). More recent figures continue to demonstrate that cancer and cardiovascular disease combined, account for 60% of all island deaths (Government of Jersey, 2021b). Older people over 65 years, make up about 17% of Jersey's population and this is expected to continue to grow by about 11,000 more pensioners living in Jersey by 2035 (Government of Jersey, 2019). The prevalence of AF in Jersey was 2025 in 2017 (1.9%), when the most recent data was collated from primary care records, and the prevalence of diabetes was 3870 (3.6%) (States of Jersey, 2017). There were 315 people recorded as having AF and diabetes at this time (0.3%) (States of Jersey, 2017).

Jersey's health service model is both private and government funded. Secondary care is free, financed by the government through tax payments, but primary care (including General Practitioners) is a private enterprise. The education system provides both public and private schooling. There is no University but there are colleges offering higher levels of education. The Government of Jersey is the largest single employer in the island, including civil servants, healthcare, education, social care, and emergency services. The finance sector employs about a quarter of the island's workforce, contributing to 40% of Jersey's economic output with employees working across globally focused organisations.

Chapter 1. Introduction.

1.1 The atrial fibrillation epidemic and exploring the association with diabetes.

This chapter will present a brief introduction to atrial fibrillation [AF] in relation to prevalence, risk factors and consequence. Diabetes will be introduced along with consideration around the links between AF and diabetes. An outline of the studies within this thesis is then provided, along with their relevance and justification by addressing associated gaps in existing research. This chapter is then concluded with sections relating to the presentation of this thesis in Alternative Format.

1.1.1 Atrial fibrillation.

There is an increasing prevalence of AF and diabetes worldwide (Hindricks et al, 2021; Lane, Skjøth, Lip, Larsen & Kotecha, 2017; Reed, Bain & Kanamarlapudi, 2021; Spencer et al, 2017). AF is a common heart rhythm irregularity, and a leading cause of stroke and stroke risk increases further when AF and diabetes coexist. Diabetes is a risk factor for developing AF (Ahmadi, Svensson, Pivodic, Rosengren & Lind, 2020) and targeted screening for such groups may be beneficial.

AF is the most common sustained cardiac arrhythmia in adults, worldwide (Hindricks et al, 2021). AF is associated with substantial morbidity and mortality, portending burden to patients, health economy and society (Hindricks et al, 2021). There is now a revised lifetime risk of one in three from one in four people of European ancestry at the index age of 55 years, who will develop AF (Magnussen et al, 2017; Staerk et al, 2018). Risk increases with age and AF prevalence is now estimated at 2-4% of the whole population (Benjamin et al, 2019) with a 2.3-fold rise expected (Chugh et al, 2014). Prevalence continues to increase worldwide for AF across age groups, but this remains highest in the older population (Hindricks et al, 2021; Schnabel et al, 2015). Prevalence of AF shows a strong age dependence from 0.5% in patients under 40 years, 5% in those over 65 years and 10-17% in octogenarians (Sankaranarayanan, Kirkwood, Dibb & Garrett, 2013; Zathar, Karunatilleke, Fawzy & Lip, 2019). It is

estimated that by 2060 the overall prevalence will at least double, because of lifestyle and ageing of populations (Miyasaka et al, 2006). The projected increase in AF prevalence in older adults is depicted in *Figure 1*. In the over 65-year-old population, AF is rarely a lone condition, usually coexisting with heart disease or other chronic co-morbid health states. The increasing population of older age and resultant increase in AF prevalence is a burdening public health concern, due to the impact on health resource and comorbidity. The increasing number of people living into older age has an impact on AF epidemiology, with AF risk doubling with each progressive decade (Magnani et al, 2016) and this may contribute towards an explanation for the projected increase in AF cases as seen in *Figure 1*. Cardiovascular ageing and age-related increase of co-morbidities also contributes to this estimated increase.

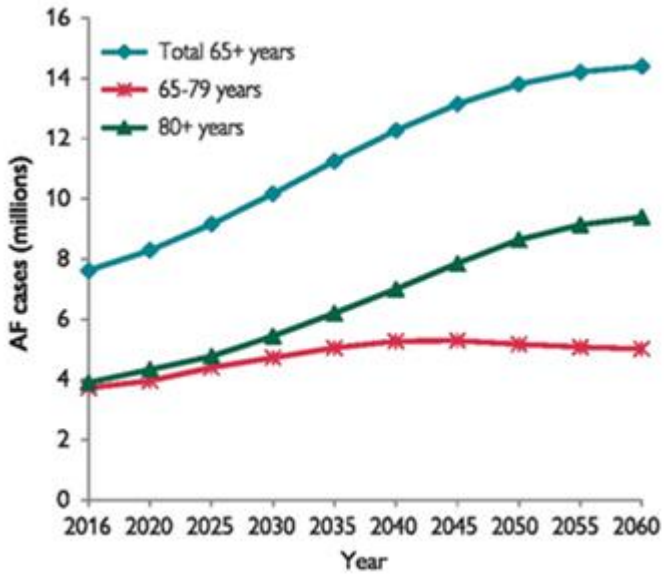


Figure 1.

AF prevalence. Projected increase in AF prevalence among people over 65 years of age, in EU 2016-2060.

Hindricks et al. (2021). Eur Heart J, 42 (5), 373–498. (Permissions granted by Oxford University Press).

Efforts to detect AF are important due to the associated risks and sequelae that undetected AF can lead to. AF is a leading cause of thromboembolism and stroke, and AF related strokes are associated with increased mortality, morbidity and healthcare

costs compared to strokes not caused by the arrhythmia (Ali & Abdelhafiz, 2016). Moreover, AF related strokes are more likely to be fatal (McGrath et al, 2013). Stroke risk increases further in the presence of comorbid risk factors including hypertension and diabetes (Friberg, Rosenqvist & Lip, 2012; Patlolla et al, 2020; Xu, Sun, Gong & Fan, 2022). Heart failure, hypertension, diabetes, coronary artery disease, obstructive sleep apnoea, chronic kidney disease and obesity are also recognised risk factors for AF and therefore targeted screening for such patient groups can be beneficial (Manolis et al, 2012; Čarná & Osmančík, 2021). Whilst AF screening studies have attempted to explore the risk and association with high-risk groups, this is typically done in combination, without exploring these risks singularly, or accounting for confounders within these populations and therefore, the AF screening research here (*Study 1, Chapter 4*), attempts to address this by focusing specifically on a population with diabetes. Some of the evidence also comes from observational studies that have used registry data to obtain the information required for the study, and therefore have not screened patients directly (Nichols, Reinier & Chugh, 2009). The methods for obtaining this AF related data and identifying AF may be disparate and impact outcomes. The variability in AF screening studies that incorporated mixed-risk groups also leads to some uncertainty around screening approach, protocol, and outcomes. The AF screening study (*Study 1, Chapter 4*) clearly sets out the screening protocol using the AliveCor® device throughout and includes a target population of people with diabetes. The detail within the study provides clear information around instrumentation, methods used, and variables incorporated within analysis and this clarity is important when interpreting results relating to predictors and prevalence of AF and in people with diabetes. The AF screening study adds another perspective by utilising the AliveCor® device in this population and provides prevalence data relating to the local island population.

Identifying AF in people with diabetes is vitally important as stroke risk and morbidity are increased with each condition alone, but more so when in combination (Patlolla et al, 2020; Xu et al, 2022). Therefore, when AF is detected through screening, as in the screening research set out in *Study 1* (*Chapter 4*), patients' stroke risk can be quantified, then reduced with anticoagulation where appropriate. Stroke and

thromboembolism risk can be assessed through the application of a stroke risk assessment tool such as the widely adopted CHA_2DS_2-VASc risk stratification tool (**C**ongestive Heart Failure, **H**ypertension, **A**ge >75 years, **D**iabetes Mellitus, Prior **S**troke / Transient Ischaemic Attack, **V**ascular disease, **A**ge 65-74 years, **S**ex category (female) (Lip, Nieuwlaat, Pisters, Lane & Crijns, 2010) (see *Table 1*). This then directs the need for oral anticoagulation which can prevent stroke by 64% and reduce risk of death by 26% when warfarin, a vitamin K antagonist, is used (Hart, Pearce & Aguilar, 2007). The use of direct oral anticoagulants [DOACs] (dabigatran, apixaban, rivaroxaban and edoxaban) can also reduce stroke risk in the presence of AF, and a meta-analysis including 42,411 patients receiving the DOACs and 29,272 receiving warfarin, showed the DOACs significantly reduced stroke or systemic embolic events by 19%, compared with warfarin (Relative Risk [RR] 0.81, 95% Confidence Interval [CI] 0.73 to 0·91) mainly due to a reduction in haemorrhagic stroke (RR 0.49, 95% CI 0.38 to 0.64) (Ruff et al, 2014). The DOACs significantly reduced all-cause mortality (RR 0.90, 95% CI 0.85 to 0.95) and intracranial haemorrhage (RR 0.48, 95% CI 0.39 to 0.59), but increased gastrointestinal bleeding (RR 1.25, 95% CI 1.01 to 1.55). Low-dose regimes of the DOACs demonstrated an overall reduction in stroke or systemic embolic events, similar to warfarin (RR 1.03, 95% CI 0.84 to 1.27), with a more favourable bleeding profile (RR 0.65, 95% CI 0.43 to 1.00), but significantly more ischaemic strokes (RR 1.28, 95% CI 1.02 to 1.60) (Ruff et al, 2014). A summary of the main four trials regarding DOACs versus warfarin is presented in *Table 2*.

Table 1. CHA_2DS_2-VASc stroke risk assessment.

Risk factor	Score
Congestive Heart Failure / left ventricular systolic dysfunction	1
Hypertension (treated or consistently above 140/90mmHg)	1
Age >75 years	2
Diabetes Mellitus	1
Prior **S**troke / TIA	2
Vascular disease (e.g., peripheral artery disease, myocardial infarction, aortic plaque)	1
Age 65-74 years	1
Sex category (female)	1
Total score Lip, et al. (2010). If the score ≥1, anticoagulation is indicated and should be considered (Hindricks et al, 2021; NICE, 2021).	0-9

1.1.2 Atrial fibrillation risk

AF risk increases in older people, along with the likelihood of having comorbid disease which further increases this risk and subsequent complications. The prevalence of AF ranges from 0.12%–0.16% in people younger than 49 years, 3.7%–4.2% in those aged 60–70 years, and 10%–17% of people aged over 80 years (Zoni-Berisso, Lercari, Carazza & Domenicucci, 2014). In addition to age, there are several causal factors associated with AF development including sex, race, genetics, and modifiable risk factors, such as weight control, alcohol consumption, exercise levels and blood pressure. Attempts to reduce the impact of behavioural effects through lifestyle adaptation is actively encouraged to optimise cardiac function and reduce the negative impact AF can have physiologically, emotionally and on patients' symptoms.

Table 2. Stroke prevention in atrial fibrillation trials, DOACs versus warfarin.

	Dabigatran (Connolly et al, 2009).	**Rivaroxaban** (Patel et al, 2011).	**Apixaban** (Granger et al, 2011).	**Edoxaban** (Giugliano et al, 2013).
Study	RE-LY	ROCKET-AF	ARISTOTLE	ENGAGE AF
Population size	18,113	14,266	18,201	21,105
Design	Probe	Double blind	Double blind	Double blind
Dose (mg)	150, 110 BD	20, 15‡ OD	5, 2.5* BD	60, 30 OD
Inclusion	Non-valvular AF + 1 risk factor	Non-valvular AF + 2 risk factors	Non-valvular AF + 1 risk factor	Non-valvular AF
Inclusion (mean CHADS)	2.1	3.5	2.1	≥2
Warfarin comparator, international normalised ratio [INR]	2-3 (64%)	2-3 (55%)	2-3 (62%)	2-3 (68%)

control (mean time in therapeutic range)				
Primary endpoint	Stroke or systemic embolism	Stroke or systemic embolism	Stroke or systemic embolism	Stroke or systemic embolism
Stroke or systemic embolism	1.69% / year in the warfarin group, vs. 1.53% / year in the 110mg of dabigatran group (RR with dabigatran, 0.91; 95% CI 0.74 to 1.11; p<0.001 for noninferiority) and 1.11% / year in the 150mg group (RR 0.66; 95% CI, 0.53 to 0.82; p<0.001 for superiority).	1.7% / year in the rivaroxaban group, vs. 2.2% / year in the warfarin group (Hazard Ratio [HR] with rivaroxaban, 0.79; 95% CI 0.66 to 0.96; p<0.001 for noninferiority).	1.27% / year in the apixaban group, vs. 1.60% / year in the warfarin group (HR with apixaban, 0.79; 95% CI 0.66 to 0.95; p<0.001 for noninferiority; p=0.01 for superiority).	1.50% / year with warfarin vs. 1.18% / year with high-dose edoxaban (HR 0.79; 97.5% CI 0.63 to 0.99; p<0.001 for noninferiority) and 1.61% / year with low-dose edoxaban (HR 1.07; 97.5% CI 0.87 to 1.31; p=0.005 for noninferiority). In the intention-to-treat analysis, there was a trend favouring high-dose edoxaban vs. warfarin (HR

				0.87; 97.5% CI, 0.73 to 1.04; p=0.08) and an unfavourable trend with low-dose edoxaban vs. warfarin (HR 1.13; 97.5% CI, 0.96 to 1.34; p=0.10).
Other outcomes including major bleeding, intracranial haemorrhage, haemorrhagic stroke, gastrointestinal bleeding, and mortality (where reported).	**Major bleeding** 3.36% / year in the warfarin group, compared with 2.71% / year in the group receiving 110 mg dabigatran (p=0.003) and 3.11% / year in the group receiving 150 mg of dabigatran (p=0.31). **Haemorrhagic stroke** 0.38% / year in the warfarin group,	**Major and nonmajor clinically relevant bleeding** 14.9% / year in the rivaroxaban group and 14.5% / year in the warfarin group (HR 1.03; 95% CI 0.96 to 1.11; p=0.44). Significant reductions in **intracranial haemorrhage** (0.5% vs. 0.7%, p=0.02) and **fatal bleeding** (0.2% vs. 0.5%,	**Major bleeding** 2.13% / year in the apixaban group, vs. 3.09% / year in the warfarin group (HR 0.69; 95% CI 0.60 to 0.80; p<0.001). Rates of death from any cause were 3.52% and 3.94%, respectively (HR 0.89; 95% CI 0.80 to 0.99; p=0.047). **Haemorrhagic stroke** was 0.24% / year in the apixaban group, vs.	**Major bleeding** 3.43% / year with warfarin, vs. 2.75% / year with high-dose edoxaban (HR 0.80; 95% CI 0.71 to 0.91; p<0.001) and 1.61% / year with low-dose edoxaban (HR 0.47; 95% CI 0.41 to 0.55; p<0.001). **Rates of death** from cardiovascular causes 3.17% / year vs. 2.74% / year (HR 0.86;

	compared with 0.12% / year with 110 mg of dabigatran (p<0.001) and 0.10% / year with 150mg of dabigatran (p<0.001). **The mortality rate** was 4.13% / year in the warfarin group, compared with 3.75% / year with 110mg of dabigatran (p=0.13) and 3.64% / year with 150mg of dabigatran (p=0.051).	p=0.003) in the rivaroxaban group.	0.47% / year in the warfarin group (HR 0.51; 95% CI 0.35 to 0.75; p<0.001). Rate of **ischemic or uncertain type of stroke** was 0.97% / year in the apixaban group and 1.05% / year in the warfarin group (HR 0.92; 95% CI 0.74 to 1.13; p=0.42).	95% CI 0.77 to 0.97; p=0.01), and 2.71% (HR 0.85; 95% CI 0.76 to 0.96; p=0.008). Rates of the key secondary end point **(composite of stroke, systemic embolism, or death from cardiovascular causes**) were 4.43% vs. 3.85% (HR 0.87; 95% CI 0.78 to 0.96; p=0.005), and 4.23% (HR 0.95; 95% CI 0.86 to 1.05; p=0.32).

*± The reduced dose was used in patients with a Creatine Clearance of 30–49 mL/min. *The 2.5mg dose of apixaban used in patients with AF and ≥2 of age ≥80 years, body weight ≤60 kg or serum creatinine ≥1.5mg/dL (133mmol/L). CHADS Congestive Heart Failure, Hypertension (treated or consistently above 140/90mmHg), Age >75 years, Diabetes Mellitus, Prior Stroke / Transient Ischaemic Attack.*

Causal influences include male sex, and this is associated with a greater risk of developing AF than in women, with double the prevalence reported (Magnusson et al, 2017). The Framingham Heart Study showed the age-adjusted period prevalence (per 1000 person-years) during 1998–2007 was 49.4 in women and 96.2 in men (Schnabel et al, 2015). Between 1998-2007, age and sex adjusted hazard ratio for incident AF with diabetes compared with people without diabetes was 1·25 (0·98 – 1·60).

Men seem to develop AF earlier than women, but women have higher risks of complications, such as stroke. AF onset in women correlates with a diminished survival advantage (Ko et al, 2016; Schnabel et al, 2015). Consistently reported risk factors for AF show differential distributions by sex, including obesity, hypertension, smoking, alcohol consumption and prevalence of cardiovascular disease (Huxley, Lopez et al, 2011). As women typically live longer than men, the absolute number of women with AF, is often greater than men (Piccini et al, 2012).

Racial differences have been identified in AF population research, demonstrating lower prevalence in individuals of African descent compared to European ancestry (Dewland, Olgin, Vittinghoff & Marcus, 2013). AF prevalence is also lower in Hispanics and Asians compared to white people (Rodriguez et al, 2015). Genetics also has a role in AF development with a 40% increased risk of AF if a first-degree relative is affected (Lubitz et al, 2017). Genes associated with AF development are more complex than originally assumed, and studies have shown AF to be a complex polygenetic condition (Andersen, Andreasen & Olesen, 2021). More than 160 genes have been associated with AF, with some rare variants in multiple ion-channel genes and gap junction and transcription factor genes (Anderson et al, 2021). The increased burden of atrial fibrosis in AF patients compared with non-AF patients, along with atrial cardiomyopathies and evidence of structural genes beyond the electrical focus of the arrhythmia, is enhancing comprehension around the pathogenesis of AF (Anderson et al, 2021).

Modifiable risk factors for AF include hypertension, an independent risk factor for AF. The mechanism involved is unclear, but several factors including left ventricular hypertrophy, diastolic dysfunction and the effects of renin and angiotensin have been

proposed (Lip, 2016). These factors can lead to left atrial stretch, fibrosis, and increased wall stress, all of which can be associated with the development of AF (Lip, 2016). Valvular heart disease significantly increases AF risk as demonstrated in the Framingham cohort (Schnabel et al, 2015). Structural valvular abnormalities increase this risk with left sided dysfunction conferring the highest risk (Darby & DiMarco, 2012). Heart valve stenosis, predominantly mitral valve stenosis, is linked through restricting blood flow obstruction from the left atrium to the left ventricle, causing an increase in pressure in the left atrium, enlarging the heart and leading to AF (De Catarina & Camm, 2014). Heart failure often coexists with AF, either precipitating or being a consequence of the arrhythmia. Both conditions share common risk factors and lead to worse outcomes by increasing complications including stroke (Kotecha & Piccini, 2015).

Obesity links with other AF causal factors including obstructive sleep apnoea [OSA], hypertension and diabetes mellitus, and not only increases AF risk, but directly influences AF outcomes. Obesity is a global epidemic and a meta-analysis of population-based cohort studies showed AF risk was increased by 49% in people who were obese (Wanahiti et al, 2008). AF risk is also increased in parallel with body mass index [BMI] and this may be attributable to the structural and electrical changes caused by obesity and pericardial fat (Wanahiti et al, 2008; Wong et al, 2011). One study demonstrated that being overweight increased the risk of having AF by 14% (95% CI 1.06 – 1.23; $p<0.001$), and by 52% if obese (95% CI 1.30 – 1.78; $p<0.001$), compared with those with normal body mass index (Baek et al, 2017). Another study showed that the association with weight and the risk of incident AF was greater in people who were overweight (HR 1.20; 95% CI 1.06 – 1.36) and obese (HR 1.95; 95% CI 1.72 – 2.21), compared to people of normal weight (Huxley et al, 2014). Complications in people with AF who are overweight have also been demonstrated with ischemic stroke, thromboembolism, or death, significantly higher in overweight (HR 1.31; 95% CI 1.09-1.56) and obese patients (HR 1.55; 95% CI 1.27-1.90) (Overvad et al, 2013). Weight control is fundamental in the management of patients with AF with evidence demonstrating the benefits as a management option alone, and alongside invasive therapy such as electrophysiology intervention for the prevention of AF recurrence

(Pathak et al, 2014; Pathak et al, 2015). OSA, whereby there are periods of breathing cessation during sleep, has a strong association with AF and obesity and this has been observed in both epidemiological and clinical cohorts (Gottlieb, 2014). Studies have also demonstrated that OSA is associated with an increased risk of AF recurrence following AF correction and this can be modified through weight loss and application of continuous positive airway pressure appliances (Gottlieb, 2014). The effects of OSA and AF recurrence were further explored in another study, demonstrating that in a multivariable model, the presence of OSA (HR 2.79; 95% CI 1.97 - 3.94; p<0.0001) compared to untreated OSA (HR 1.61; 95% CI 1.35 - 1.92; p<0.0001) were highly associated with AF recurrence (Nielan et al, 2013).

Alcohol consumption that exceeds safe drinking guidance is associated with increased risk of AF and a recent meta-analysis of prospective studies, revealed a positive association between alcohol intake and AF risk (Zhang et al, 2022). Moderate and high alcohol intake significantly increases AF risk, and more so in men (Zhang et al, 2022). The meta-analysis by Zhang et al (2022) included thirteen studies, with a total of 645,826 participants and 23,079 cases of AF. When compared with people who did not drink alcohol, or who were seldom-drinkers, the pooled adjusted HRs of AF were 1.30 (95% CI 1.20 –1.41) and 1.00 (95% CI 0.96 –1.05) for high and low alcohol consumption, respectively (Zhang et al, 2022). Moderate alcohol intake significantly increased the risk of AF in males (HR 1.21; 95% CI 1.10 – 1.33) but not in females (HR 1.02; 95% CI 0.91 – 1.14) (Zhang et al, 2022).

Another modifiable risk is that of exercise, with the general belief that regular exercise is beneficial for improving overall cardiovascular health, reducing blood pressure, controlling weight, and enhancing cardiometabolic efficacy (Hindricks et al, 2021; Seccia & Calo, 2018). One study looked at the effect of AF risk with exercise over 12 years and the risk of AF decreased with increasing levels of leisure-time exercise (RR 0.85; 95% CI 0.75 - 0.95) for more than four hours per week versus less than one hour per week and walking or bike riding (RR 0.81; 95% CI 0.72 - 0.92) for 40 minutes a day or more, versus almost never (Drca, Wolk, Jensen-Urstad & Larsson, 2015).

Whilst exercise is beneficial for modifying risk factors that can increase AF risk, this is slightly offset in endurance athletes where an increased risk of atrial arrhythmias has been seen (Mont, Elosu & Brugada, 2009). A systematic review and meta-analysis of six case-control studies including 655 athletes and 895 controls were compared, demonstrating 147 (23%) versus 116 (12.5%) cases of AF among athletes compared with controls (ref). The overall risk of AF was significantly higher in athletes than in controls (OR 5.29; 95% CI 3.57 - 7.85; p=0.0001) (Abdulla & Nielson, 2009). The mechanisms may be relatable to increased atrial pressure and pro-arrhythmia risks, along with changes to the atrial substrate, including myocardial fibrosis and myocardial inflammation, increased atrial premature beats, and increased vagal tone leading to bradycardia and decreased atrial refractoriness (Flannery, Kalman, Sanders & La Gerche, 2017; Guasch, Mont & Sitges, 2018).

Furthermore, endocrine disease including diabetes (explored further within this chapter) and thyroid dysfunction have been linked to an increased risk of AF. Metabolic Syndrome is a constellation of modifiable conditions including obesity, dyslipidaemia, hypertension, and insulin resistance (Kumar & Gehi, 2012) and is another risk factor for cardiovascular morbidity and AF with various components contributing to the pathogenesis of AF. A meta-analysis of Metabolic Syndrome and its individual components with risk of AF, included six cohort studies, totalling 30,810,460 patients (Zheng et al, 2021). Results showed an increased risk of AF (HR 1.57; 95% CI 1.40 – 1.77; p<0.01) and the components including abdominal obesity (HR 1.37; 95% CI 1.36 – 1.38; p<0.01), elevated blood pressure (HR 1.56; 95% CI 1.46 – 1.66; p<0.01), elevated fasting glucose (HR 1.18; 95% CI 1.15–1.21; p<0.01) and low high density cholesterol (HDL) (HR 1.18; 95% CI 1.06–1.32; p<0.01) was also associated with an increased risk of AF, while high triglyceride (HR 0.99; 95% CI 0.87–1.11; p=0.82) was not (Zheng et al, 2021).

Modifiable risk factors, such as those briefly introduced here, are prevailing contributors to AF development as depicted in *Figure 2.* Progression and control of these risk factors is advocated through early intervention and direct patient involvement (Hindricks et al, 2021). Integrated and patient-centred care is important

for effective outcomes and overall wellbeing. Adjunctive treatment of these risk factors is increasingly recognised as an essential part of AF management.

1.1.3 Integrated atrial fibrillation care.

Integrated AF care, delivered by an interdisciplinary team with the patient central to treatment options and decisions, offers an important individualised approach towards achieving successful AF management (Hindricks et al, 2021). The patient-centred approach involves exploring, assessing, and respecting individual goals, values, and preferences, leading to shared decision making (Lane, Barker & Lip, 2015; Lane, Meyerhoff, Rohner & Lip, 2018; Seaberg et al, 2014). Working together to reach shared decisions and treatment plans is supported by national guidance, whereby embedding shared decision making at an organisational level is promoted, along with personalised care supported by the appropriate health professionals, agencies, and carers (NICE, 2021; NICE, 2021a). The integrated AF management team may comprise different health professionals along with family and carers, according to the patients' needs and availability of services. *Figure 2* depicts the range of people that might be relevant for this multidisciplinary team approach, and it is important that this team is utilised effectively, whilst moving towards a more integrated way of working which may require behavioural change from stakeholders to facilitate (Lip, Lane & Potpara, 2018).

The Atrial fibrillation Better Care [ABC] pathway [A – Anticoagulation / Avoid Stroke, B – Better symptom management, and C – Cardiovascular and Comorbidity optimisation] is a holistic pathway which streamlines integrated care of people with AF (Lip, 2017). Implementation of the ABC pathway has shown to be advantageous when compared to usual care and associated with a significant lower risk of all-cause death, first hospitalisation, stroke, major bleeding (Proietti, Romiti, Olshansky, Lane & Lip, 2018) and lower healthcare costs (Pastori, Farcomeni, Pignatelli, Violi & Lip, 2019). This pathway approach features in European guidance relating to AF management and a specific set of international standards of outcome measures are proposed, to collect relevant data from clinical practice and determine whether integrated AF

management has had an impact on specified outcomes (Seligman et al, 2020). Improvements in hard endpoints such as death, cardiovascular events and stroke has been demonstrated through adherence to the ABC pathway in independent studies (Guo et al, 2020; Pastori, Pignatelli, Menichelli, Violi & Lip, 2019; Proietti et al, 2018; Yoon et al, 2019). The ABC pathway can help operationalise the necessary components required to facilitate integrated AF care, along with the incorporation and support from decision aids and patient education platforms (Berti et al, 2013; Lane & Lip, 2019).

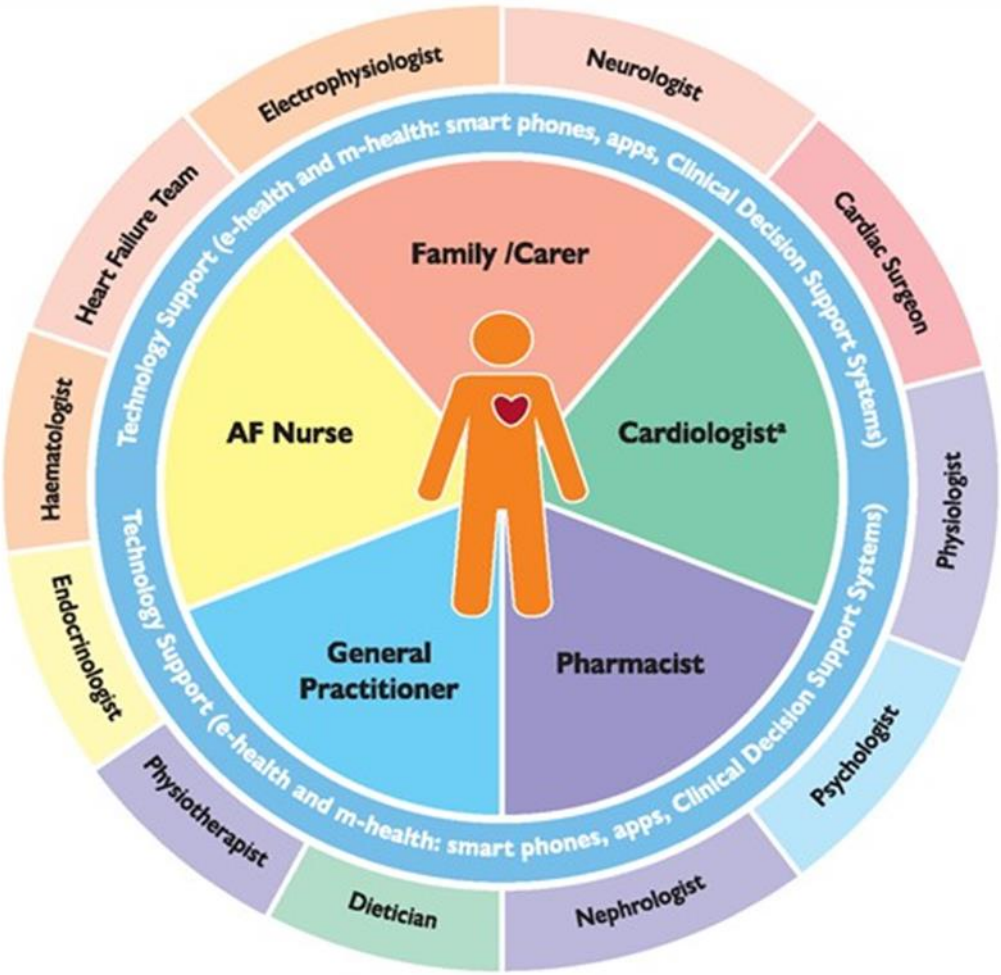


Figure 2.

Integrated atrial fibrillation management and the multidisciplinary team (an example).

a) According to local standards, this could be a general cardiologist with special interest in arrhythmias/AF or an electrophysiologist.

Hindricks et al. (2021). Eur Heart J, 42 (5), 373–498. (Permissions granted by Oxford University Press).

The ABC pathway identifies 'A – Anticoagulation / Avoid stroke' and assessing individuals' risk using a stroke and thromboembolic risk stratification scoring tool to identify patients eligible to receive anticoagulation. 'B – Better symptom control' refers to controlling heart rate, which often in itself is enough to improve AF related symptoms (Alobaida & Alrumayh, 2021; Lip, 2017). Pharmacological options for rate control can be used in combination with rhythm control strategies which are designed to restore and maintain normal heart rhythm. Treatment options may include cardioversion, antiarrhythmic medications, and catheter ablation. Symptom related treatment should be tailored to the individual needs with regular reassessment. 'C – Cardiovascular risk factors and concomitant diseases', includes detection and management of concomitant disease, unhealthy lifestyle factors and cardiometabolic risks (Lip, 2017). Modifiable lifestyle risk factors that could have an impact on the burden and consequence of AF along with AF related symptoms include obesity, alcohol consumption and exercise levels. Specific cardiovascular comorbidities associated with AF include hypertension, heart failure, coronary artery disease, diabetes mellitus and sleep apnoea. Targeted treatment whereby the burden of concomitant disease can be improved, could lead to improved AF related outcomes and symptoms.

1.1.4 Atrial fibrillation screening tools

The AliveCor® device is the ECG monitoring tool of focus here, in the systematic review (*Chapter 2*) and in the AF screening study (*Study 1, Chapter 4*), but there exist several other monitoring applications that can be used to record an ECG rhythm. These include implantable devices, traditional Holter monitors [HM], ECG based devices and photoplethysmography [PPG] technology. Signal acquisition may be through electrodes connected to the skin as in ECG based systems, or via an optical technique using a light source and photodetector whereby peripheral pulse waveforms are analysed by detecting changes in light intensity which reflects the tissue blood volume from the skin surface, such as the fingertip (Varma et al, 2021).

An ECG is a graph of the hearts electrical activity and is produced using electrodes applied to the skin which detects movement of a positive charge through the

structures of the heart. The ECG graph represents voltage versus time and is displayed through deflections to form the ECG waveform, labelled PQRST (*Figure 3*). The P wave represents atrial depolarisation, the QRS complex represents ventricular depolarisation and the T wave, ventricular repolarisation (Madona, Basti & Zain, 2021). The ECG can be displayed as a single-lead view, as with the AliveCor® device, or with additional leads such as the 12 lead ECG which requires more electrode connections to the limbs and precordium (*Figure 4 and 5*). The single-lead ECG is useful for heart rhythm interpretation, but additional leads are required when assessing patients for cardiovascular disease beyond a rhythm check (e.g., myocardial infarction). Single-lead ECG systems use two electrodes to detect a single ECG signal. Electrode placement is important as this determines the ECG signal obtained, with a single-lead, lead-I view, displayed when electrodes are placed between the right and left arms of the body horizontally (*Figure 4*) (Abdou & Krishnan, 2022).

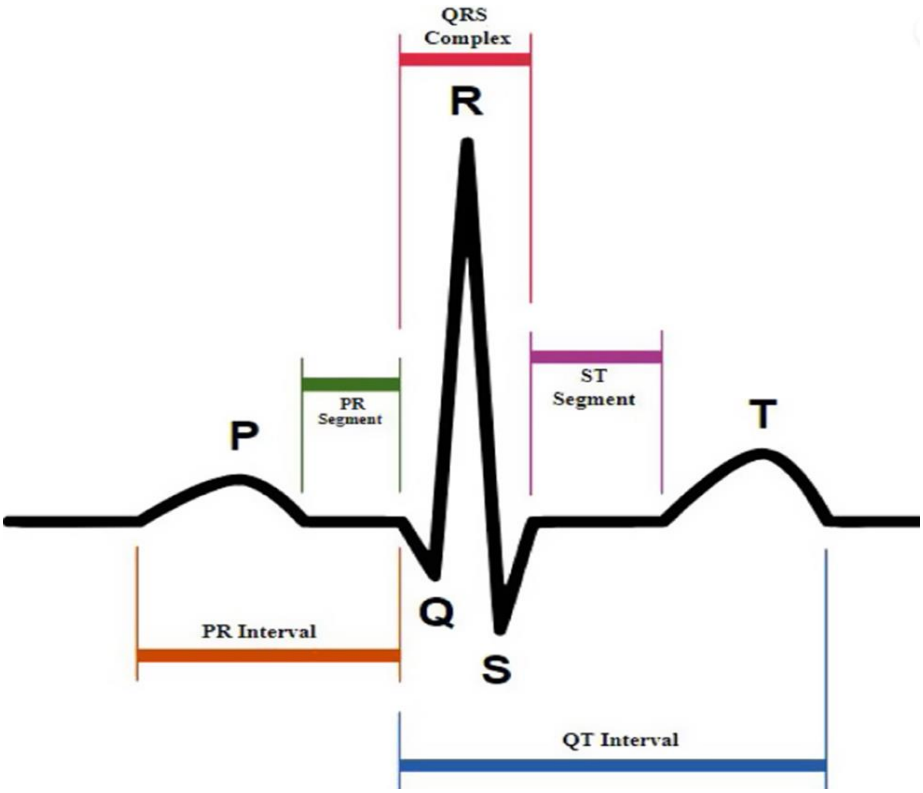
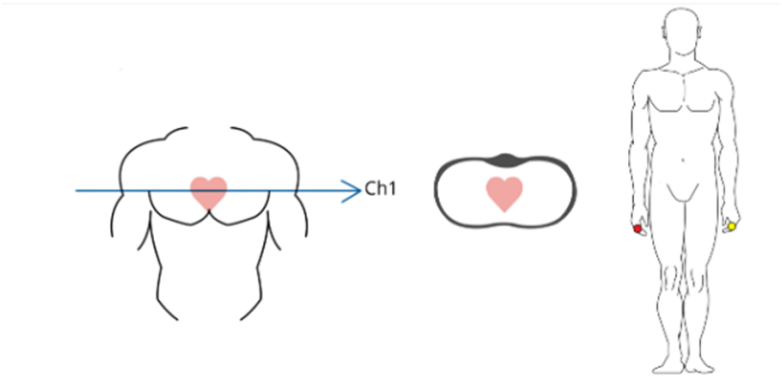
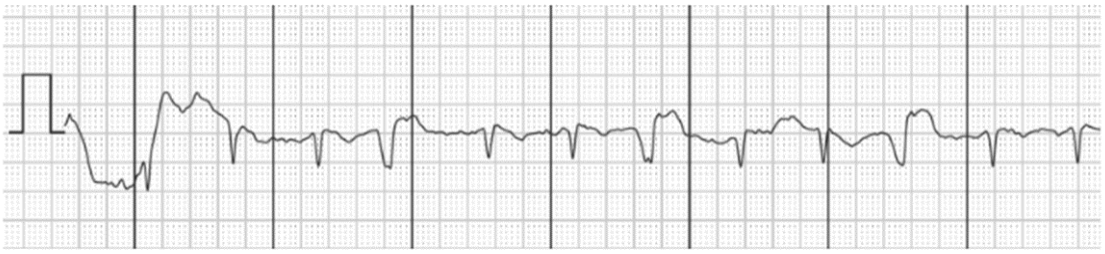


***Figure 3**. **The ECG pattern, representing atrial and ventricular electrical activity**.*

Madona, Basti & Zain, 2021. (Permissions granted by Elsevier Publisher).



a) Single Lead ECG - Electrode position and visual axes. (*Ch 1 represents 'channel 1', a one lead view). The red and yellow dots on the hands represent electrode positioning for the single lead ECG device, such as the Kardia® device*).



b) Example of a single-lead ECG rhythm strip, Lead I (*produced by electrodes connected to fingers on the hands, as in image a) above*).

Figure 4.

Single-lead ECG. Electrode positioning and ECG rhythm strip.

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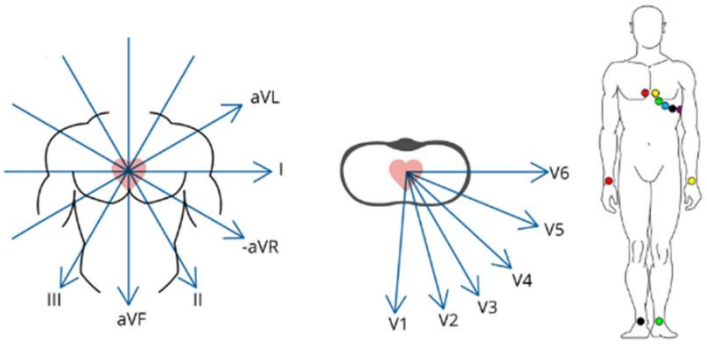
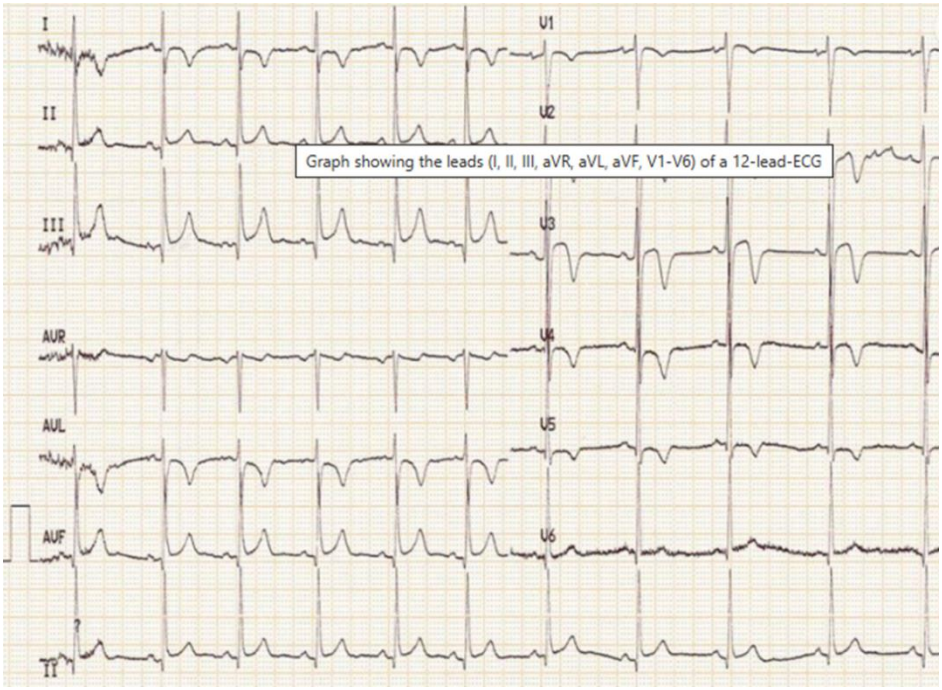


a) 12 lead ECG - Electrode position and visual axes (the letters and numbers represent the electrode positioning on the body, corresponding with the coloured dots on the body image). This reveals an ECG graph as in image b).



b) Example of a 12 Lead ECG, (produced by electrodes connected to the limbs and precordium, as in image a) above).

Figure 5.

12 lead ECG. Electrode positioning and ECG example.

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Figure 6.

The Kardia® ECG device with two fingers applied to the electrodes, producing a single-lead ECG on a smartphone.

AliveCor.com, https://www.researchgate.net/figure/AliveCor-Kardia-Mobile-single-lead-handheld-ECG-Image-used-with-permission-from_fig2_323763753. (Permissions granted by AliveCor.com)

ECG alterations can be present in patients with diabetes, such as prolongation of the QTc interval sometimes observed in hypoglycaemia, (the time between ventricular depolarisation represented by the QRS complex, and ventricular repolarisation, the T wave, adjusted for heart rate), sinus tachycardia, changes reflective of left ventricular hypertrophy, decrease of T wave amplitude (as seen with aging and post-ischaemia), changes in heart rate variability and ST segment and T wave changes (representing the interval between ventricular depolarisation and repolarisation) (Gupta, Gupta, Kulshrestha & Chaudhary, 2017; Schroeder et al, 2005; Sellers et al, 2014; Stern & Sclarowsky, 2009). Whilst some of these changes can be non-specific or normal variants, others can be representative of silent ischaemia, underlying cardiovascular disease, or early markers of diabetic autonomic neuropathy (Mather & Gupta, 2006). Myocardial fibrosis related changes can be present and before cardiac involvement is clinically evident. The importance, therefore, of the ECG in patients with diabetes, is evident, and this coupled with their increased risk of cardiovascular disease, supports this research.

Conventional ambulatory ECG monitoring devices, with the ability to record the ECG continuously or intermittently, can detect a range of arrhythmias but inconvenience

and duration of monitoring can limit implementation and effectiveness (Steinberg et al, 2017). ECG based devices include handheld and patch systems, both with inherent advantages and disadvantages (*Table 3*). Some of these operate as stand-alone devices without accessories but some require additional hardware (Varma et al, 2021). Most are now equipped with algorithms for arrhythmia detection, and these are being updated regularly, to optimise the sensitivity and specificity particularly around AF monitoring. AF is usually detected by analysing the RR interval on the ECG, along with the absence of P waves (Ghodrati, Murray & Marinello, 2008). Some can also monitor specific intervals on the ECG such as the QT interval or ST segment analysis, which might be relevant when monitoring patients who may be at risk of cardiac events e.g., if taking QT-prolongation medications. Cutaneous patch monitors are typically single-use and can record the ECG continuously or intermittently, operating through electrodes embedded into the patch (Varma et al, 2021).

Smartphone and smartwatch-based devices have become popular among consumers (Varma et al, 2020) and allow the user to perform recordings usually of up to 30 seconds or longer, by placing fingers of each hand on the two electrodes, usually located on the phone case or external card (*Figure 6*, as with the AliveCor® device). The ECG electrical signal is transmitted wirelessly to a smartphone or iPad and the tracings can be reviewed on the smartphone or equivalent device, electronically stored, or transmitted (Varma et al, 2020). Photoplethysmographic technology allows for arrhythmia detection using hardware already present on most consumer devices (e.g., smartwatches and fitness bands) through a downloadable application (Varma et al, 2021). Automated algorithms can analyse generated pulse waveforms to detect AF. In smartphones, this technology uses the phone's camera to measure a fingertip pulse waveform, but rapid, irregular conduction can be challenging for detection, yet the performance of algorithms interpreting these PPG signals has demonstrated high agreement with ECG rhythm strips (McManus et al, 2016; Proesmans et al, 2019).

A recent study comparing the accuracy of five smart devices for identifying AF, found differences in the number of inconclusive tracings, reducing the sensitivity and specificity (Mannhart et al, 2023). The authors summarise that manual review of the

tracings is required in about one-fourth of cases (Mannhart et al, 2023). The PPG technology has also been incorporated in smartwatches to measure heart rate and rhythm (Dörr et al, 2019; Guo et al, 2019). Implantable loop recorders [ILRs] continuously monitor the ECG with recordings assisted through algorithm selection e.g., ECGs saved if the heart rate falls below forty beats per minute or the heart pauses for three seconds or more, or shortly before or after patient activation during symptoms (Milstein et al, 2020). Enhanced algorithms around AF detection have resulted in greater interest and utilisation in cryptogenic stroke (Milstein et al, 2020). Automatic oscillometric blood pressure [BP] monitors derive heart rhythm regularity algorithmically (Chen, Lei, & Wang, 2017). Devices with this capability have shown promise as screening tools for AF, with an ability to identify AF when at least two of three consecutive measurements show pulse irregularity (Kane, Blake, McArdle, Langley, & Sims, 2016).

Accuracy of mHealth devices for AF detection has been assessed in around 500 studies, as described in recent systematic reviews (Giebel & Gissel, 2019; Lowres et al, 2019; O'Sullivan et al, 2020) and their capabilities vary, according to study populations and technologies utilised. *Figure 7* depicts some of these options and *Table 3* details some of the advantages and disadvantages for the different solutions, along with sensitivity and specificity data. Utilisation largely depends on patient and health professional choice, availability, cost, and monitoring purpose, for example, is an existing arrhythmia being monitored for stability or paroxysms or is the aim to detect abnormalities not yet diagnosed. The frequency of symptoms may also impact monitoring choice and the appropriateness for the individual must be considered.

Table 3. Summary of heart rhythm monitoring devices with sensitivity and specificity for AF detection.

Device type	Pros	Cons	Sensitivity	Specificity
Conventional ECG Holter monitor [HM]	Continuous recording. Variable recording durations. Arrhythmia detection in the absence of symptoms.	Impractical and inconvenient for some patient groups (e.g., manual workers, cognitive impairment). Discomfort. Infrequent symptoms may be missed. Additional personal for analysis. Artefact through movement. Possible delays to full analysis report.	96.3% [a.]	96.8% [a.]
Implantable loop recorder [ILR]	Ability for patients to activate recordings to coincide with symptoms. Longer duration of monitoring. Enhanced algorithms for AF detection. Additional functions e.g., often implanted	Invasive with under the skin implantation. Risk of infection. Cost of device. Ongoing monitoring and burden to analyst. ECGs recorded via patient	81.6 - 96.1% [b,c,d]	85.4 - 99.9% [b, c, d]

	for syncope, via remote monitoring. Convenience. Alerts provided. Recurrent cost savings through avoidance of additional or repeated ECG monitoring.	activation or automated algorithm. Problems with connectivity. Administration burden.		
Cardiovascular implantable electronic devices [CIEDs]: Pacemakers and implantable cardioverter defibrillators.	Early detection of events. Remote monitoring. Convenience with an existing device in place. Reduction in healthcare visits. Alerts provided for enhanced safety. Recurrent cost savings once implanted through avoidance of additional ECG monitoring.	Short subclinical episodes of AF may cause deliberation over treatment action. Administration burden. May be dependent on patient to send downloads of monitoring information. Reliance on technology.	80% [e.]	98% [e.]
mHealth ECG based monitoring.	Single-lead and multi-lead options, continuous or intermittent monitoring. Patient control. Patient activation during	Over-treating through false positives (if patient activation necessary and / or silent episodes). Oversight should	Single lead devices 94-98% [f,g,h,i.]	Single lead devices 76-95% [f,g,h,i.]

Examples: Handheld, patch monitoring systems, bio textiles, smartphone with watch-based devices. Examples include: Zenicor, MyDiagnostick, Omron HeartScan, Merlin Event ECG, AliveCor, KardiaMobile, Huawei smartphone,	symptoms. Convenience. Some can provide real-time ECG. Portable. Enhanced algorithms for AF detection. Can store ECGs which can be saved to the user's phone or uploaded to a computer (for review by a health professional which may be accessed via web-based platforms). Patch-based devices waterproof with up to fourteen days monitoring. Potentially more analysable data due to continuous monitoring. No patient activation needed. But has ability to mark time of symptoms during monitoring if	be provided by a health professional. Patient reliant. Neurotic behaviours through over-screening or excessive utilisation. Some devices e.g., smartwatches are costly. Some need additional hardware or accessories. User confidence with the relevant technology. Potential for lead reversal errors. Possible delays to receiving full analysis if patch-based devices sent off for results. Interference, artefact and poor connection between electrodes and skin.	Watches 97-99% [j,k,l,m,n]. Zenicor 96% [o]. MyDiagnostick 60.5 - 100% [p,q]. Omron 94.4% [r]. Merlin 93.9% [r]. AliveCor 98%, 71.4%, 36.8%, 72.7% [f,s,t]. CardioRhythm 93% [t].	Watches 83-94% [j,k,l,m,n]. Zenicor 92% [o]. MyDiagnostick 68.8 - 96.1% [p,q]. Omron 94.6% [r]. Merlin 90% [r]. AliveCor 97%, 99.4%, 96.1%, 98.1% [f,s,t]. CardioRhythm 98% [t].

ZioPatch, CardioRhythm, chest straps, wrist bands and vests.	desired. No lead-reversal errors. Patch / bio textiles deigned for comfort during physical activity e.g., exercise. Bio textiles have single or multi-lead options along with event activation. ECG signals can be stored for later analysis (cloud-based, memory cards, global positioning system). Watches / smartphone-based devices allow for spot-checks, easy access and rapid ECG acquisition. Enhanced algorithms in some devices can detect ectopic beat activity. Diagnostic accuracy.	Smartphone-based devices e.g., AliveCor not recommended for use with pacemakers / implantable cardioverter defibrillators. Limitations for people with tremor when holding some devices. Misclassification of ECG rhythm when automated algorithm incorporated to provide immediate feedback. Screening of younger patients without cardiovascular disease and thromboembolic potential may be low. Patch based can cause skin irritation.		

		Maintaining charge of bio textiles can be challenging. Short duration recordings from some devices.		
mHealth using non-ECG techniques e.g., pulse photoplethysmography [PPG] Examples: CardioRhythm, Pulse-Smart app, Fibricheck, smartwatches such as AppleWatch,	Patient control. Patient activation during symptoms. Convenience. Portable. PPG technologies allow for arrhythmia detection using hardware already present on most consumer devices through downloadable applications e.g., smartwatches, fitness bands. Analysis through an automated algorithm. Less motion artefact than ECG sensors. Passive and opportunistic measurements possible. Non-intrusive. Lower cost.	Over-treating through false positives. Missed detection of significant events (if patient activation necessary and / or silent episodes). Oversight should be provided by a health professional. Patient reliant. Neurotic behaviours through over-screening or excessive monitoring. Screening of younger patients without cardiovascular disease and thromboembolic potential	Smartphone apps: 89.9-98.5% [m,u,v,w,x,y,z]. FibriCheck 95% [aa]. KardiaBand 93%. Smartwatches 97.3% [j,k,l,m,n,bb].	Smartphone apps: 91.4 - 100% [m,u,v,w,x,y,z]. FibriCheck 97% [aa]. KardiaBand 84%. Smartwatches 88.6% [j,k,l,m,n,bb].

Fitbit, CardioSense.		may be low. Rapid irregularly conducted AF may produce variable pulse pressures that challenge detection.		
Oscillometry e.g., blood pressure monitors. Examples: Omron, MicroLife, WatchBP. HealthSense.	Irregularities detected whilst checking blood pressure (dual purpose). Ease of activation. Patient or physician activated. Widely available. Familiarity.	ECG rhythm not visible. Irregular beats presumed AF.	93-100% cc,dd,ee,ff,gg.	86-94% cc,dd,ee,ff,gg.

a. Jiang, Huang, Ye & Chen, (2021); **b**. Cho et al, (2020); **c**. Cotter et al, (2013); **d**. Kusiak et al, (2020); **e**. Yao et al, (2019); **f**. Desteghe et al, (2017); **g**. Jacobs, Kaasenbrood, Postma, van Hulst & Tieleman (2018); **h**. Kaasenbrood et al, (2016); **i**. Wiesel, Abraham & Messineo (2013); **j**. Bumgarner et al, (2018); **k**. Nemati et al, (2016); **l**. Tison et al, (2018); **m**. William et al, (2018); **n**. Nelson et al, (2020); **o**. Doliwa, Frykman & Rosenqvist, (2009); **p**. Tieleman et al, (2014); **q**. Karreget et al, (2021); **r**. Kearley et al, (2014); **s**. Lau et al, (2013); **t**. Chan et al, (2016); **u**. McManus et al, (2016); **v**. Brasier et al, (2019); **w**. Lahdenoja et al, (2018); **x**. Lowres et al, (2014); **y**. Orchard et al, (2016); **z**. Yan et al, (2018); **aa**. Proesmans et al, (2019); **bb**. Mannhart et al, (2023); **cc**. Stergiou, Karpettas, Protogerou, Nasothimiou, & Kyriakidis, (2009); **dd**. Wiesel, Fitzig, Herschman & Messineo, (2009); **ee**. Wiesel, Wiesel, Suri & Messineo (2004); **ff**. Willits, Keltie, Craig & Sims (2014); **gg**. Tang et al, (2022).

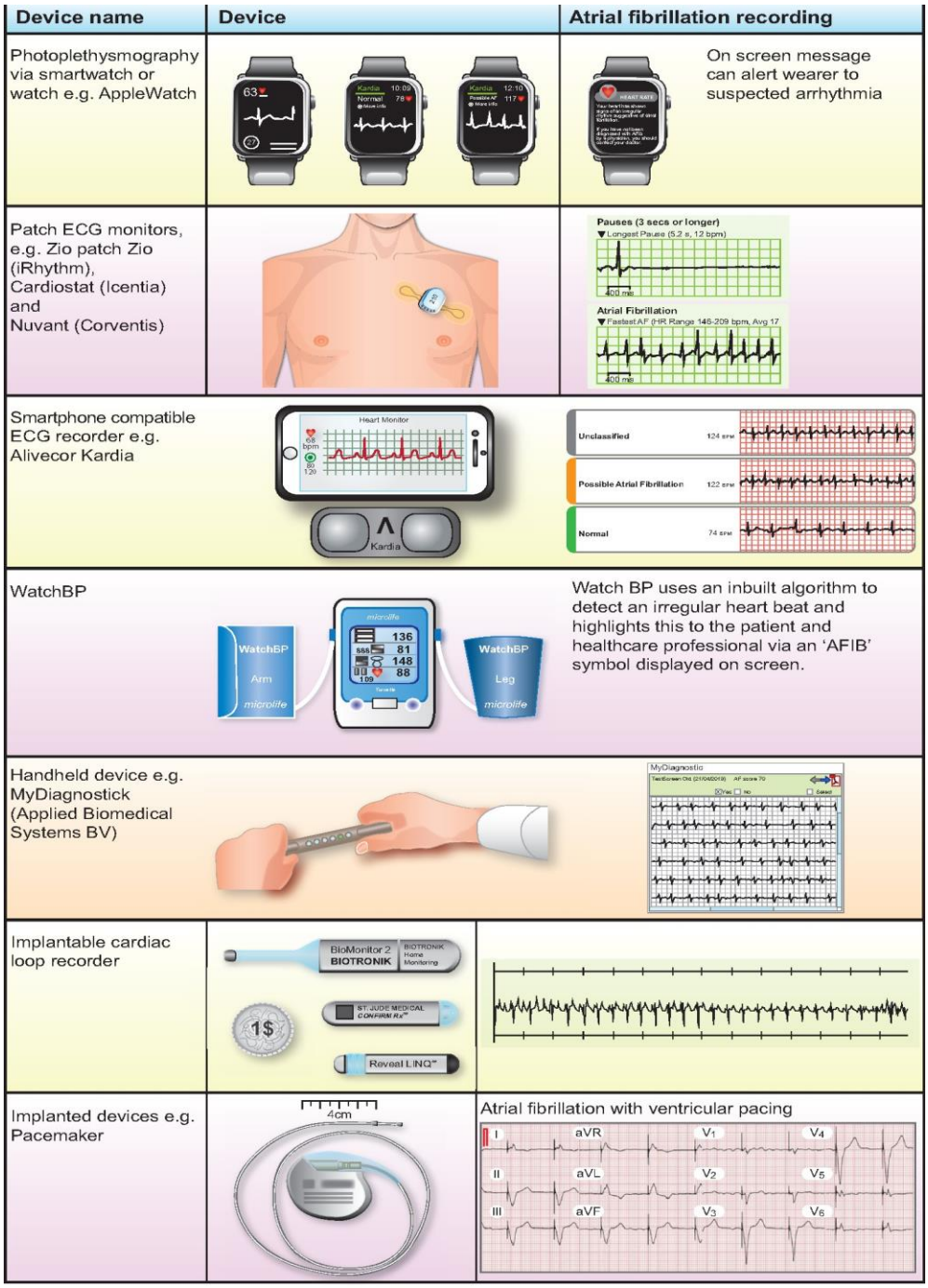

Figure 7.

ECG monitoring devices.

Jones et al, 2020. European Heart Journal, 41(10). (*Permissions granted by Oxford University Press*).

1.1.5 Diabetes.

Diabetes is one of the biggest epidemiological challenges worldwide, partly attributable to the growing epidemic of obesity and adiposity and by 2030, it is estimated the number of people with diabetes (type 1 and 2) will increase to 552 million people (Reed et al, 2021). Diabetes is the fourth leading cause of death in most developed countries and complications from diabetes (e.g., coronary artery disease, neuropathy, stroke, and renal failure) result in reduced life expectancy, increased disability, and huge health costs (Leon & Maddox, 2015; Tabish, 2007). In 2018-2019 there was an estimated 3.9 million people diagnosed with diabetes in the United Kingdom [UK], which is equal to 8.6% of the population who are over 16 years of age (Diabetes UK, 2019a). About 90% of adults currently diagnosed have type 2 diabetes and about one million people are likely to have undiagnosed type 2 diabetes (Diabetes UK, 2019b). Diabetes prevalence is higher in men than in women at 9.6% versus 7.6% (Public Health England [PHE], 2016). There is also a clear association between increasing age and higher diabetes prevalence, from 9% aged 45 to 54 years to 23.8% aged 75 years and over (PHE, 2016).

The prevalence and trend of diabetes and comorbid disease in Jersey, Channel Islands where *Studies 1* and *3* were located, (*Chapters 2* and *6*), continues to grow in a similar way to the UK. Prevalence of health conditions in Jersey and their multi-morbidity, demonstrates that three-quarters of patients with a long-term condition have either hypertension, obesity, diabetes, or a combination of the three (States of Jersey, 2017).

Diabetes has been considered an independent risk factor for AF (Nichols et al, 2009) and 1.4 to 2.1-fold higher than in people without diabetes (Movahed, Hashemzadeh & Jamal, 2005). This is represented in the CHA_2DS_2-VASc stroke risk stratification scoring system (*Table 1*) (Lip et al, 2010). Stroke risk in people with diabetes, is approximately double that of people without diabetes (Hill, 2014) and in one quarter of patients who have AF and diabetes, the cause of stroke is unknown (Du et al, 2009). The risk of stroke is increased 5-fold when AF exists without diabetes (Du et al, 2009) but when they coexist, the risk of stroke is significantly higher than when just one of these

conditions exist. Following stroke there is an increased risk of new onset cardiovascular complications (Buckley et al, 2022) and these patients then have greater than 50% prevalence of recurrent stroke at five years (Buckley et al, 2022).

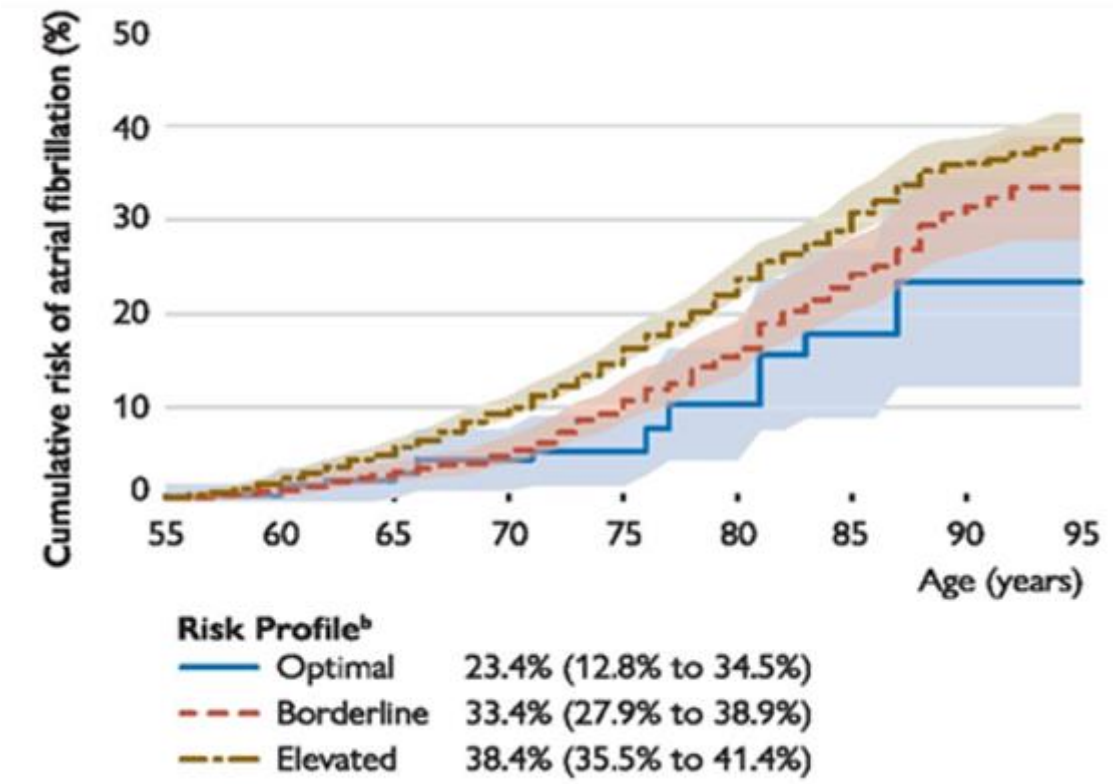

Figure 8.

Atrial fibrillation risk with risk factors. Lifetime risk of atrial fibrillation increases with increasing risk factor burden.

Hindricks et al. (2021) Eur Heart J, 42(5), 373-498. (Permissions granted by Oxford University Press).

a) *Smoking, alcohol consumption, body mass index, BP, diabetes mellitus (type I and II), history of myocardial infarction or heart failure. b) risk profile optimal – all risk factors are negative or within the normal range; borderline – no elevated risk factors but >1 borderline risk factor; elevated - >1 elevated risk factor.*

Evidence relating to AF risk in people with diabetes has shown diabetes to be one of the most common concomitant diseases in patients with AF (Murphy et al, 2007), yet data varies in terms of prevalence across diverse study designs. The Framingham study showed an early indication that diabetes was an independent risk factor for AF with odds ratio of 1.4 for men (95% CI 1.0 - 2.0) and 1.6 for women (95% CI 1.1 - 2.2) after 38 years follow-up (Benjamin et al, 1994). AF and diabetes affect the global population with some variability in regional prevalence (Alwafi et al, 2020; Dai et al, 2020; Joseph et al, 2021; Lin et al, 2020; Lippi, Sancahi-Gomar & Cervellin, 2021). AF and diabetes are however, both long-term medical conditions that affect the world's population and are therefore, relevant to the wider discussion around targeting and screening for AF in people with diabetes. Outcomes and knowledge gained, can be transferable across regions with the fundamental aim being to enhance comprehension around these often-concomitant conditions, whilst accepting the epidemiological, ethnicity and population disparities.

The Global Burden of Disease study demonstrated a continued increase in diabetes prevalence in most developed and developing countries with some variation in geographical distribution (James et al, 2018; Lin et al, 2020). The countries with highest prevalence were China, India, United States, Indonesia, and Mexico (James et al, 2018; Lin et al, 2020). The Global Burden of Disease study also includes data on AF prevalence, incidence, and mortality and analysed by age, sex, year, socio-demographic index, and location (James et al, 2018). AF mainly occurred in developed countries but showed an unfavourable trend in countries with lower socio-demographic index (James et al, 2018). Therefore, whilst the studies for this thesis are in Jersey and the UK, a representation of the literature and research from other countries are presented to demonstrate the worldwide burden of these chronic conditions and research relevance.

Prevalence of AF in people with diabetes was higher in a cross-sectional survey after adjustment for age and sex (Zhou & Hu, 2008) and a retrospective analysis of the VALUE (Valsartan antihypertensive long-term use evaluation) study showed patients with hypertension and diabetes had a significantly higher event rate of new onset AF compared with those without diabetes (Aksnes et al, 2008). A cohort study of 1385

participants aged 30-84-years, based in the USA, explored the association of BMI, diabetes, hypertension, and blood pressure levels with risk of permanent atrial fibrillation (Thacker et al, 2013). Medical records and ECGs were reviewed to explore AF incidence and recurrence over 5-years, and the accumulative incidence of AF was 24%, with diabetes and hypertension not associated with permanent AF. Compared with normal BMI, a BMI of 25.0-29.9 (overweight), 30.0-34.9 (obese 1), 35.0-39.9 (obese 2), and 40.0 kg/m(2) or more (obese 3) were associated with HRs of permanent AF of 1.26 (95 % CI 0.92 - 1.72); 1.35 (0.96 - 1.91); 1.50 (0.97 - 2.33); and 1.79 (1.13 - 2.84), adjusted for age, sex, diabetes, hypertension, blood pressure, coronary heart disease, valvular heart disease, heart failure, and prior stroke. The authors state the benefits of having a lower BMI may include a lower risk of permanent AF (Thacker et al, 2013).

A systematic review and meta-analysis of observational studies investigating the association of diabetes with the likelihood of paroxysmal or non-paroxysmal AF, included twenty articles with sample sizes of 64 to 9816 participants, an age range from 40 to 75 years with women representing 24.8 to 100% of participants (Alijla et al, 2021). Of the eight studies exploring the cross-sectional association of diabetes with non-paroxysmal AF versus paroxysmal AF, six showed a positive association and two showed no association (Aliijla et al, 2021). Fourteen studies investigated the longitudinal association of diabetes with 'more sustained' AF types versus less sustained AF and two showed a positive association and twelve showed no association. In the meta-analysis, patients with AF and diabetes were 1.31-times more likely to have non-paroxysmal AF than people without diabetes (8 cross-sectional studies; pooled Odds Ratio [OR] 1.31; 95% CI 1.13 – 1.51; I2 = 82.6%) and in the longitudinal studies, patients with paroxysmal AF was associated with 1.32-times increased likelihood of progression to non-paroxysmal AF (pooled OR 1.32; 95% CI 1.07 – 1.62; I2 = 0%) (Alijla et al, 2021). Their conclusions suggest that diabetes is associated with an increased likelihood of non-paroxysmal AF rather than paroxysmal AF (Alijla et al, 2021). Data extrapolation from the Health Improvement Network between 2001-2016 in the UK, examined the annual prevalence and treatment of AF in people with diabetes (Alwafi et al, 2020). AF prevalence increased from 2.7 (95% CI

2.5 – 2.8) in 2001 to 5.0 (4.9 – 5.1) in 2016 per 100 persons (Alwafi et al, 2020). Anticoagulant prescribing was also analysed in these patient groups and results demonstrated that in patients with type 2 diabetes and AF, aged 60–79 years, male and with a BMI of 25 or more, were more likely to receive anticoagulation (adjusted OR 1.3 (1.2–1.5) for aged 60–79, 1.3 (1.2–1.4) for male sex and 2.0 (1.9–2.2) for BMI 25 or more, respectively) (Alwafi et al, 2020).

The prevalence of diabetes in people with AF was higher than in controls in an analysis of residents in Japan (20% versus 12%) and a multivariate analysis showed diabetes to be independently associated with AF (Iguchi et al, 2008). A systematic review and meta-analysis including seven prospective cohort studies and four case-control studies (total AF cases n=108,703, total participants n=1,686,097) demonstrated that the summary estimate indicated that patients with diabetes had approximately a 40% greater risk of AF compared to people unaffected (RR 1.39; 95% CI 1.10 - 1.75; p<0.001). Studies that had adjusted for multiple risk factors reported a smaller effect estimate compared to age-adjusted studies (RR 1.24; 95% CI 1.06 - 1.44, versus 1.70, 1.29 - 2.22; p=0.053). The mechanisms underpinning a relationship the authors state to be unclear but do conclude that diabetes is associated with an increased risk of subsequent AF (Huxley et al, 2011).

Another study, focusing on AF risk factors in women and the relationship between incident AF and type 2 diabetes, (n=34,720), who were followed for a median of 16.4 years, demonstrated that compared to women without diabetes, women with diabetes had an age adjusted HR for new-onset AF of 1.95 (95% CI 1.49 - 2.56; p<0.0001) (Schoen, Pradhan, Albert & Conen, 2012). In multivariable analyses adjusting for baseline confounders, the HR was substantially attenuated, but diabetes remained a significant predictor of incident AF (HR 1.37; 95% CI 1.03 - 1.83; p<0.03). In time-updated models adjusted for changes in AF risk factors and cardiovascular events, the HR for diabetes was attenuated further and became nonsignificant (HR 1.14; 95% CI 0.93 - 1.40; p<0.20) (Schoen et al, 2012). This study, therefore, suggests that whilst there is a relationship between diabetes and incident AF, the increased risks associated is predominantly influenced by changes of other AF risk factors (Scheon et al, 2012). AF and the relationship to other risk factors in postmenopausal

women was explored in a prospective observational study (n=93,676, 8252 excluded with prevalent AF) who were followed for an average of 9.8 years for cardiovascular outcomes (Perez et al, 2013). Of the remaining sample, 8252 developed incident AF and age, hypertension, obesity, diabetes, myocardial infarction, and heart failure were independently associated with incident AF (Perez et al, 2013). Hispanic and African American participants had lower rates of incident AF (HR 0.58; 95% CI 0.47 - 0.70 and HR 0.59; 95% CI 0.53 - 0.65, respectively) than Caucasians (Perez et al, 2013).

In a study whereby data was extrapolated from a national health database, risk factors were analysed alongside incident AF (Son, Lim, Cho & Park, 2016). Age, sex, BMI, hypertension, ischemic heart disease and heart failure ($p<0.05$ each) were significant after adjusting for these variables, but diabetes was not (Son et al, 2016). Data from Danish nationwide registries from 1992 to 2012 were searched for people over 18 years of age without prior AF and/or diabetes (Pallisgaard et al, 2016). The total study cohort included 5,081,087 people and were divided into a background population without diabetes and a diabetes group. AF incidence rates per 1000 person years were divided in four age groups from 18 to 39, 40 to 64, 65 to 74 and 75 to 100 years giving incidence rates of 0.02 (95% CI 0.02 - 0.02), 0.99 (95% CI 0.98 - 1.01), 8.89 (95% CI 8.81 - 8.98) and 20.0 (95% CI 19.9 - 20.2) in the background population and 0.13 (95% CI 0.09 - 0.20), 2.10 (95% CI 2.00 - 2.20), 8.41 (95% CI 8.10 - 8.74) and 20.1 (95% CI 19.4 - 20.8) in the diabetes group, respectively. The adjusted incidence rate ratios in the diabetes group with the background population as reference were 2.34 (95% CI 1.52 - 3.60), 1.52 (95% CI 1.47 - 1.56), 1.20 (95% CI 1.18 - 1.23) and 0.99 (95% CI 0.97 - 1.01) in the four age groups, respectively (Pallisgaard et al, 2016).

Another systematic review and meta-analysis of the relative risk of AF in people with diabetes was undertaken by Xiong et al (2018) and machine learning-assisted screening, identified twenty-nine studies (n=8,037,756). A pooled analysis demonstrated that patients with diabetes had an approximate 49% greater risk of developing AF (RR 1.49; 95% CI 1.24 – 1.79) compared with people without diabetes (Xiong et al, 2018). After adjustment for at least one of the three common risk factors (hypertension, cardiac disease and obesity), the RRs were lower (1.20; 95% CI 1.15 – 1.26; 1.27, 95% CI 1.11 – 1.45; 1.22, 95% CI 1.09 – 1.38) but when adjustments for all

three risk factors were included, the estimated overall risk of AF in patients with DM was lower (RR 1.23; 95% CI 1.03 - 1.46)After adjusting for hypertension, obesity and heart disease, the RR was 23%. Multivariate adjustment for confounders showed a higher risk of AF in women (RR 1.38; 95% CI 1.19 – 1.60) compared to men (RR 1.11; 95% CI 1.01 – 1.22; p<0.001) (Xiong et al, 2018). A prospective case-control study (n=36,258, controls n=179,980) of the Swedish National Diabetes Registry including people with type 1 diabetes were matched for age, sex, and county of residence over twelve years (Dahlqvist et al, 2017). AF was diagnosed in 749 (2%) of participants with diabetes and 2882 (2%) of controls, adjusted HR 1·13 (95% CI 1·01 - 1·25; p=0·029) in men and 1·50 (95% CI 1·30 -1·72; p<0·0001) in women (p=0·0019 for interaction). The excess risk of AF in the presence of diabetes increased with worsening glycaemic control and renal complications (Dahlqvist et al, 2017). Compared to the general population, the risk of AF in men with type 1 diabetes was slightly raised but was 50% higher in women (Dahlqvist et al, 2017). However, in the development of a risk score for AF in the Framingham cohort, diabetes was not a significant predictor of AF (Schnabel et al, 2009). Diabetes was not identified as a predictor for AF in multivariate logistic regression analysis in a community-based AF screening study, (Chan & Choy, 2017), neither was diabetes an independent predictor for AF on the post hoc analysis from ALLHAT trial (Antihypertensive and lipid-Lowering treatment to prevent heart attack trial) (Haywood et al, 2009).

This heterogeneity between epidemiological, screening and prevalence studies, leads to some uncertainty around the associations between diabetes and AF, and whilst the literature seems to demonstrate a tendency towards an association, the diverse study designs, methods, and populations, results in an uncertain conclusion. Therefore, attempts to provide focus by targeting people with diabetes specifically, in the screening, prevalence and predictors study (*Study 1, Chapter 4*), aims to address this group specifically by providing further evidence in this area of research. Studies that have incorporated research into AF in the presence of diabetes, are summarised in *Table 4*.

Table 4. AF screening research incorporating people with diabetes.

Study	Cohort characteristics	Design	Results
Chan & Choy, 2017.	Total participants *n*=13,122. Eligibility criteria: Age ≥18 years.	Epidemiological study. Territory-wide community-based systematic screening using the AliveCor® device.	101/13,122 newly diagnosed AF (0.8%), 66/101 (65.3%) asymptomatic. CHA2DS2VASc score of participants with new AF 3.1±1.3. Incidence of AF detection 1.8%. AF detected and / or self-reported 8.5%. People with diabetes n=1944 (14.8%), diabetes and new AF n=29 (28.7%). Diabetes and newly detected AF or self-reported, n=232/1515 (20.9%). Multivariable logistic regression analysis showed independent predictors of AF as age, sex, height, weight, body mass index, history of heart failure, valvular heart disease, stroke, hyperlipidaemia, coronary artery disease, peripheral artery disease and cardiothoracic surgery.
Chan et al, 2016.	Total participants *n*=1013. Eligibility criteria: Hypertension, diabetes, aged ≥65 years. Excluded if had a pacemaker or	Prospective screening study. AliveCor® ECG device recording then 3 PPG wave-forms using an iPhone with CardiioRhythm application. If	AF screening study including people with diabetes, (no data on high-risk groups). More tool specific comparing outcomes of two digital screening devices. AF in 28 (2.7%) patients with 5 (17.9%) newly diagnosed. Diabetes in 371 (36.6%) of participants.

	implantable cardioverter defibrillator.	AF seen, 12 lead ECG to confirm. Recruited via a general out-patient clinic in Hong Kong.	
Davis et al, 2012.	Total participants *n*=3960. Aged >45 years. Eligibility criteria: Ability to reach study centre, terminal illness, immobility, absence of a psychiatric disorder.	Prevalence, non-experimental, observational, epidemiological study. A pre-specified analysis of a previous study to evaluate the evidence of left ventricular dysfunction (Davis et al, 2001). Clinical assessment, 12 lead ECG, echocardiogram, clinical history. Mortality tracked for 8 years. Recruitment via	AF in 78 (2%) of patients. Comorbid conditions included heart failure (*n*=782), myocardial infarction, hypertension, angina, or diabetes (*n*=1062). AF prevalence 1.6% in women and 2.4% in men, rising with age from 0.2% aged 45-54 to 8.0% >75-year-olds. Half of all AF patients ≥75 years. 175/782 patients with heart failure had AF (22.4%), 14/244 (5.7%) myocardial infarction, 15/388 (3.9%) with hypertension, 15/321 (4.7%) with angina, and 11/208 (5.3%) with diabetes had AF. Adjusting for age and sex, mortality 1.57 times higher for those in AF.

		16 primary care practices in England.	
Godin et al, 2019.	Total participants *n*=7585 (42% of people eligible). Eligibility criteria: >65-year-olds, no known AF.	184 Canadian primary care physicians using an AliveCor® device for three months (and survey).	AF detected in 471 patients (6.2%). Anticoagulation therapy initiated in 270 patients (57%). Physicians reported high perceived clinical value (94%) and ease of integration (89%). Diabetes was a trigger to screen in 8% of the cohort, as was age ≥ 65 years, hypertension, cardiovascular disease, an irregular pulse and people exhibiting symptoms e.g., palpitations or dizziness.
Gumprecht et al, 2021.	Total participants *n*=3014 (mean age 77.5 years, 49% female). Eligibility criteria: > 65 years.	Representative sample from cross-sectional NOMED-AF study. Telemonitoring vest used to screen for AF. Polish and European population.	881 (29.2%) diagnosed with diabetes. Mean screening duration 21.9 ± 9.1 days. AF in 680 (22.6%) of the study population. AF prevalence higher with concomitant diabetes versus those without diabetes (25%, 95% CI 22.5-27.8% vs 17%; 95% CI 15.4–18.5% respectively, $p < 0.001$). Diabetes commonly associated with silent AF (9%; 95% CI 7.9–11.4 vs 7%; 95% CI 5.6–7.5 respectively, $p < 0.001$), and persistent/permanent AF (12.2%; 95% CI 10.3–14.3 vs 6.9%; 95% CI 5.9–8.1 respectively, $p < 0.001$) compared to people without diabetes. Longer duration screening associated with more AF detected, with and without diabetes (5% vs 4.5%

			respectively, p < 0.001). Different independent risk factors associated with AF in people with and without diabetes, including thyroid disease, peripheral/systemic thromboembolism, hypertension, physical activity, and prior percutaneous coronary intervention/coronary artery bypass graft surgery.
Heo et al, 2020.	Total participants *n*=608. Eligibility criteria: no known AF.	Sample from *n*=1738 participants from a previous study (mSToPS trial, Steinhubl et al, 2016). ECG patch fourteen days, twice, over four months, followed for one year.	Ninety-six (15.8%) of study participants with diabetes also had chronic kidney disease and over follow-up, nineteen new cases of AF detected. AF newly diagnosed in 7.3% of participants with chronic kidney disease and 2.3% in those without (p< 0.05) over follow-up. Risk of incident AF three times higher in people with kidney disease relative to those without (HR 3.106; 95% CI 1.2–7.9). After adjusting for the effect of age, sex, and hypertension, risk of incident AF still significantly higher with chronic kidney disease (HR 2.886 ;95% CI 1.1–7.5).
Hicks et al, 2019.	Total participants *n*=500.	Screening study via pulse taking by Podiatrists (*n*=45) during annual foot screening	One new case of AF identified from the total participants.

		reviews. Three- month pilot. North of England.	
Kaasenbrood et al, 2020.	Total participants *n*=17,107. Eligibility criteria: >65 years, no known AF.	Cluster randomised controlled trial. One year follow up period. Fifteen GP surgeries in intervention arm (using MyDiagnostick), sixteen followed usual care.	In the intervention arm, 10.7% of eligible patients (*n* = 919) screened. Newly diagnosed AF similar in intervention and control practices (1.43% versus 1.37%, p=0.73). Screened patients more likely to have comorbidities, including hypertension (60.0% versus 48.7%), type 2 diabetes (24.3% versus 18.6%), and chronic obstructive pulmonary disease (11.3% versus 7.4%), than eligible patients not screened in the intervention arm.
Kalia et al, 2020.	Total participants *n*=149.	Cross-sectional study (feasibility and utility) using the AliveCor® device (30 second recordings). Secondary care clinics for diabetes and vascular care.	AF was detected in 2 of 149 patients (1.3%), with CHA2DS2-VASc-derived annual stroke risk of 4%. Possible AF in two further cases, rhythm irregularities insufficient to affirm diagnosis. In nineteen patients (12.8%) ≥2 premature atrial or ventricular ectopic beats identified. QRS complex broadening evident in 4.0% of cases. ECG quality high in 74.5% of ECGs and rhythm regularity assessed in 99.3% of cases.

Kim et al, 2020.	Total participants *n*=2422. Expanded study *n*=5366. Eligibility criteria: ≥60 years.	Screening study. Community dementia screening programme then expanded to include nine Senior Welfare Centres. The AliveCor® device then 12 lead ECG to confirm suspected AF.	Of the 2,422 subjects, 124 had AF on AliveCor® with prevalence of AF 3% (95% CI 2.4–3.8). The positive predictive value (PPV) 58.9% (95% CI 50.1–67.1). From this 124, 73 had AF confirmed on 12 lead ECG. Of those with AF, 65.8% (95% CI 54.3–75.6) newly diagnosed. In the expanded study, 289 had AF on the AliveCor® device and prevalence 2.6% (95% CI 2.2–3.1), PPV 48.8% (95% CI 43.1–54.5).
Kyrikoulis et al, 2019.	Total participants *n*=136 (age 73.8 ± 7.1 years, 63% men). Eligibility criteria: >65 years or 60-65 years with hypertension, diabetes, or cardiovascular disease.	Diagnostic accuracy of FreeScan, Maisense pocket-size self-BP monitor (with AF algorithm detection). BP measurements with simultaneous Holter ECG monitoring.	Data from five valid BP measurements for participants = total 680 readings versus ECG, revealed specificity 99%, sensitivity 67%, and diagnostic accuracy 93% for AF diagnosis. Readings with device notification “Instability” (29%) or “Error” (20%) were discarded. When “Arrhythmia” notification considered as an AF diagnosis, the sensitivity improved (93%, 96%, and 93%, respectively). Analysis of AF diagnosis when defined as at least three of five readings indicating “AF” or “Arrhythmia”, demonstrated specificity, sensitivity, and diagnostic accuracy for AF detection 94%, 100%, and 95%, respectively.

Salvatori et al, 2015.	Total participants *n*=308. Eligibility criteria: Age ≥65 years and hypertension. Excluded if unable to attend the study centre.	Observational, cross-sectional study. 12 lead ECG, medical history. 48- hour Holter monitor if no AF detected on initial ECG (*n*=274). Recruitment from GP's and a medicine-stroke unit in Perugia, Italy.	AF known and confirmed by ECG in 4/308 participants (1.3 %). Holter monitoring in 300 people, mean age 70 ± 4. 274/300 analysed (others uninterpretable due to artefact). Holter monitoring showed AF in 27/274 participants (10 %; 95 % CI 6.4-13.5 %), 18 of these patients revealed AF in the first 24 hours of monitoring. People with diabetes *n*=42/274 (15%) in this study and *n*=2/27 (7%) also had AF. Diabetes was not a predictor for AF in multivariate analysis.
Samol et al, 2013.	Total participants *n*=132. 76 years mean age (64 ± 14 years SD). Eligibility criteria: Age ≥18 years, ≥ one risk factor from hypertension, diabetes, left ventricular hypertrophy, myocardial infarction, C-reactive	Prevalence study, non-experimental, observational. Screening using patient operated, single channel ECG recorder (Omron hcg-801-e, Germany). Recruitment through diabetes, hypertension, and	AF in 7/132 patients (5.3%), 4 in stroke survivors, 2 with diabetes, 1 with hypertension, median CHADS2 score 2. Risk of AF higher when multiple risk factors present (7% when diabetes and hypertension co-exist) and 11% when all 3 risk factors present. Participants with diabetes n=36, (27%) in the study, 3/36 having AF (43%).

	protein >3mg/Dl, peripheral vascular disease, kidney disease, heart failure NYHA III/IV or ejection fraction <50%, ischaemic stroke, TIA. Excluded if known AF.	dyslipidaemia outpatient clinics (*n*=76) or stroke unit (*n*=56) at the University of Muenster, Germany.	
Sanmartin et al, 2012.	Total participants *n*=1532 (877 women, mean age 72.5 years). Eligibility criteria: Age ≥65 years and the 'presence of other risk factors' (not specified) or cardiovascular disease. Excluded with a history of AF or atrial flutter.	Observational, non-experimental. During 'Pulse Week', history taken regarding vascular risk factors, symptoms, blood pressure, and 15 second pulse check. Irregularities checked with 12 lead ECG. Recruited from 3 health centres in Pontevedra, Spain and tertiary referral hospital.	Hypertension in 833/1532 (54%), 232 had diabetes (15%), 61 a previous stroke (4%), and 88 myocardial infarction (6%). ECGs in 187 participants. AF detected in 30 out of 197 by ECG, 17 patients newly diagnosed AF, 8 in people with diabetes (47.1%).

Sun et al, 2014.	Total participants *n*=11,956 (11,341 completed). Eligibility criteria: Permanent residents, ≥35 years of age. Excluded if pregnant, cancer diagnosis or mental disorder.	Cross-sectional study. Medical history, 12 lead ECG, fasting blood tests, BP, BMI, and echocardiogram. Participants questionnaire. Recruitment from a clinic setting in Liaoning Province, China.	Prevalence of AF 139/11,341 (1.2%). Rose steeply with age (0.1% 35-44 years of age, 4.6% ≥75 years); no significant sex difference at any age. People with diabetes n=1,171 (10%). Diabetes with AF n=34 (24.5%). Diabetes and AF present in 2.4% of men and 3.3% of women. Independent risk factors for AF included age (OR 1.89; p<0.001), diabetes (OR 2.07; p=0.001), history of myocardial infarction (OR 5.91; p<0.001), low left ventricular ejection fraction (OR 1.85; p=0.005), and low physical activity (OR 1.72; p=0.003), whereas obesity, hypertension, cholesterol and triglyceride levels, smoking, alcohol consumption, left ventricular hypertrophy, and family history of AF not significant contributors.
Svennberg et al, 2015.	Total participants *n*=7173 (13,331 invited, 53.8% participation). Eligibility criteria: 75-76-year-olds.	Randomised controlled, non-blinded cohort study. Medical history including cardiovascular risk factors. Handheld ECG for intermittent recordings over	New AF in 218/7173 patients (3%; 95% CI 2.7-3.5) and of these, AF in 37 (0.5% of the screened population) on first ECG. Previous diagnosis of AF known in 9.3% (n=666; 95% CI, 8.6-10.0). Total AF prevalence in the screened population 12.3%. Of participants with known AF, 149 (2.1%; 95% CI, 1.8-2.4) had no OAC treatment. In total, 5.1% (95% CI, 4.6-5.7) of screened population had untreated AF. 29 (13.3%) had diabetes. Known AF seen in 666 of the total

		2 weeks, 12 lead ECG when inconclusive. Recruited via a screening centre in Stockholm County or Halland Province, Sweden.	number and 135 (20.3%) had diabetes. As risk factors accumulated, so did AF prevalence. Heart failure then stroke then diabetes, were strongest predictors for AF.
Targher et al, 2013.	Total participants *n*=400. Eligibility criteria: Type 2 diabetes, free from AF at study entry. Excluded if taking antiarrhythmic drugs, moderate-severe aortic and mitral valve disease, hyperthyroidism, malignancy, end-stage renal disease, liver disease (of know aetiology) or missing liver ultrasound.	Prospective screening study. Annual ECG on patients with type 2 diabetes and non-alcoholic fatty liver disease. Follow up for 10 years. Recruited from a diabetes clinic in Negrar, Italy.	During follow up, 42/400 (10.5%) incident AF. Non-alcoholic fatty liver disease associated with an increased risk of incident AF (OR 4.49, 95% CI 1.6-12.9, p<0.005). Adjustments for age, sex, hypertension, and left ventricular hypertrophy and PR interval on the ECG did not attenuate association between non-alcoholic liver disease and incident AF (adjusted-OR 6.38, 95% CI 1.7-24.2, p = 0.005). Other independent predictors of AF were older age, longer PR interval and left ventricular hypertrophy.

Turakhia et al, 2015.	Total participants *n*=75. All male, age 69 ± 8.0 years. Eligibility criteria: Age ≥55 years and ≥2 risk factors including coronary disease, heart failure, hypertension, diabetes, sleep apnoea. Excluded if known AF, stroke, TIA, pacemaker, defibrillator, palpitations, or syncope in the previous year.	Prospective screening study. Wearable patch-monitoring, 2 weeks continuous ambulatory ECG monitoring (iRhythm Technologies, Inc). Single centre at the Veterans Affairs Palo Alto Health Care System, California.	AF detected in 4/75 (5.3%). People with diabetes *n*=42 (56%). No data provided on AF prevalence in people with diabetes. Combined diagnostic yield of sustained atrial tachycardia/AF 11%. In people without sustained atrial tachycardia/AF, 11 (16%) had ≥30 supraventricular ectopic complexes per hour. Monitoring effective and feasible with AF identified in 1 in 20 participants and sustained atrial tachycardia / AF identified in 1 in 9 people. High prevalence of frequent ectopics and atrial tachycardia.
Zhang et al, 2021.	Total participants *n*=8240. Eligibility criteria: ≥65 years, no known AF.	Randomised controlled trial comparing different screening frequencies using the AliveCor® device. Assigned to annual or quarterly screening groups	Participants randomly assigned to annual screening (*n*=4120), quarterly screening (*n*=3090), and quarterly screening plus (*n*=1030), with a mean number of ECGs 1·6 for annual screening, 3·5 for quarterly, and 5·2 for quarterly screening plus. Incident cases of AF =73, 26 in annual screening group (4·1 per 1000 person-years), 47 in the quarterly screening group (6·7 per 1000

		(latter assigned 3:1 ratio quarterly vs quarterly screening plus). April 2017 – June 2018, median follow up 2.1 years. Five community health centres in Shanghai, China.	person-years). Significant increase in quarterly screening group and AF detection, compared with annual screening (HR 1·71; 95% CI 1·06–2·76; p=0·029). 40 incident cases in quarterly screening (7·2 per 1000 person-years; HR compared to annual screening, 1·83; 95% CI 1·12–3·00; p=0·017) and seven in the quarterly screening plus group (4·8 per 1000 person-years; HR compared with annual screening, 1·24; 0·54–2·86; p=0·61). No significant difference was noted between quarterly screening and the quarterly screening plus group (HR of quarterly screening plus compared with quarterly screening, 0·68; 0·30–1·52; p=0·35).

Different theories suggest this relationship may be causal, where diabetes leads to an increased risk of AF, because of pathological changes in atrial tissue due to hyperglycaemia, or from deviation in autonomic nervous tone (see *Figure 9*) (De Sensi, De Potter, Cresti, Seven & Breithardt, 2015). Alternatively, AF and diabetes share multiple risk factors including hypertension, OSA and obesity and the relationship may therefore be correlational (see *Figure 9 and Figure 10*). The physiological link between the two disease groups is multifactorial but includes higher levels of systemic inflammatory markers in people with diabetes particularly when glycaemic control is poor (*Figure 9*) (Raposeriras-Roubin et al, 2012). Chronic systemic inflammation can lead to higher levels of atrial myocyte breakdown and fibrosis and consequentially, provides a source of AF initiation (Saunders, Mathewkutty, Drazner & McGuire, 2008). Furthermore, diabetes impacts coronary microvasculature and results in left ventricular diastolic dysfunction and subsequently, atrial structural remodelling (*Figure 9*) (Andersson et al, 2010).

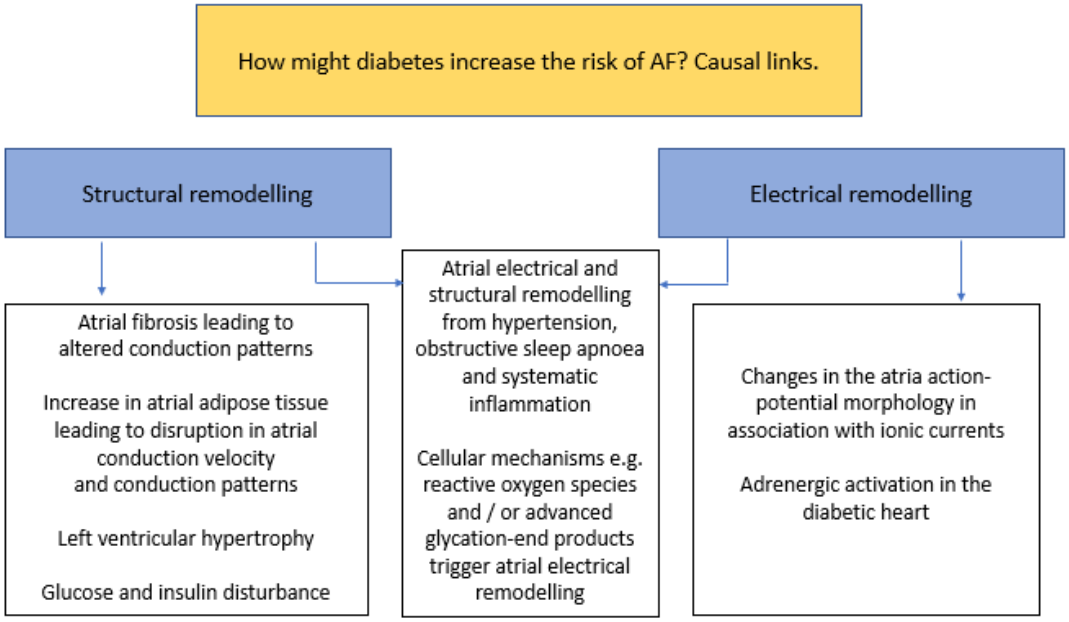

Figure 9.

Causal links of AF in people with diabetes.

(The text under each heading correlates with this form of remodelling; the two central blocks of text, feature both structural and electrical remodelling).

There is also evidence that duration of diabetes and diabetes control can impact on the risk of AF development, and their contribution will be investigated in this research (*Study 1, Chapter 4*). A population-based case-control study found that people with treated diabetes for more than five years, had a higher risk of developing AF by up to 40% (Dublin et al, 2010). The risk of developing AF in people with diabetes was 3% higher for each additional year of diabetes duration (95% CI 1-6%) (Dublin et al, 2010). A meta-analysis of seven cohort and four case-control studies totalling 1,686,097 participants concluded there to be an association between diabetes and an increased risk of subsequent AF but remained speculative about the mechanisms that might underpin the relationship between the two disease groups (Huxley, Filion, Konety & Alonso, 2011). The summary estimate indicated that patients with diabetes had an approximate 40% greater risk of AF compared to people without diabetes, (RR 1.39; 95% CI 1.10 - 1.75; p=<0.001) (Huxley et al, 2011), supporting the findings from the research by Dublin et al (2010). Discrepancies in observational study findings have been reported, with equivocal results; however, this may be due in part to methodological challenges (e.g., effect size and limited power) (Agmon et al, 2001; Ahmadi et al, 2020; Movahed, Hashemzadeh & Jamal, 2005; Stewart, Hart, Hole & McMurray, 2002; Wilhelmsen, Rosengren & Lappas, 2001). A population-based cohort study examined 37,209 individuals aged 66 years or older with AF and diabetes over a ten-year period. The primary outcome was hospitalisation for stroke at one year. The analysis revealed a rise in stroke HRs corresponding to the duration of diabetes, which plateaued after a decade (Abdel-Qadir et al, 2022). In comparison to patients with diabetes lasting less than five years, those with a duration of ten years or more exhibited a significantly higher stroke rate (HR 1.45, 95% CI 1.16 - 1.82, p=0.001). However, a duration of five to ten years showed no significant difference (Abdel-Qadir et al, 2022). Moreover, the study investigated diabetes control through HbA1c levels, uncovering a higher stroke rate in patients with a glycated haemoglobin exceeding 8% compared to those with levels between 6% and 7% (HR 1.44, 95% CI 1.12 - 1.84, p=0.004) (Abdel-Qadir et al, 2022).

Additional research by Dublin et al (2010) examined the impact of HbA1c on AF development, revealing an adjusted OR of 1.06 (95% CI 0.74 - 1.51) for people with

diabetes with an HbA1c level at or below 7%. The OR increased as HbA1c levels rose (Dublin et al, 2010).

A recent meta-analysis supported the connection between higher glucose levels and increased AF incidence (Qi et al, 2017), while other studies found a significant association between HbA1c levels above 6.3% and elevated AF risk (Zhao et al, 2020). Furthermore, a study involving two million participants with and without diabetes demonstrated a linear correlation between increased HbA1c levels and excess AF risk (Ahmadi et al, 2020).

The prospective cohort Atherosclerosis Risk in Communities (ARIC) study observed a positive linear association between HbA1c and AF risk in people with and without diabetes (HR 1.13; 95% CI 1.07 - 1.20 and HR 1.05; 95% CI 0.96 - 1.15 per 1%-point increase, respectively (Huxley et al, 2012). Nonetheless, no association was found between fasting glucose or insulin levels in non-diabetic participants, while a significant association emerged for fasting glucose in people with diabetes (Huxley et al, 2012).

Ahmadi et al (2020) evaluated the risk of AF in individuals with type 2 diabetes in relation to a 1.0% (10.0 mmol/mol) higher mean HbA1c, revealing a modest impact on AF development with a risk increase of 1.0-4.0% per 10 mmol/mol higher mean HbA1c. This study also considered the excess risk of AF in patients with renal complications, discovering a persistently elevated risk even when HbA1c was at or below 6.9% (52 mmol/mol) and normoalbuminuria was present (HR 1.16, 95% CI 1.14-1.19, $p<0.0001$) (Ahmadi et al, 2020). Contrarily, a Mendelian randomisation analysis found no causal role for fasting glucose (OR 0.95, 95% CI 0.82 - 1.09 per mmol/l, $p=0.49$) and HbA1c levels (OR 1.01, 95% CI 0.85 - 1.17 per mmol/mol %, $p=0.88$) in AF development (Harati et al, 2019). However, it has been suggested that HbA1c variability might initiate atrial fibrillation in individuals with type 2 diabetes (Gu, Fang, Zhang & Wang, 2017).

However, studies have also suggested that it might be glycaemic fluctuations, rather than hyperglycaemia, that contributes to AF risk (Gu et al, 2017). Glycaemic fluctuations have shown strong correlation with increased oxidative stress rather than

chronic hyperglycaemia, suggesting that wide variations in glucose levels may be a more important risk factor for AF (Monnier et al, 2006).

Finally, in a recent cohort study, long-term glycaemic variability was significantly associated with new-onset AF (Hsu, Yang, Chuang, Yu & Lin, 2021). The highest HbA1c score was significantly associated with increased risk of AF (HR, 1.29, 95% CI 1.12 – 1.50, p<0.001), total mortality (HR 2.43, 95% CI 2.03 – 2.90, p<0.001), cardiac mortality (HR 1.50, 95% CI 1.06 –2.14, p=0.024) and non-cardiac mortality (HR 2.80, 95% CI 2.28 – 3.44, p<0.001) (Hsu et al, 2021).

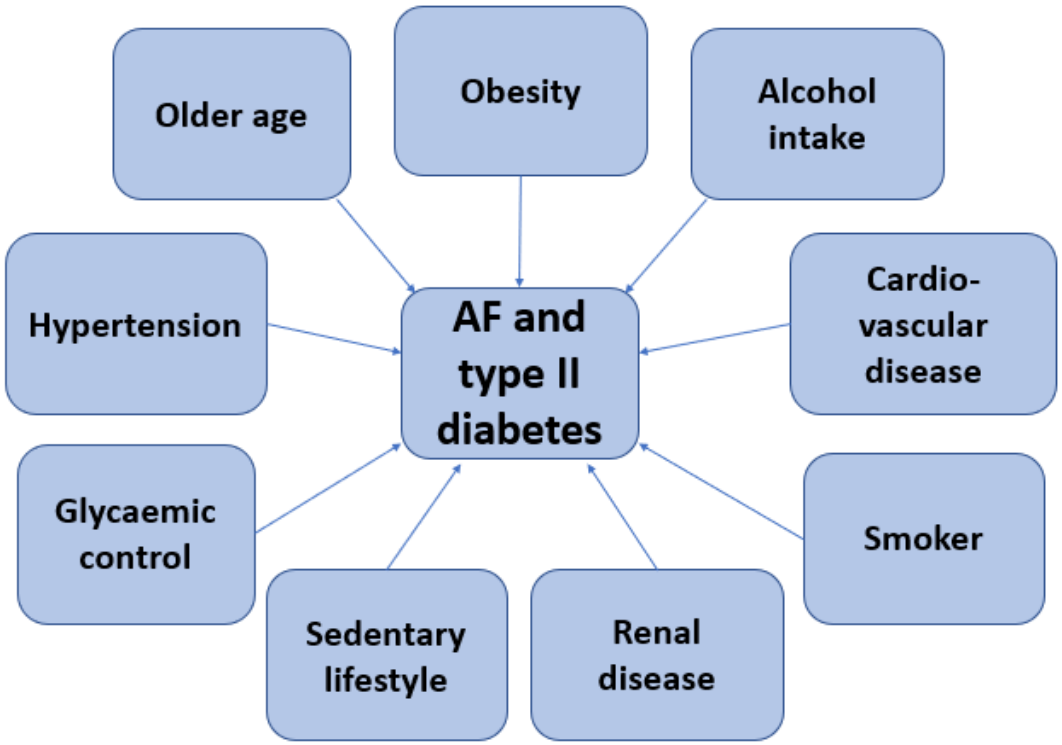

Figure 10.

AF and diabetes shared risk factors.

1.1.6 Quality of Life

Detecting AF is also important for reasons beyond the physiological effects of the arrhythmia and necessitates diagnosis to identify negative consequences to emotional wellbeing, psychological health, and overall quality of life [QoL]. QoL became more prominent in healthcare and research since the World Health Organisation [WHO] defined health as beyond purely the absence of disease, but encompassing physical, mental, and social wellbeing (WHO, 2020). Perhaps even more pertinent than a definition, is the paradigm shift from the historical medical model and hierarchy assumed between a medical professional and patient, to the shared partnership and decision making around managing health. This movement away from medicalised outcomes as the goal in treatments, encompasses patients' QoL as central to appropriate and individualised care.

QoL is a broad ranging concept, based on individuals' perception and developed through beliefs, experiences and expectations (Aliot, Botto, Crijns & Kirchoff, 2014). QoL is subjective and relative to goals and standards, often originating from individuals' culture and value systems (Sazlina, 2015). QoL can be measured by using generic or disease specific QoL instruments, many of which have been used across a range of conditions (Rabin & Charro, 2001). There are strengths and weaknesses of both generic and specific measures and consideration should be given to the most suitable instrument for its purpose. By design, specific QoL tools measure elements of the respective disease whereas generic QoL tools, reflect general health and functioning rather than factors more applicable to people with specific disease. Scores can be influenced by patient demographics and comorbidities which are often prevalent in older people with AF.

In published AF studies alone, the variability in QoL instruments used can make outcome comparability challenging. The plethora of QoL measuring instruments can make for complex decisions regarding the optimal tool, and this range reflects a lack of consensus on an optimal approach to measuring QoL (Reynolds, Ellis & Zimetbaum, 2008). There is, however, consensus that QoL has multiple dimensions, and they are

most appropriately measured by asking the individual to score these 'domains' themselves (Jenkins et al, 2005).

The Medical Outcomes Study Short Form Health Survey [SF-36] is one of the most consistently used generic QoL scales in AF studies, along with the SF-12 (derived from the SF-36), (Ware & Sherbourne, 1992) and the European QoL Measure [EuroQOL/EQ-5D] (EuroQoL Group, 1990). The SF-36 consists of a 36-item questionnaire that assesses eight health concepts and generates physical and mental component summary scores (Ware & Sherbourne, 1992). These domains include physical functioning, social functioning, general health, role limitations due to physical problems, role limitations due to emotional problems, and vitality (Ware & Sherbourne, 1992). The SF-36 is the most widely validated generic instrument available and has been used to study QoL in a variety of conditions, not just of a cardiac nature (Reynolds et al, 2008). The EuroQOL covers five dimensions of health status including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (EuroQoL Group, 1990). The domains are rated on three levels ranging from no problems to severe problems and has also been extensively validated in both cardiac and non-cardiac populations (Reynolds et al, 2008).

Cardiac-specific questionnaires have been applied to AF and QoL related research, although some have not been designed for AF specifically. The Arrhythmia Symptom Checklist: Frequency and Severity, was developed for evaluating the impact of early catheter ablation and pacing on a variety of arrhythmias and asks respondents to rate the frequency and severity of symptoms commonly associated with AF (Bubien et al, 1996). The Fibrillation Registry Assessing Costs, Therapies, Adverse events, and Lifestyle study [FRACTAL] (Reynolds, Lavelle, Essebag, Cohen & Zimetbaum, 2006) recommended that generic tools are not ideal for measuring AF and an AF-specific questionnaire should address the spectrum of QoL domains affected by AF. A dedicated QoL instrument has been developed by the German Competence Network on AF [AF Network, AFNET] by covering generic domains as per the SF-36 and EuroQoL but adds elements from validated depression scales (Kirchhof et al, 2007). Assessing elements that are more specifically related to AF increases the sensitivity to changes in patients' health status, and in clinical trials have greater statistical power than

generic instruments regarding discrimination between patients free from arrhythmia and those with AF recurrence (Aliot et al, 2013; Berkowitsch et al, 2003). A systematic review of the measurement properties of AF-specific health related QoL questionnaires by Kotecha et al (2016), demonstrated good reliability with internal consistency and test re-test reliability for four of the included tools (Atrial fibrillation 6 [AF6] (Harden et al, 2009), AF Effect on QoL [AFEQT] (Spertus et al, 2011), AF QoL Questionnaire [AFQLQ] (Yamashita et al, 2005) and AF-QoL (Arribas et al, 2010). The content, construct and criterion validity, and responsiveness, was only positively rated in the AFEQT (Kotecha et al, 2016). The AFEQT showed strong evidence for two of the nine measurement properties in the review (covering reliability, validity, and responsiveness), the AFQoL had good evidence of one of the nine properties and none for the remaining questionnaires included (Kotecha et al, 2016). Whilst there is good argument to consider AF specific tools, when the coexistence of chronic disease is under enquiry, a generic tool is felt more appropriate as aspects integral to the disease specific tool may be less transferable and may potentially, inaccurately reflect QoL components of the comorbid disease. This research also focuses on the general population rather than participants within trials for which the disease specific tool had been devised. AF-specific QoL measuring tools are listed in *Table 5,* although some of these are not QoL surveys specifically but rather symptom severity scales.

AF can affect QoL in several ways including anxiety and depression and there is some evidence linking AF to cognitive decline (Alonso & Arenas de Larriva, 2016; McCabe, 2009). AF can also affect energy levels and can make daily activities more difficult due to physical symptoms, such as breathlessness, palpitations, fatigue, dizziness, and chest discomfort. Physical difficulties can impact on emotional wellbeing, which can lead to an accumulation of ongoing effects that may be detrimental to QoL. QoL research in and around AF management has focused primarily on optimising heart rate or rhythm control and where AF causes physical symptoms (Aliot et al, 2014; Carlsson et al, 2003; Duff et al, 2003). Research has examined QoL in patients who have shown intolerance to or are refractory to rhythm stabilising treatments (Berry, Stewart, Payne, McArthur & McMurray, 2001; Bubien, Knotts-Dolson, Plumb & Kay, 1996; Son, Baek, Lee & Seo, 2019; Thrall, Lane, Carroll & Lip, 2006). Additionally, QoL

has been assessed in patients who have undergone cardioversion, ablation therapy, pacemaker insertion, advanced cardiac device implantation or surgical intervention (Jessurun et al, 2000; Kay et al, 1998; Newman et al, 2003; Tse et al, 2004).

It is, however, worth noting that outcomes from QoL studies from interventional clinical trials, may be biased towards the symptomatic group of people with AF, with less generalisability to the general population with AF, many of whom exhibit no symptoms. Similarly, subgroups of participants from clinical trials have been targeted and the often open-label design of catheter ablation studies for example, can impose bias towards the intervention group (Aliot et al, 2014; Carlsson et al, 2003; Duff et al, 2003). The QoL research (*Study 2, Chapter 5*) seeks to explore how AF affects individuals with or without diabetes, away from a clinical trial or treatment intervention. AF can impact physically, psychologically, and socially and understanding this influence in the general population is important when contemplating the optimal management and treatment paths.

Patients with AF often take anticoagulation to reduce their stroke risk and research has explored the impact anticoagulation has on QoL. Treatment with oral anticoagulation may affect QoL due to the changes this might impose on lifestyle and the increased risk of bleeding (Ng et al, 2019). Treatment satisfaction with anticoagulation is associated with better treatment adherence and therefore, subsequent improvements in QoL (Keita et al, 2017). QoL depending on the type of anticoagulant taken has also been considered with one study demonstrating comparable QoL if warfarin or DOACs are used (Ng et al, 2019). Another study using the SF36 showed that the physical-emotional aspect was the most compromised and drug interactions with medicines that impacted on anticoagulant effects influenced a more negative perception of the QoL (Almeida, Noblat, Passos & do Nascimento, 2011). Health related QoL in patients with controlled anticoagulant status treated with DOACs or warfarin was better than in patients with uncontrolled anticoagulation (Almeida et al, 2011).

Table 5. AF-specific QoL measuring tools.

QoL instrument	QoL domains	Scoring
AF Effect on QoL survey [AFEQT] (Spertus et al, 2011).	42-item questionnaire explores impact of AF and treatments. 6 domains relating to symptoms, social, emotional, and physical functioning, daily activities, treatment satisfaction and concerns. Refined and renamed into 2 domains – 7-items exploring psychological domain and 11-items exploring physical activity.	7-point Likert responses ranging from the most severe limitation/symptoms to no limitation/symptoms. Higher scores indicate better health status.
AF-QoL (Arribas et al, 2010).	18-item questionnaire with three domains, psychological, physical, and sexual activity. Psychological domain includes seven items, the physical domain includes eight items, and the sexual activity domain includes three items. Patients rate this according to the previous months symptoms.	5-point Likert scale, 'totally agree', 'sufficiently agree', 'neither agree nor disagree', 'sufficiently disagree', and 'totally disagree'. Scoring between 0 (worst QoL) and 100 (best QoL).
AF QoL Questionnaire [AFQLQ] (Yamashita et al, 2005).	Variety and frequency of symptoms and symptom severity. Limitations of daily and special activities including anxiety.	Scales for each domain, then transformed to create Physical and Mental Component Summary

		scores. Higher scores indicate well health status.
QoL in AF [QLAF] (Braganca et al, 2010)	Based on clinical manifestations and usual treatments including palpitations, breathlessness, chest pain, dizziness, medications, intervention (including cardioversion, ablation). Less time to administer when compared to QLAF and SF-36 with good internal consistency.	Sequential scores, some yes / no questions are not scored. Higher numbers indicate worse QoL.
Arrhythmia Symptom Checklist, Frequency and Severity (Bubien et al, 1996)	16-items, developed to measure patients' perception of the frequency and severity of arrhythmia-related symptoms. To discern sequential changes in patients' symptoms with AF who are undergoing ablation, pacemakers. Validated for use in patients with permanent or paroxysmal AF.	Lower scores represent less symptomatic impact, with scores ranging from 0 to 64 for symptom frequency and from 0 to 48 for symptom severity.
University of Toronto AF Severity Scale [AFSS] (Dorian, 2001).	9-items. AF burden, duration and AF severity, well-being, AF symptoms and healthcare utilisation and demographic data and current AF status.	5-point Likert scale Individual symptoms attributable to AF are scored then totalled and the higher score, denotes indicating increased AFSS.

European Heart Rhythm Association [EHRA]-AF symptom scale (Hindricks et al, 2021).	Symptoms attributable to AF that reserve or reduce on restoration of normal rhythm or with adequate rate control.	I, None, IIa, Mild (normal daily activity not affected), IIb, Moderate (normal daily activity not affected but troubled by symptoms), III, Severe (normal daily activity affected) and IV, Disabling (normal daily activity discontinued).
Canadian Cardiovascular Society Severity in AF Scale [CCS-SAF] (Dorian et al, 2006).	AF related symptoms and determination of symptom-rhythm correlation on daily function and QoL. Determined by (S), symptoms attributable to AF; (A), association between symptoms (palpitations, dyspnoea, dizziness/syncope, chest pain, weakness/fatigue) and documentation of AF or treatments for AF and (F), functional consequences of these symptoms on daily function and QoL.	4-point severity scale from no effect on functional QoL to severe effect.

QoL in people with diabetes has also been assessed using generic and disease specific tools. As with AF related research, the SF-36, SF-12 and EuroQol have been used commonly in diabetes-based research (Abedini, Bijari, Miri, Shakhs & Abbasi, 2020; Al-Abadla, Elgzyri & Moussa, 2022; Al-Shehri, Taha, Bahnassy & Salah, 2008; Engström et al, 2019; Jankowska & Golicki, 2022; Huang et al, 2008; Long et al, 2021; Mehović, Janković & Tafi, 2021; Mulhern & Meadows, 2014; Wukich, Sambenedetto, Mota, Suder & Rosario, 2016). Diabetes-specific tools are detailed in *Table 6* and include the Audit of Diabetes-Dependent Quality of Life [ADDQoL] (Bradley et al, 1999), Diabetes Quality of Life [DQoL] (The DCCT Research Group, 1988), the Diabetes-Specific Quality of Life Scale [DSQOLS] (Bott, Mühlhauser, Overmann & Berger, 1998), the Appraisal of Diabetes Scale [ADS] (Carey et al, 1991), and Diabetes Health Profile instruments [DHP-1] (Meadows et al, 1996; Mulhern & Meadows, 2007). These measure domains of health, assessment of social and psychological wellbeing and role activities but differ slightly in how they assess personal constraints and physical functioning. Just the DQoL asks about treatment satisfaction. A review of these disease specific tools highlighted the ADDQoL and the DQoL to be the more widely used when assessing QoL in people with diabetes, also demonstrating better validity (construct validity was assessed specifically) and reliability than the ADS but less feasible to use in daily practice (Nair & Kachan, 2017). The ADDQoL is a well validated measure and utilised across different countries with translations available in more than eighty languages (Bradley et al, 1999; Ostini, Dower & Donald, 2012; Papazafiropoulou et al, 2015). The tool has demonstrated feasibility, internal consistency, and convergent validity, with good psychometric properties (Bak et al, 2018; Levterova et al, 2018; Ostini et al, 2012). The ADS is suggested as an optimal choice however, owing to the short duration of time taken to complete along with evidenced validity (Nair & Kachan, 2017). Subsequent appraisal has demonstrated internal consistency in studies relating to adaption to a diagnosis of diabetes and when used alongside other QoL measures (Patil, Patil & Patil, 2021; Satish, 2021; Trief et al, 1998).

***Table 6. Diabetes-specific QoL measuring tools*.**

QoL instrument	QoL domains	Scoring
The Diabetes Quality of Life Measure [DQOL] (The DCCT Research Group, 1988).	Four dimensions (46 items) of diabetes impact assessed: Satisfaction, treatment impact, anxiety for complications and social issues. Lower scores in this scale are associated with diabetic complications and glycaemic control. Completion time of approximately ten minutes. Originally oriented for type 1 diabetes, now used in both type 1 and type 2.	5-point Likert scale. Individual domain and total scores 0 (lowest possible QoL) to 100 (highest possible QoL).
The Diabetes-Specific Quality of Life Scale [DSQOLS] (Bott et al, 1999).	Six dimensions, 64 questions: Social relations, leisure time restrictions and flexibility, physical complaints, worries about the future, diet restriction, and daily hassles. Used with people who have type 1 diabetes to assess treatment goals, treatment satisfaction and diabetes related distress. Completion approximately 15-30 minutes.	6-point Likert scale, 'point of view', 'treatment satisfaction' and 'personal importance of treatment goals'.
The Diabetes Quality of Life Clinical Trial	Eight domains, 57 questions measuring physical function, energy, health distress, mental health, satisfaction, treatment satisfaction, treatment flexibility, and frequency of symptoms.	Total scores converted to 100-point scale, 0 (poor QoL) and 100 (highest QoL).

Questionnaire-Revised [DQLCTQ] (Shen et al, 1999).		
The Appraisal of Diabetes Scale [ADS] (Carey et al, 1991).	7-item self-reporting scale, focusing on patients with diabetes' feelings and attitudes and the psychological effect of diabetes.	5-point scale. Lower scores are superior.
The Diabetes Integration Scale-39 [ATT39] Scale and the revised Diabetes Integration Scale-19 [ATT19] (Dunn, Smartt, Beeney & Turtle, 1986).	The ATT19 is a short version of the ATT39, measuring psychological adjustment and attitudes toward diabetes using a 19-item self-report questionnaire, rather than the original 39-items. Includes assessment of perceived levels of stress, adaptation, guilt, alienation, illness conviction, and tolerance for ambiguity.	5-point Likert-scale, from 1 (completely disagree) to 5 (completely agree), 16 items reverse scored (high score reflects a positive attitude towards having diabetes and better adjustment).
The Questionnaire on Stress in Patients with Diabetes [QSD]and the	45-items and 8 dimensions that could be sources of stress for people with diabetes: Leisure and work time, relationship with partner, with doctor,	5-point Likert scale ranging from 'slight problem for me' to 'a very big problem for me'.

revised version [QSD-R] (Herschbach et al, 1997).	hypoglycaemia, therapy, physical symptoms, and anxiety about diabetic complications.	
The Type 2 Diabetes Symptom Checklist [DSC] (Grootenhuis et al, 1994).	Scale comprising 34-items, assessing symptoms including hypoglycaemic, cardiac, neuropathic, psychological, and vision-related. The Diabetes Symptom Checklist-Revised (DSC-R) explores cognitive distress, fatigue, hyper and hypo-glycaemia across 8 domains in type 1 and 2 diabetes.	6-point Likert type, responses ranging between "0 -not at all" and "5 -extremely troublesome".
The Problem Areas in Diabetes Scale [PAID-1] and the revised PAID-2 and PAID-5 (Polonsky et al, 1995).	Four dimensions and twenty items, focusing on overall emotional, interpersonal, treatment-related, and physician-related distress. Available in languages other than English.	6-point Likert scale, the degree to which the item is problematic. Total score reflects the level of emotional distress. A score of 40 signifies high levels of diabetes-distress; 0-16 low diabetes distress, 17-39 moderate distress.
The Audit of Diabetes-Dependent Quality of Life [ADDQoL] (Bradley et al, 1999).	Two overview items, one measures generic overall QoL, and 19 items focus on the impact of diabetes on specific aspects of life. Domains include leisure activities, working life, journeys time, holidays, physical health, family life, friendships and social life, close personal relationships, sex life, physical	Scales range from -3 to +1 for 19 life domains (impact rating) and 0 to +3 in attributed importance (importance rating). Ratings

	appearance, self-confidence, motivation, people's reactions, feelings about the future, financial situation, living conditions, dependence on others, dietary and drinking behaviours. Respondents asked to evaluate how life would compare without diabetes.	multiplied for a weighted rating (ranging from −9 to +3). Lower scores reflect poorer QoL.
Diabetes Health Profile instrument [DHP-1] (Meadows et al, 1996; Mulhearn & Meadows, 2007).	The DHP-1 (32 questions) is used with people with type I diabetes and measures psychological distress, barriers to activity and disinhibited eating. The DHP-18 (18 questions) measures the same three constructs but can be used in type I or type II diabetes. The DHP-1 was devised following interviews with people with diabetes requiring insulin, a literature review and professional.	4-point Likert scale ranging from 0-3. Domain scores transformed to a common score range of 0-100, with 0 representing no dysfunction.

The Diabetes Quality of Life [DQOL] measure was introduced in the Diabetes Control and Complications Trial, a randomised controlled trial comparing the efficacy of two treatment regimens on the development of complications from type I diabetes (Jacobson, de Groot & Samson, 1994). Validity, test-retest reliability, and internal consistency has been demonstrated in people with type 1 diabetes (DCCT Research Group, 1988) and when translated into other languages (DCCT Research Group, 1988). A trend was observed toward increasing scores with more complications, suggesting divergent validity (Cheng, Tsui, Hanley & Zinman, 1999). The Diabetes-Specific Quality of Life Scale [DSQOLS] was orientated around treatment assessment, and factor analysis showed this to be a reliable and valid measure, helping to distinguish between treatment and diet regimens, social inequalities, assessment of individual goals, identifying motivational deficits and tailoring of individual treatments (Bott et al, 1999).

The Diabetes Quality of Life Clinical Trial Questionnaire-Revised [DQLCTQ] was designed for use in multinational clinical trials and domains included items drawn from the Medical Outcomes Study [MOS] (Tarlov et al, 1989) and DQOL measures (Jacobson et al, 1994), along with newly constructed domains developed from patient focus groups and expert clinician panels (Shen et al, 1999). Validation and revisions to the DQLCTQ were made following data collection from two multinational clinical trials of patients with type I and type II diabetes from four countries with all domains able to discriminate between diabetes type, metabolic control, sex, and self-perceived diabetes control (Kotsanos et al, 1997). Also developed for use in clinical trials, along with epidemiological research, was the Type 2 Diabetes Symptom Checklist [DSC], designed to measure differences in symptoms and symptom severity that may or may not be diabetes related, whilst also detecting changes over time (Grootenhuis et al, 1994). The psychometric properties present this as a valid and reliable tool for utilisation in clinical trials but with less use in clinical practice (Naegeli, Stump & Hayes, 2010).

Psychosocial factors and their impact on diabetes control and treatment satisfaction and compliance is a focus in many of the diabetes QoL measures, including the Questionnaire on Stress in Diabetic Patients [QSD] (Duran, Herschbach, Waadt, Zettler & Strian, 1995), the Problem Areas in Diabetes Survey [PAID] and Diabetes Integration Scale-39 [ATT39] Scale (Dunn et al, 1986). The reliability, construct validity, and discriminant validity were proven when assessed in people with type I and type II diabetes in the QSD and replicated in the revised version [QSD-R] (Duran et al, 1995; Herschbach et al, 1997). The psychosocial adjustment is the focus of PAID survey, and one study using this measure found the level of emotional distress to be a contributor to adherence of self-care behaviours (Welch, Jacobson & Polonsky, 1997). The PAID survey has demonstrated favourable construct validity with evidence of discriminant validity from its ability to detect differences between diabetes type (Welch et al, 1997). Time for completion can impact on choice of QoL instrument and a five-item short form of the PAID survey along with a single-item measure for rapid screening of diabetes-related emotional distress was developed after identifying the strongest psychometric properties (McGuire et al, 2010). The PAID-5 has satisfactory sensitivity (94%) and specificity (89%) for recognition of diabetes-related emotional distress with the one-item screening question selected as 'worrying about the future and the possibility of serious complications', which has concurrent sensitivity and specificity of about 80% for the recognition of diabetes-related emotional distress (McGuire et al, 2010).

1.1.7 Qualitative research around AF and diabetes.

There exists an abundance of literature focusing on qualitative research around AF with a varied focus. This includes patient experiences of having the arrhythmia in the differing ways it may exist e.g., paroxysmal, persistent, or permanent, views on how patients learn of their diagnosis, the impact AF and treatments can have on QoL and patients understanding of the arrhythmia (McCabe, Schumacher & Barnsason, 2011; Son et al, 2019; Wang et al, 2022). Living with recurrent symptomatic AF was explored with patients via open-ended interviews and themes included feeling uninformed,

how to be clear of AF, managing unpredictable symptoms, the emotional distress, hope for a cure and effects on QoL (McCabe et al, 2011). The need for accurate information along with support and counselling was summarised, as was the need for advice over how to manage AF and its symptoms and the necessity of psychoeducational programs to educate patients and their families about AF self-management (McCabe et al, 2011).

A systematic review explored patient experiences across the trajectory of AF and their synthesis revealed negative experiences around delays to diagnosis, available support, disappointments around treatment failure and concerns regarding the unpredictability of symptoms (Wang et al, 2022). How family members experience and cope with a close relative having AF has also been researched along with ways to support both patients and their carers (Rosenström, Risom, Ejlertsen, Hove & Brødsgaard, 2021). A phenomenological interview study with family of patients with AF found that the essence of the phenomenon was experiencing less panic and finding peace, which emerged from four patterns including post-AF experience, enhanced understanding of AF, interaction with a nurse specialist and aspects around AF becoming manageable (Rosenström et al, 2021). When a family-focused nursing intervention facilitated by specialist nurses was introduced, these aspects were addressed, resulting in reduced worry and greater support from family and carers (Rosenström et al, 2021).

AF screening from a stakeholders and health professionals' perspective has been explored, including how, when and where this should be undertaken, with less focus on patient views, hence the interview-based study within his work (Engler et al, 2022, Utterbogaart et al, 2021) (*Study 4, Chapter 6*). Thematic analysis of semi-structured interviews with healthcare professionals and regulators identified themes around screening for AF, the lack of national screening programmes, patient-led screening initiated through personal devices, screening inequality and use of single-lead devices in primary care as a feasible way to implement screening (Engler et al, 2022). Knowledge required from patients regarding their AF has been a focus within qualitative research, including ways key messages are communicated. Research relating to educational needs of patients with AF and self-management revealed the

importance of individualised, modernised, and integrated care, with a multimodal approach (Ferguson et al, 2022). Appropriate education around AF along with medication management has been shown to optimise patient engagement and concordance with treatments (Haridas & Bhat, 2018). Having relevant knowledge and counselling around AF has also been shown to improve QoL (Altiok, Yilmaz & Rencüsoğullari, 2015). Their research focused on determining patient perceptions of AF, their wishes and coping behaviours and as a result of the content analysis, emerging themes focused around their physical, mental, emotional and societal status regarding AF and major limitations resulted from warfarin use and disease symptoms (Altiok et al, 2015). Appropriate follow and ongoing monitoring were also felt to be very important to patients ongoing management.

From a diabetes perspective, qualitative research has adopted a similar focus, with research exploring challenges faced by people with diabetes, patient perspectives regarding their care, psychosocial behaviours, and the impact on QoL (Bukhsh et al, 2020; Engström, Leksell, Johansson & Gudbjörnsdottir, 2015; Fink, Fach & Schröder, 2019; Gillani, Sulaiman, Abdul & Saad, 2017; Ndjaboue et al, 2020; Peng et al, 2022). Interviews and focus groups have been the methods predominantly used to ascertain patients' experiences whilst facilitating feedback from patients, carers, and health professionals. Attitudes and behavioural control over a diagnosis of diabetes and challenges experienced by patients living with the condition features often, particularly around medication adherence (Bukhsh et al, 2020; Fink et al, 2019; Gillani et al, 2017; Peng et al, 2022). Self-care barriers and aspects that help facilitate positive behaviours has also been considered in the research, with type 1 and type 2 diabetes, revealing the influence family and peers can have, in the context of parenthood and the positive and negative impact from role models (Gopalan et al, 2022). Patient reported outcomes measures and what was felt important to patients in terms of capturing the appropriate outcomes was sought through semi-structured interviews with content analysis (Engström et al, 2016). Two important aspects were identified including how the patient feels inn general and with regards to their diabetes management and support regarding their care (Engström et al, 2016).

Similar themes are therefore evident from the literature around AF and diabetes adopting a qualitative approach. The psychosocial and physical elements around chronic disease are a common focus along with perspectives around disease management, medication concordance and behavioural aspects of adjusting to and controlling the disease. The impact on QoL and barriers imposed around daily life reveal both conditions to negatively impact on QoL in the presence of AF and diabetes, but enquiry around their combined impact is less explored.

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This thesis provides coverage of a systematic review and three research studies. The aim of this programme of research is to develop a comprehensive understanding around screening for AF in people with diabetes with the over-arching title being 'Should we be screening people with diabetes, for atrial fibrillation?' *Study* 1 focuses on the screening of patients with diabetes for AF (*Chapter 4*). *Study 2* provides insight into the effects AF and then AF and diabetes as a combined diagnosis, has on QoL (*Chapter 5)*. *Study 3* offers an exploration of patients' understanding, views and experiences of AF and AF screening through interviews with patients who have an existing diagnosis of AF and diabetes (*Chapter 6*). Further discussion then centres around the implications of AF screening and whether people with diabetes should be targeted as a high-risk group.

A summary of each of the research studies in this thesis is provided next. This is followed by a section relating AF to the recent pandemic and links to cardiovascular disease. The chapter is then concluded with a description of how this thesis is presented and justification for adopting the Alternative Format.

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1.2 Summary of research studies.

Systematic Review: Effectiveness of the AliveCor® device *(Chapter 2, Paper 1).*

Effectiveness of a single lead AliveCor® electrocardiogram application for the screening of atrial fibrillation: a systematic review.

The systematic review explores the effectiveness of the AliveCor® device in clinical practice and screening related research. There are several ECG monitoring devices now available, and therefore, it is important to examine the utility and effectiveness to ensure they are appropriate for the designated purpose. The AliveCor® ECG device is a commonly used tool for single-lead ECG monitoring and uses a single lead, normally analogous to lead I, displaying a real-time ECG on a smartphone or tablet device.

The feasibility, validity, and utility of the AliveCor® device are critiqued from eligible research, following a comprehensive and systematic search of published and grey literature, whilst applying key terms (see *Appendix 1* for the search history). Feasibility metrics include process (recruitment, retainment, response, participant willingness), resources (staff, training needs, equipment, space, costs), management (research capacity, information technology, databases, software, staffing impact) and scientific outcomes (data collection materials, extraneous variables, treatment effects, statistics, outcomes measures). This information is extrapolated from the applied papers. These metrics were originally described in relation to pilot and feasibility studies, with subsequent application to research relating to feasibility of interventions such as planning around a randomised controlled trial or the validity of an intervention (Lermouth & Motl, 2018; Thabane et al, 2010; Tickle-Degnen, 2013). These metrics were therefore employed due to their relevance within this research, where screening for AF (the intervention) in various populations and across diverse study designs were included. A feasibility critique has not been undertaken by applying these metrics to ECG monitoring devices to the author's knowledge. Effectiveness of ECG monitoring devices explored via validity studies has more commonly been researched. This paper therefore provides a thorough exploration of the wider aspects encompassing the AliveCor® device that are arguably fundamental

when considering the utility, consumer acceptance and effectiveness of these devices. Validity is explored by extracting sensitivity and specificity data from the critiqued studies and this provides evidence relating to the accuracy and ability to diagnose AF or exclude according to the inbuilt algorithms or manual interpretation. Overall effectiveness is considered by incorporating the aforementioned data along with wider issues surrounding screening approaches, costs, and appropriateness of this as an ECG recording device.

Whilst there are research papers emerging, particularly in relation to comparison of ECG monitoring devices, this is the only systematic review whereby the AliveCor® device is the focus. This therefore provides a thorough analysis of this tool, which is of relevance to health professionals when contemplating ECG monitoring devices for their own use, or more widely for departments or organisation.

The systematic review includes research up until 2018, and therefore an up-to-date search was undertaken from this time, until the time of writing (February 2023). Community based screening for AF using the AliveCor® device was undertaken in a Korean elderly population demonstrating AF prevalence of 3% (95% CI 2.4–3.8) and a PPV of 58.9% (95% CI 50.1 – 67.1) (Kim et al, 2020). When the study was expanded to include participants from senior welfare centres, AF prevalence was 2.6% (95% CI 2.2 – 3.1) and the positive predicted value [PPV] 48.8% (95% CI 43.1 – 54.5) (Kim et al, 2020). Participants with diabetes accounted for 24.2% of the study population and AF co-existed with diabetes in nineteen out of seventy-three patients (26%, p=0.679) (Kim et al, 2020). Screening frequency was explored in a study based in China and participants were randomised between quarterly and annual ECG screening programmes, using the AliveCor® device (Zhang et al, 2021). No significant interaction was observed for AF detection between screening groups and the predefined subgroups, defined according to age, sex, BMI, having hypertension or diabetes (Zhang et al, 2021). A study whereby participants were recruited from diabetes and vascular outpatient clinics included 2422 participants and of the seventy-three with diagnosed AF, nineteen had diabetes (26%, p=0.679) (Kalia et al, 2020). Primary care clinics was the site of recruitment in a Canadian screening study (Godin et al, 2019).

An opportunistic screening approach was taken, and diabetes was a trigger to screen patients in 8% of the cohort, deemed a high-risk group by physicians undertaking the screening (Godin et al, 2019). No further detail is however given on how many people with diabetes, had AF from the screening episode.

(Please note, the ECG device is referred to predominantly in this thesis, as the AliveCor® device. During the research process, the device was rebranded as Kardia®, also known as KardiaMobile® so to ensure the published papers are contemporary, Kardia® is used herein. In the remaining chapters, the AliveCor® device is the reference).

Study 1: AF screening study (*Chapter 4, Paper 2*).

A cross sectional study evaluating atrial fibrillation prevalence in patients with diabetes using the AliveCor® application for screening.

This research aims to determine whether people with diabetes have a higher prevalence of AF than the general population and whether screening is beneficial for this sub-population. This study also aims to evaluate the effectiveness of AF screening in this targeted population by determination of associated demographics and risk factors.

Previous screening research has included mixed high-risk groups, often including people with diabetes, but not with diabetes as the lone, target group. Evidence relating to increased AF risk in people with diabetes is based on previous screening research which has considered diabetes within analysis. This is important to understand, as then people with diabetes (or other conditions considered high-risk) can be targeted in screening programmes where resource can be directed more appropriately and where prevalence is higher. The health of these patients can then be optimised in terms of onward cardiovascular and arrhythmia risk reduction through treatments and lifestyle advice. Detection of AF is important as stroke risk can be

stratified and then patients offered appropriate management to reduce stroke risk. Prevalence studies have already described an association between these two chronic conditions, and therefore, exploring this in more detail but with one disease group as the specifically targeted group in *Study 1*, aims to add important information within this area of enquiry.

This study involves detecting the heart rate and rhythm of the participant, obtained through pulse palpation along with utilisation of a single lead ECG heart monitor, transmitted using an application (the AliveCor® device) with a mobile phone. Whilst the AliveCor® device has been used in AF screening research, this has not been done in patients with diabetes specifically. The study location is Jersey, Channel Islands, and is the only study of its kind, where this island sub-population is recruited. Patients' heart rate and rhythm are documented along with demographics and risk factors. Within this study, data collection is undertaken with participants who have diabetes, from two localities (GP practices and the hospital outpatient diabetes centre). Comparing detection rates between the two independent locations is of interest when analysing results, as patients with diabetes and AF are commonly managed in different settings, with varying presentations.

Study 2: Quality of Life Study (*Chapter 5, Paper 3*).

A comparison study of quality of life among people with AF and people with AF and diabetes as a combined diagnosis.

Quality of Life is an essential consideration when managing the health and wellbeing of patients and assists in interpretation of symptoms, functional status, perceptions, experiences, and expectations (Aliot et al, 2014). Comprehension of QoL is important as this knowledge can influence further recommendations relating to AF, earlier intervention and selecting the most appropriate management for patients in these disease groups. It has previously been shown that AF and diabetes can both negatively impact QoL but with less insight into how diabetes can further worsen QoL in AF when present as a dual diagnosis.

QoL data are obtained through utilisation of the 36-Item Short Form Health Survey [SF-36] instrument, a validated survey used extensively in health-related QoL assessment (Ware & Sherbourne, 1992). This prospective, observational study is carried out via the use of a popular arrhythmia website. The survey is offered for completion by volunteers affected by a) AF alone and b) people who have AF and diabetes. The website has a wide user profile and regularly offers surveys for completion. The SF-36 has been utilised with both the AF and diabetic population but not specifically with these groups together. Neither has this been compared to another single-disease patient group. This data therefore provides findings that are relevant when exploring the impact of AF on QoL and when disease exists beyond AF alone. The lack of data regarding QoL in people with AF and diabetes together, is therefore addressed here, with the knowledge that this feedback could help direct lifestyle adjustments and treatments in accordance with the domains of QoL compromise.

Study 3. Qualitative interviews (*Chapter 6, Paper 4*).

Should we be screening people with diabetes for atrial fibrillation? Exploring patients' views.

This qualitative study explores patients' understanding of AF and their views on health screening. Participants were eligible if they had taken part in *Study 1* (*Chapter 6*) and received a diagnosis of AF during their screening episode. Their experiences of AF screening, along with feedback around the screening tool used, is explored. Patients' views on how we can incorporate screening into routine care is also sought in this study.

This study employed one-to-one in-depth semi-structured interviews with patients who had diabetes and were given the diagnosis of AF. The research questions for this study centre around patients' understanding of AF, their views on screening for AF when diabetes exists and views on the screening tool used.

This, therefore, provides novel feedback in this context, whereby patients are central to the data obtained. Patients are voluntarily attending screening invitations, so doing this in such a way that is agreeable to the patient, will hopefully encourage screening uptake. Employing an acceptable screening method should contribute to patients' comfort and willingness to participate.

In this research, people were interviewed who received an AF diagnosis and this addresses a gap in the evidence which does not appear to have been focused on specifically, before. Neither has this been explored with patients in a specific disease group, in this instance, having diabetes. This, therefore, offers a new perspective on patient feedback about AF screening overall, the AliveCor® device in this context and patients' understanding of AF.

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Throughout the research and as these studies evolved, adjustments altered the original research proposal. Recruitment was widened to include more GP surgeries (from one to three) for the AF screening study due to suboptimal numbers from one GP surgery alone and additional help was sought from a colleague based at the diabetes centre who assisted with data collection. An additional study was later designed, to gain the perspective from patients with regards to AF screening. This is an area much less explored and rather predominated by views of health professionals and general screening debate. This enabled the application of an alternative methodology, using semi-structured interviews, therefore adding an important element in addressing the overarching research focus.

The four research papers cover different aspects around AF, diabetes, health screening, screening tools, patient interpretation and QoL. These multi-faceted concepts are however, interlinked by a common theme, that being AF. AF management is complex, but the overall approach should be one that focuses on the patient in a way that optimises health and reduces associated negative consequence. AF and diabetes both present as a significant public health concern.

This public health burden, experienced through increasing prevalence in chronic disease, has contributed to an intensifying search for undiagnosed AF and the importance of AF screening is recognised by cardiovascular societies including the European Society of Cardiology [ESC], the National Institute for Health and Care Excellence [NICE] and the National Heart Foundation of Australia and New Zealand (Brieger et al, 2018; Hindricks et al 2021; NICE, 2021). In the rapidly expanding digital technology era, digital applications to assist in healthcare screening are developing in a way in which these can be invaluable for modern healthcare and AF management, where prevalence continues to increase.

1.3 Structure of the thesis.

This thesis is set out in accordance with the Lancaster University guidance on presentation of a thesis in Alternative Format. Following the introduction, *Chapter 2* presents the systematic review as the first paper. This provides a review of a commonly used ECG recording device and one that is used in *Study 1* (*Chapter 2*, *Paper 1*). The decision to write this review around this tool, was considered along with supervisory support, to avoid duplication of work undertaken for a Masters dissertation, in which a systematic review was written directly relating to screening for AF in people with diabetes.

The methodology chapter (*Chapter 3*) follows, detailing theoretical and philosophical principles in relation to the three research studies. Methods used along with the research design are justified for each study. Ethical implications are discussed, and this chapter concludes with theoretical and conceptual considerations around health screening.

The chapters that follow, introduce each research study with papers in their published format. A cover page between papers, detailing the paper title and page numbers is included as a requirement within the Alternative Format guidance. This is explained as necessary to ensure pagination is followed sequentially and not confused by standalone page numbers assigned to the journal published papers.

The discussion chapter, *Chapter 7* of the thesis, explores the contribution and originality of this research, then each of the four papers in turn. This is followed by a collaborative and integrated discussion around AF screening – 'to screen or not to screen' - which aims to bring together all encompassing aspects around AF screening based on findings from this research and the wider evidence base. The limitations, implications, and recommendations, linking back to the theory, conclude this chapter.

Finally, the thesis conclusion considers the overarching research question set out at the start of the thesis by summarising and reflecting on the research undertaken. Recommendations for future work is presented, along with demonstration of new knowledge that this research contributes. Reference list formats differ slightly between journal papers and the APA reference style adopted throughout the remaining thesis chapters.

1.4 Justification for submission in Alternative Format.

Alternative Format was chosen as an attractive option for producing publishable papers in a field of great interest. Building on publications already produced, but now within primary research, was of interest, and offered an opportunity to do so with guidance. Dissemination of research is important and whilst the inherent merits of the traditional thesis were considered, the ability to publish and share the work offered additional reward.

The level of contribution by the lead researcher and author of this thesis was high, with the majority of the work completed independently. Establishing research aims and objectives, hypotheses and research design were supported through supervision. Data collection, analysis and writing was completed by the lead researcher. Academic supervisors provided oversight and guidance for various aspects relating to the research studies, including research proposals, ethical committee submissions, discussions around research design, statistical analyses, and review of the papers. The clinical supervisor assisted with initial guidance over the primary research focus and contributed by reviewing papers prior to publication. The clinical supervisor also

provided clarification over areas relating to clinical aspects of the research, including advice relating specifically to the AF screening study and protocol.

Chapter 2.

2.1 Effectiveness of a single lead AliveCor® electrocardiogram for the screening of atrial fibrillation: a systematic review.

This paper presents a systematic review of the single-lead AliveCor® ECG monitoring device. This is a commonly used tool by health professionals and patients and offers an alternative to the traditional Holter style ECG monitors. The AliveCor® device is one of several digital and remote ECG monitoring options now available. The AliveCor® device connects with a smartphone or tablet device and produces a real-time ECG.

This review presents a detailed analysis of the feasibility, utility, and validity of the AliveCor® device through the critique of eligible AF screening studies that have employed this device in their research.

When considering approaches and methods for AF screening, it is important to contemplate the most appropriate tool for diagnosis and patient tolerability. The AliveCor® device offers a practical solution for ECG monitoring in the mobile health [mHealth] era, where advances in technology continue to evolve and modernise screening opportunities. The feasibility and validity of an ECG montoring device is important when considering the overall utility and effectiveness of mHealth applications.

The AliveCor® device is the ECG monitoring tool used in the AF screening study (*Study 1, Chapter 4, Paper 2*) and therefore, this paper introduces and explores the evidence around this validated ECG monitoring device.

2.2 Effectiveness of a single lead AliveCor® electrocardiogram application for the screening of atrial fibrillation.

Paper 1.

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Chapter 2.

Effectiveness of a single lead AliveCor® electrocardiogram application for the screening of atrial fibrillation: a systematic review.

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Chapter 2.

Abstract

Background: Increasing prevalence of atrial fibrillation has a significant impact on health, society, and healthcare resource utilisation, due to increased morbidity, mortality, risk of stroke and reduction in quality of life. Early diagnosis allows for treatment initiation, a reduction in complications and associated costs, and so innovation to improve screening and enable easy access are needed Developments in digital technology have significantly contributed to the availability of screening tools. The single-lead electrocardiogram AliveCor® (Mountainview, California, USA) device offers the opportunity to provide heart rhythm screening and has been used extensively in clinical practice and research studies.

Methods: This review investigates the feasibility, validity, and utility of the AliveCor® device as a tool for atrial fibrillation detection in clinical practice and in wider research. Databases searched included PUBMED, CINAHL, MEDLINE and World of Science, plus grey literature search. Search terms related to atrial fibrillation, screening and AliveCor® with adults >18 years. Feasibility metrics were applied including process, resource, management, and scientific outcomes. Studies not written in the English language were excluded. Validity of AliveCor® was explored by extracting sensitivity and specificity data from eligible studies and overall effectiveness analysed by incorporating the above, with wider issues surrounding screening approaches, cost effectiveness and appropriateness of AliveCor® as a screening tool.

Results: The AliveCor® device screening was reviewed in 11 studies matching inclusion criteria. Atrial fibrillation detection rates ranged from 0.8% to 36% and this largely correlated to the study population, where wider age inclusion and mass / population screening represented lower atrial fibrillation detection. Recruitment from higher-risk groups (older age, targeted localities, chronic disease) identified higher numbers with atrial fibrillation. Feasibility metrics demonstrated AliveCor® as an effective tool of choice in terms of process, resources, and management. Duration of screening time had an impact on rates of atrial fibrillation detection. There was however significant heterogeneity between studies reviewed.

Conclusion: The AliveCor® device offers a convenient, valid, and feasible means of monitoring for atrial fibrillation. Further analysis of electrocardiograms produced by AliveCor® may be necessary in some circumstances. The AliveCor® electrocardiogram device can be successfully implemented into both opportunistic and systematic screening strategies for atrial fibrillation.

Keywords:

atrial fibrillation, screening, arrhythmia, detection, AliveCor®, ECG

Conflicts of interest and sources of funding:

None declared.

Abbreviations:

AF	Atrial fibrillation
CHA_2DS_2-VASc	Congestive cardiac failure, Hypertension, Age, Diabetes, Stroke, Vascular disease, Age, Sex - stroke risk stratification scoring system (2 represents a score of 2 being assigned to the patients' risk for that category)
ECG	Electrocardiogram
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICER	Incremental cost effectiveness ration
MMAT	Mixed methods appraisal tool
NNS	Number needed to screen
QALY	Quality adjusted life year

1. Introduction.

1.1 Background.

Atrial fibrillation (AF) is increasing in prevalence with one in four people developing this common arrhythmia in later life (1). AF is a leading cause of stroke, with as many as 15-20% of strokes being related to the arrhythmia (2). In addition, AF can often be asymptomatic and therefore the diagnosis may not be detected prior to a debilitating stroke. However, AF can be detected through various screening tools and approaches and the development of digital health technologies to assist with AF screening has led to further advances in this area. Screening for AF has received significant focus with a dedicated international and multidisciplinary collaboration established in 2016 (AF-

Screen), whose aim it is to promote discussion and research about unknown or untreated AF, as a way to reduce stroke and death (3).

The AliveCor® (Mountainview, California, USA) heart monitor provides a portable ECG recorder and works with a compatible mobile device such as a smart phone. More recently, the device has been rebranded as Kardia® but for the purpose of this paper we will continue to use the term 'AliveCor® device', as the traditional name is what many recognise the device as. To use the device, two fingers are placed on each of the two electrodes on the pocket-sized metal pad and an instant ECG recording is displayed. The ECG reading is enabled by the wireless transmission to the AliveCor® app. and like other devices, uses a single ECG lead, normally analogous to lead I. The AliveCor® device is an event-type monitor recommended for use in England when episodes are more than 24 hours apart (4). It has been studied extensively and offers a convenient and practical approach to portable ECG event monitoring or screening. The AliveCor® device can be used as a single-point-in time screening tool, obtaining individual brief recordings, or used repeatedly for intermittent screening. (Throughout this review when ECG is mentioned, this will refer to the ECG reading from the AliveCor® device. Where this relates to a more traditional 12 lead ECG, this will be documented as 12 lead ECG).

1.2 Why is this review needed?

There is growing evidence relating to the use of digital apps and tools for the detection of AF and arrhythmias. The AliveCor® device has been used in clinical practice since 2011 and there is a plethora of research from across the world, where it has been the tool of choice. The device has demonstrated high sensitivity and specificity in screening studies (5,6). Targeted screening in chronic disease groups such as diabetes, has been suggested as an optimal approach, rather than mass screening of the population due to time and cost efficiency (7,8). Utilising an appropriate screening tool for the purpose is equally as important as the approach and this review,

therefore, seeks to explore and review evidence relating to the utilisation and effectiveness of the AliveCor® device in AF screening studies to date.

There has been one recent systematic review with meta-analysis on screening tools for AF detection, but this incorporated an array of handheld and Holter style ECG monitoring (9). The AliveCor® device did feature within this review, being the tool utilised in 5 of 54 eligible studies. This previous review concluded that portable ECG devices offer an efficient screening option for AF compared with 24-hour Holter monitoring.

2 Objectives.

2.1 Objectives.

The objective of this review is to explore and analyse the clinical effectiveness of the AliveCor® device in AF screening studies:

The utility of the device in the eligible studies is evaluated in terms of appropriateness and feasibility as a tool in practice.

The validity of the device as a screening tool in terms of sensitivity and specificity is also explored and where relevant, compared to the evidence of other screening tools used in the reviewed research.

Finally, the screening approach undertaken within the research is examined with regards to the strategy e.g. is it single-point-in-time, intermittent or continuous. This is considered in the discussion section of this review. The objectives of this review will be achieved by answering the following primary questions:

- How useful and beneficial (utility) is the AliveCor® device in AF screening studies and how can this be related to the wider clinical effectiveness through implementation?
- How easy and convenient is the tool to use and is it feasible to consider widespread application of the device as a tool of choice in further research

studies and clinical practice, also considering cost implications as a resource of choice?

- How valid is the device in the eligible studies and how does this compare to other methods of screening in comparison studies analysed in this review?

2.2 Inclusion and exclusion criteria.

Inclusion criteria are set out in *Table 1*. The AliveCor® device was only available for use from 2011, hence the reason for this date inclusion. An initial brief scoping review exercise identified a propensity towards observational studies and therefore it was important to include all methodologies and not just experimental designs. Furthermore, screening studies are often conducted within a cross-sectional design, and this was demonstrated in the located studies, hence an important consideration when designing eligibility criteria. Whilst AF is the arrhythmia of interest here, atrial flutter and atrial arrhythmia were included as this difference in arrhythmia is not always clearly defined in searches.

Table 1. Inclusion and exclusion criteria.

Inclusion	**Exclusion**
▪ Studies screening for AF / atrial flutter / atrial arrhythmia using the AliveCor® device / Kardia ▪ People aged 18 years and over ▪ Papers in the English language ▪ 2011 onwards (when AliveCor® device was founded) ▪ All methodologies	▪ Studies not screening for AF / atrial flutter / atrial arrhythmia ▪ Screening studies that did not use the AliveCor® device / Kardia ▪ People under 18 years of age ▪ Papers in alternative languages (not English)

Chapter 2.

3 Methods.

3.1 Search strategy

The search strategy aimed to find both published and unpublished studies. The search strategy was undertaken in three stages. Initially a search for published studies was undertaken using databases including MEDLINE, CINAHL, PUBMED, World of Science, Cochrane Library, Clinical Trials database, European Union Clinical Trials register, the National Institute for Health Research and Evidence Based Medicine. The exploratory stage of searching for relevant studies was facilitated through the use of key words, Boolean operators and associated Medical Subject Headings [MeSH] terms. Results were then screened as per eligibility criteria at title and abstract until a final selection was obtained for full text review. Then, the reference lists of the final full text studies were reviewed for eligibility. Only texts in the English language were included in the search process, and dates were set from January 1st 2011, to December 28th 2018.

Formalising the search question was aided by contextualising using the PICO framework, which offers the contextual components of population/problem, intervention, comparison/control, and outcome (10). The review question was combined using PICO headings. Keywords were entered into the search databases utilising Boolean operators. Results were further refined by including only human adults aged over 18 years. When entering search criteria, 'all adults 19+ years' was offered as the adult years option in the MEDLINE and PUBMED database and 'all adults' in CINAHL.

Unpublished studies were located by searching databases for grey literature including eThoS, ERIC, WorldCat, Google, Google Scholar and keyword internet searching. Grey literature is materials and research produced outside of normal commercial or academic publishing and can include academic papers, theses and dissertations, government reports, conference papers, and ongoing research (11). Grey literature may increase the comprehensiveness of systematic reviews' and provide a balanced picture of available evidence but can bring methodological challenges through the diverse formats in which the literature is available (11). All search strategies are detailed in full, in *Appendix 1A*.

3.2 Search results.

The PRISMA flow diagram offers diagrammatic representation of identification, screening, eligibility, and inclusion of studies for this review (*Figure 1*). Combined search results are demonstrated, totalling an initial 1120 studies. There were 811 studies remaining after removal of duplicates and this number was screened at title and abstract. The majority of search results was excluded at this stage as they failed to match even the primary study requirements e.g. not screening for AF (n=761 excluded). Where there was discrepancy or uncertainty over the applicability of located studies, the clinical supervisor for this research acted as the second reviewer, where he performed a blind review of the studies. Principally, some of the papers inaccurately represented inclusion criteria, instead incorporating an array of screening methods and other chronic disease. For example, screening for cancer arose as did methods of screening such as radiological imaging. Despite utilising the AND Boolean operator to combine searches, further studies of relevance which truly incorporated screening exclusively within this patient group (people with AF) were not located. The search was therefore widened (using the Boolean operator OR) to consider alternative terms for screening as per MeSH suggested terms. MeSH alternatives were not always applicable and alongside 'screening', produced irrelevant terms including 'cancer screening' and 'bowel screening'. This failed to expose supplementary papers despite adopting a comprehensive and methodical approach (*Supplementary Digital Content - Appendix 1A*).

Various results were returned via Google basic search, Google scholar, WorldCat, EThOS and ERIC. Of these results, none were relevant for full text inclusion. Additional databases searched included the Cochrane Library, Clinical Trials database, the European Union Clinical Trials Register, the Centre for Evidence Based Medicine, National Institute for Health Research and the AliveCor Clinical Research pages. Of these, six results reached the full text review.

3.3 Study selection.

Combined results, removal of duplicates and citation screening resulted in 50 full-text articles accessed and screened against selection criteria, independently by two

reviewers. Of these 50 full-text articles, 39 were excluded (*Figure 1*). Reasons for non-selection included research not using the relevant screening tool, results not incorporating the full research (e.g. conference paper or poster only and lack of response when authors were contacted for the research), trials not yet complete or published and research not looking for AF exclusively. One author of a protocol did respond to explain their full study would be published later in 2019. The authors of all excluded pilot studies were contacted without response. From the final 11 papers, reference lists were hand searched, identifying 20 further reports for consideration. Of these, 17 were excluded at abstract and the remaining three were accessed for full text review, with one being included in the final review. Therefore, a total of 11 research papers were eligible for inclusion into this review.

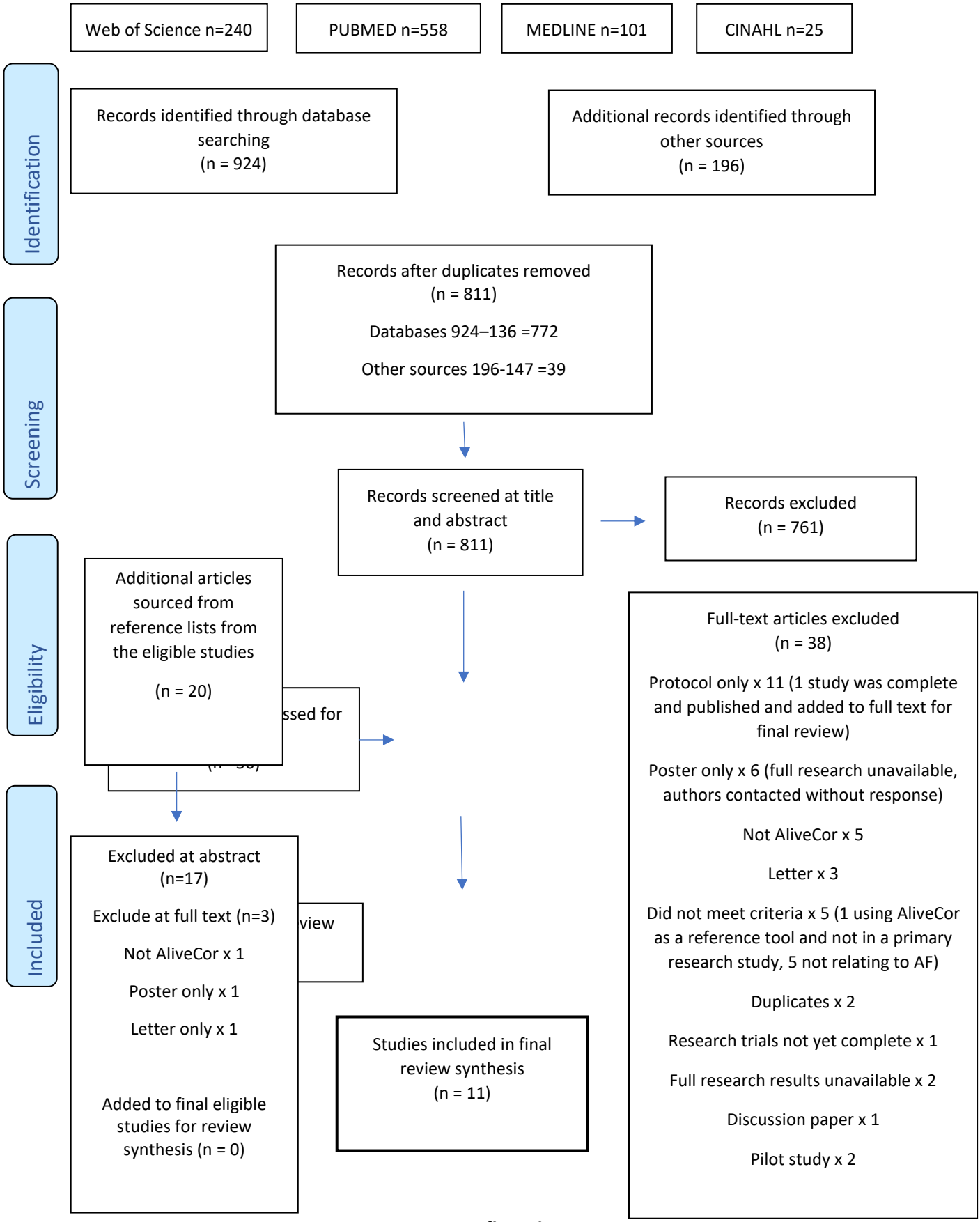


Figure 1. PRISMA flow diagram

Authors of the final 11 eligible studies were contacted by email for further information regarding similar ongoing or completed studies or unpublished literature. No replies were received and therefore no further studies were identified. Finally, local professionals in the fields of diabetology and cardiology were consulted to validate sources of enquiry. Feedback failed to suggest additional literature sources from the diabetes specialists, but three screening studies were suggested from cardiology with two being duplicates and one not meeting full criteria. Characteristics of the final included studies are presented in *Table 2*. It is worthy of mention that some of the eligible studies are from similar author groups e.g., Soni et al. wrote two of the papers and there are some similarities between their study designs (19,20). Lowres et al. also features as the lead author in two studies but there are more differences between their protocols (6,18). It is recognised that research conducted by the same research groups could impose bias to the studies included within this review.

Table 2. Characteristics of included studies.

Study	Design	Setting	Participants	Interventions	Outcomes	Inclusion criteria	Exclusion criteria
Chan & Choy. Screening for atrial fibrillation in 13,122 Hong Kong citizens with smartphone electrocardio-gram (12).	Feasibility screening study, observational cross-sectional design.	Territory-wide community-based, Hong Kong.	13,122 voluntarily participated.	Single lead AliveCor recordings along with interviews relating to AF symptoms and medical conditions. Anthropometric measurements taken.	101 of 13,122 had newly diagnosed AF (0.8%). Prevalence of AF detection was 1.8% and for AF detected or self-reported, was 8.5%. Independent predictors of AF were age, sex, height, weight, BMI, heart failure, valvular heart disease, stroke, coronary artery disease, hyperlipidaemia, and peripheral artery disease.	Age ≥18 years.	None reported.
Chan et al. Effectiveness of a non-governmental organisation led	Population based screening study.	Community based, territory wide AF screening program, Hong	Total of 11,574 participants volunteered, 9236 female (79.8%), mean	AF screening using AliveCor, recording for 30 seconds then interpreted by	AF was seen in 244 participants (2.3%, 95% CI 2-2.6%, 172 female and mean age 79.5 ± 7.9 years). AF was newly	Aged 50 years and over.	None specified.

large scale community atrial fibrillation screening program using the smartphone electrocardio-gram: an observational cohort study (13).		Kong. 108 screening community centres were used.	age 78.6 ± 8.1 years).	cardiologist. AF patients were contacted by telephone for a baseline questionnaire, repeated 9 months later (medical history, symptoms).	diagnosed in 74 participants (0.69%, 95% CI 0.54-0.84%), 36 being asymptomatic. The number needed to screen for 1 newly diagnosed patient was 145. Of the questionnaire co-morbidities, 70/244 had hypertension, followed by diabetes. Dyspnoea was the most common symptom. Sensitivity and specificity of the automated algorithm in AF detection was 75% (95% CI 70-80%) and 98.2% (95% CI 59.3-70.5%) respectively. Positive predictive value was 64.9% (95% CI 59.3%-70.5%) and the negative		

					predictive value was 99.5% (95% CI 99.4-99.6%).		
Desteghe et al. Performance of handheld electrocardio-gram devices to detect atrial fibrillation in a cardiology and geriatric ward setting (14).	Non-randomised blinded observational study.	Hospitalised patients in cardiology and geriatric wards in a Belgian tertiary care hospital.	Participants screened, totalled 445. After exclusions, 320 were screened on the cardiology ward and 125 on the geriatric ward.	Each patient held two handheld devices (MyDiagnostick and AliveCor), after an ECG by 12 or 6 lead (cardiology and geriatric respectively). This was a usability, accuracy and cost-effectiveness study.	On the cardiology ward, sensitivity for AliveCor was 36.8% and specificity 96.1%. MyDiagnostick had 60.5% sensitivity and 93.3% specificity. On the geriatric ward, sensitivity for AliveCor was 72.7% and specificity was 98.1%. AF prevalence was 35.6% and 36% at the cardiology and geriatric wards, respectively.	≥18 years.	Participants unable to hold the hand-held devices, <18 years and patients in isolation.
Evans et al. Feasibility of using mobile	Prospective, observational study.	Kijabe Hospital, Kenya. Healthcare	50 African adults, 66% female. Mean	Participants recruited in a 2-week period.	Outcome measures included feasibility (study completion and	Not specified. Notes English or	Terminal illness or debilitating

ECG recording technology to detect atrial fibrillation in low-resource settings (15).		clinics including diabetes, ophthalmology, internal medicine, male inpatient ward and the emergency department.	age 54.3 ± 20.5 years.	Screened using the AliveCor ECG recorder.	recruitment within the study time frame) and screening yield using the ECG tool (ability to detect AF). AF detected in 4/50 participants (8%). 100% study completion within time frame. Additionally, 5 health providers who assisted with data collection answered questions relating to ease of use, internet access and use of mobile devices and all answered affirmatively.	Swahili speaking included.	neurological condition.
Halcox et al. Assessment of remote heart rhythm sampling using the AliveCor	RCT.	Enrolled via GP records and screening undertaken at participants homes. Follow	1001 enrolled (500 in the intervention arm, mean age 72.6 years and 48% male;	Participants were randomised 1:1 to an intervention (iECG) group or routine care	In the iECG group, 19 participants were diagnosed with AF versus 5 in the routine care arm (95% CI 1.4-10.4, *P*=0.007) at a cost per	>65 years with a CHA2DS2-VASc of ≥2 not already taking anticoagulation. Access to the	Pacemaker implantation,

heart monitor to screen for atrial fibrillation (16).		up provided by consultation and telephone.	routine care group mean age, 72.6 years and 45% male).	group. The intervention group recorded twice weekly iECGs plus additional recordings if symptomatic, over 12 months.	diagnosis of £8255. Stroke / systemic embolic events were 6 versus 10 in the iECG versus routine group respectively. iECG patients were confident and not anxious about using AliveCor. An almost 4-fold increase in likelihood of a diagnosis of AF being made over a year using this approach was identified.	internet and be able to operate the AliveCor system.	
Lown et al. Screening for atrial fibrillation using economical and accurate technology (17).	Case-control study	3 GP practice surgeries in Hampshire, UK.	418 participants aged >65 years	Single screening visit to the GP surgeries, to assess the accuracy of 2 wearable ECG sensing devices (Polar-H7 and Firstbeat	82/418 at the study visit had AF and or/or atrial flutter (19.6%) and 336/418 without. Sensitivity (95% CI range), specificity and overall accuracy of the 4 devices were AliveCor 87.8% (78.7%-94%), 98.8%	>65 years of age.	Pacemaker, deemed unsuitable by the GP (terminal illness, bedridden), lacked capacity, previous skin

				Bodyguard 2) for the detection of AF. Comparison then to 2 established AF detection devices (AliveCor and WatchBP) followed by 12 lead ECG and interpretation by a panel of cardiologists.	(97%-99%), 96.7% (94.4%-98.2%), WatchBP 96.3% (89.7%-99.2%), 93.5% (90.3%-95.9%), PH7 96.3% (89.7%-99.2%), 98.2% (96.2%-99.3%), 97.9% (96%-99%) and BG2 96.3% (89.7%-99.2%), 98.5% (96.6%-99.5%), 98.1(96.3%-99.2%).		reaction to the electrode gel.
Lowres et al. Feasibility and cost-effectiveness of stroke prevention through community screening for	Cross-sectional study.	Ten pharmacies, community based, in Sydney Australia.	1000 participants, 436 male and mean age (± SD) 76 ±7 years.	Brief medical history, pulse palpation, AliveCor recording.	New AF was found in 1.5%, mean age 79 ±6 years. AF prevalence was 6.7%. AF detection was reported as 98.5% sensitivity and 91.4% specificity using an automated algorithm.	>65 years of age.	Severe coexisting medical condition e.g., severe dementia or terminal illness.

atrial fibrillation using iPhone ECG in pharmacies (6).							
Lowres et al. Self-monitoring for atrial fibrillation recurrence in the discharge period post-cardiac surgery using an iPhone electrocardio-gram (18).	Feasibility study, cross-sectional design.	Royal North Shore Hospital and North Shore private hospital, Sydney, Australia.	42 participants completed the monitoring required for this study (mean age 69 ±9 years, 80% male).	AliveCor ECG recordings post-operatively (post cardiac surgery). Demographics, medical history, post-op complications and knowledge of AF recorded.	Participants accepted the AliveCor device and self-monitoring identified 24% (95% CI 12-39%) with an AF recurrence within 17 days of hospital discharge. Only 30% had symptoms of AF. AF knowledge increased.	No history of AF discharged home in sinus rhythm, who had experienced a transient episode of AF following cardiac surgery. Age ≥18 years.	History of AF prior to surgery.
Soni et al. High burden of unrecognised atrial fibrillation in rural India: an innovative community	Observation-al screening study after randomly selecting participatory communities.	Anand District, Gujarat in India. Random selection of 6 villages from 30. Community screening.	Total of 355 participants aged ≥50 years. Almost 2 thirds were >55 years and nearly half	Screening using AliveCor and collection of pulse data. Both pulse and AliveCor data was recorded for	AF was diagnosed in 12 participants (5.1% CI 95% 2.7-8.7). Just 1 participant had persistent AF and 9 screened positive once. The first screening identified 7 with AF and	Residents ≥50 years in the recruited communities.	None stated.

based cross sectional screening program (19).			were female. Due to malfunction, 120 participants were not screened and excluded.	2 minutes each on 5 consecutive days over 6 weeks. Questionnaire relating to demographics, lifestyle, and medical history.	the remaining 5 were identified on day 4. Hypertension was present in half of the positive AF screenings.		
Soni et al. Age and sex stratified prevalence of atrial fibrillation in rural western India: results of SMART-India, a population-based screening study (20).	Population based, observational (cross sectional) screening study.	Rural Western India, 50 villages.	Screening in 7 participants in each of six age and sex strata (age 40-55, 56-65, 66-75, 75+ and male and female) from 50 villages. Total of 2100 participants.	iECGs were collected from 2074 participants and 1947 responded to a questionnaire. The study spanned 12 months and asked participants to make 3	AF identified in 33 participants (1.6%), 2 thirds on the first ECG. AF prevalence was higher in males (2.3% vs 1%, p=0.03) and older people (age group 40-55 = 0.6%, 56-65 = 0.9%, 66-75 = 2.1%, 75+ = 5.6%, p<0.01). The highest prevalence of AF (7.2%) was in men over 75 years.	Men and women aged ≥45 years in the selected villages, as stated in the study protocol (separate paper) SMART-India, Soni et al., (2017).	Not stated.

				recordings over a 5-day period.			
Tarakji et al. Using a novel wireless system for monitoring patients after the atrial fibrillation procedure: the iTransmit study (20).	Non-randomised, single blinded study.	Single tertiary centre, Cleveland Clinic, Ohio, USA.	60 patients recruited (mean age 60 ± 12 years) and 55 completed the study. Data collected over 5 months.	There were 389 recordings made with an AliveCor and traditional transtelephonic monitor, used simultaneous whenever the patient had symptoms or at least once a week. AliveCor recordings were reviewed by 1 of 2 blinded electrophysiologists and compared with analysis of the traditional	Sensitivity and specificity for the detection of AF and atrial flutter with AliveCor was compared to the traditional monitor. K coefficient was 0.82 (excellent agreement between both monitors). When AF and atrial flutter were combined, sensitivity was 100% and specificity 97% for the AliveCor. Patients preferred to use the AliveCor over the traditional monitor (92%) with just 2% finding AliveCor difficult to use. AF incidence was 10.5% (n=41/389 recordings).	Patients with AF undergoing ablation (with or without atrial flutter). Possession of an iPhone 4, 4S or 5. Age ≥18 and ≤75 years, history of paroxysmal or persistent AF. Willing to use AliveCor.	Patients unwilling or unable to use AliveCor / their phones and those residing outside the USA.

				monitoring. Patients later surveyed for opinions of both monitoring tools.			

4. Quality appraisal.

Appraisal of methodological quality of the eligible studies was assessed using the Mixed Methods Appraisal Tool, version 2018 [MMAT] (22) (*Supplementary Digital Content - Appendix 1B*). Whilst the research studies included here are quantitative, they adopt different designs and therefore a tool that incorporates experimental and non-experimental appraisal, offers ease of application and comparability. The algorithm incorporated within the MMAT assists the reviewer in selecting the most appropriate checklist to appraise the methodological quality of the research. The MMAT offers five categories of study design, and this review applies three of these – quantitative randomised controlled trials, quantitative non-randomised trials and quantitative descriptive. *Table 3* demonstrates to what extent the methodological quality criteria is evident in the research study.

The majority of the eligible studies that were appraised had a quantitative descriptive design, with two quantitative non-randomised and just one study as a randomised controlled trial. This was unsurprising when considering the nature of the eligible studies and focus of this systematic review. Overall, the methodological quality was high. Where criteria were uncertain, this related more to the study design and the quality criteria not being directly applicable, rather than inaccurate representation or error.

Halcox et al. provided limited details relating to randomisation, only in that a simple 1:1 allocation was applied (16). Baseline characteristics were compared between the standard care and intervention group using statistical testing and were highly comparable. The outcome assessors were not blinded to the intervention. The study team identified closer contact with the intervention participants, raising the possibility that relevant events may have been missed in routine care patients.

Table 3. Assessment of methodological quality of included reviews.

Quantitative randomised controlled trials

Study and GRADE*	**S1** Are there clear research questions?	**S2** Do the collected data allow to address the research questions?	**Q1** Is randomisation appropriately performed?	**Q2** Are the groups comparable at baseline?	**Q3** Are there complete outcome data?	**Q4** Are outcome assessors blinded to the intervention provided?	**Q5** Did the participants adhere to the assigned intervention?
Halcox et al. (16). **GRADE** 1B	Yes	Yes	Yes	Yes	Yes	No	Yes

Quantitative non-randomised

Study and GRADE*	**S1** Are there clear research questions?	**S2** Do the collected data allow to address the research questions?	**Q1** Are the participants representative of the target population?	**Q2** Are measurements appropriate regarding both the outcome and intervention (or exposure)?	**Q3** Are there complete outcome data?	**Q4** Are the confounders accounted for in the design and analysis?	**Q5** During the study period, is the intervention administered (or exposure occurred) as intended?
Desteghe et al. (14). **GRADE** 2c	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lown et al. (17). **GRADE** 1C	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Quantitative descriptive

Study and GRADE*	**S1** Are there clear research questions?	**S2** Do the collected data allow to address the research questions?	**Q1** Is the sampling strategy relevant to address the research question?	**Q2** Is the sample representative of the target population?	**Q3** Are the measurements appropriate?	**Q4** Is the risk of nonresponse bias low?	**Q5** Is the statistical analysis appropriate to answer the research question?
Chan & Choy (12). **GRADE** 1B	Yes	Yes	Yes	No	Yes	Yes	Yes
Chan et al. (13). **GRADE** 1B	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear
Evans et al. (15). **GRADE** 2B	Yes	Yes	No	No	Yes	Yes	Unclear
Lowres et al. (6). **GRADE** 1B	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lowres et al. (18). **GRADE** 2B	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Soni et al. (19). **GRADE*** 1C	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Soni et al. (20). **GRADE** 1C	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Tarakji et al. (21). **GRADE** 2B	Yes	Yes	Yes	Yes	Yes	Yes	Yes

***GRADE** of Evidence denotes the Grade and Quality of Evidence Assessment (see section 5.3).

In the quantitative descriptive studies, sampling strategies varied. Soni et al. used random selection in terms of location and participants recruited (19,20). The remaining studies in this group employed consecutive recruitment, whereby eligible participants were approached for enrolment. These studies were of a cross-sectional, observational design, and whilst sampling did not adopt the probability method, the study design outlined their criteria. For example, Chan et al. screened 11,574 people in their community screening programme with minimal exclusion criteria (53.6% participation rate from the members in the screened communities) (13). Whilst large numbers of participants were screened in their research study, it is unclear how representative the sample was. There was no identification of specific disease groups, only that people over 50 years were recruited. Chan and Choy provided their recruitment numbers and total population for the city, but no further breakdown in terms of statistical representation of this population (12). They did, however, highlight that their research was not that of a targeted nature, and overall prevalence and incidence with numbers needing treatment was provided. Statistical tests used were outlined but these were not presented in their publication.

Whilst there were no significant concerns in terms of methodological quality with the research by Lowres et al. they reported that 24% of participants approached, declined to take part in the study (18). This was explained as many people feeling overwhelmed post-surgery, reflecting lower numbers recruited (n=44). An earlier study by the group provided fewer results and discussion relating to the feasibility aspect of their study in relation to cost-effectiveness, with the latter predominating the outcomes of their publication (6).

In the quantitative non-randomised studies, confounders were not clearly outlined. Confounding aspects relating to utilisation of the AliveCor® device may include tremor, ability to operate, experience or previous use, dexterity, artefact, and clarity of transmission. Confounding bias was generally low as anticipated confounding factors were accounted.

5. Results.

5.1 Feasibility considerations.

The feasibility of utilising the AliveCor® device in clinical practice relates to the overarching concept of whether employing the use of this heart rhythm screening tool in clinical practice is possible. Whilst we know the device is already utilised in clinical environments and by patients, the components necessary to make this practical and achievable whilst providing value in terms of accuracy, is important when reviewing overall effectiveness.

The feasibility of implementation of the AliveCor® device as a heart rhythm screening aid in AF screening studies was high. Implementation feasibility is defined as a high proportion of people invited for screening taking it up, along with sufficiently low barriers and resource drain (23). Processes relating to recruitment and retention of participants were favourable in the eligible studies, with lower numbers of recruitment evident in some studies and this can be seen in *Table 4*, which also highlights the ability to screen all participants involved (15,17,18,21). Drop-out rates were low in all eligible studies, perhaps reflecting the study design, compliance, and ease of use with the AliveCor® device. The minimal number (n=5/60) who did drop-out of the research studies were for reasons including moving away from the geographical study location (n=1), purchasing a replacement mobile phone of an alternative brand (n=1) and withdrawal of consent (n=3) (17). In a post-operative study of research of AF recurrence, two participants failed to complete the study (reasons unexplained) (18). These two studies reflected a design requiring self-recording of ECGs once away from the research team at either specified times or frequencies throughout the follow-up period.

Resources were problematic in the study by Soni et al. whereby a proportion of participants had to be excluded due to malfunction of the device (19). Acceptability from users was encouraging, retention rates were high, with all those recruited

remaining engaged with the study, and when compared to other devices for rhythm monitoring, the AliveCor® device was rated favourably (14,17) (*Table 4*). In a comparison study using four screening devices, the AliveCor® device was rated the most comfortable device to use (17). Desteghe et al. did not formally evaluate user-friendliness, but no patients objected to using either AliveCor® or MyDiagnostick (14). They offered justification for acceptability of both devices such as immediate visualisation of the ECG recording where diagnosis and judgement can be made regarding quality and clarity with the AliveCor® device. Training requirements for physicians were minimal (e.g., pharmacists in the study by Lowres et al. but tuition for patients was more time consuming) (6). Some patients needed further tuition following the initial guidance (19). However, Evans et al. identified the AliveCor® device to be a feasible service in low-resource settings when used in a hospital in Kenya (15). Availability of mobile devices and internet received an affirmative response when health professionals were asked about their access (15).

Data processing, time and resource intensiveness are metrics in the management aspects of feasibility studies (detailed in *Table 4*). This varied according to the study design and method of ECG analysis. In the studies by Desteghe et al. and Lowres et al., manual interpretation was implemented, and the remaining studies relied upon the automated algorithm for ECG interpretation, with professional overview of the abnormal or non-diagnostic ECGs (14,18). Furthermore, the number of ECG recordings made impacted upon time for data gathering and processing. Single screening episodes would pose less demand on the study team compared to those for whom protocol demanded repeated ECG recordings.

Scientific components incorporated qualities relating to factors that interfered with obtaining diagnostic ECGs and these were referred to in most studies e.g., tremor and inability to hold the device (see *Table 4*). Statistical testing was generally as outlined in the study design but not all the tests were displayed in the published article.

Table 4. Metrics of feasibility in the eligible studies.

Research	**Process** Processes that are key to the success of the study, recruitment rates, response, proportion who remain interested, willingness of participants to be randomised and ease of doing so. Ability to screen all participants.	**Resources** Time and resource problems occurring during the study, retention of participants, reason for attrition, appropriate eligibility criteria, barriers and refusals, compliance with protocol, participant reaction to data collection, access to and cost of equipment, space and time, suitability of intervention in the setting, clinician training needs and competence. Obstacles.	**Management** Research site capacity – phone lines, IT, databases, equipment usage – backups, personnel time, data processing time, data completeness, software appropriateness, audit, fidelity, clinician adherence to protocol. Staffing impact.	**Scientific** Data collection materials, extraneous variables threatening validity, acceptability of intervention, data variability and stats analysis, treatment effect.
Chan & Choy (12).	13,122 recruited in Hong Kong community screening programme. Little other detail provided.	Little detail provided.	Technical ease highlighted with volunteers able to use the device with minimal training.	Interpretability was very high with 0.4% non-diagnostic. Sensitivity of detecting new AF in >60 years of age was 98% and

				29.2% specificity. NNS for 1 new AF was 129.
Chan et al. (13).	Not a feasibility study but elements to consider. 11,574 participants from a population of 7.34 million (participation rate 53.6% CI 52.9-54.3%). High number of screening sessions in 108 centres.	Single screening episode but all recordings sent for review by a cardiologist (labour intensive) for diagnostic clarity against automated algorithm.	Total of 19.3 hours were consumed in cardiologist's interpretation time for the entire screening programme with 1 minute for every 10 AliveCor recordings.	AliveCor recordings were uninterpretable in 7.2% of recordings (95% CI 6.7-7.7%). AF confirmed in 2.3% (95% CI 2-2.6%) of participants and new AF in 0.69% (95% CI 0.54-0.84%). The NNS for 1 new case of AF was 145. Sensitivity in detecting AF was 75% (95% CI 70-80%) and sensitivity 98.2% (95% CI 98-98.4%).
Desteghe et al. (14).	A non-randomised blinded study across 2 departments in a tertiary care hospital. No patients refused to take part.	Barriers included inability to hold the device correctly, excluding 7% and 21.4% of cardiology and geriatric ward patients. Usability was lower in the geriatric ward patients	All ECGs independently reviewed by 2 electrophysiologists. Manual interpretation increased sensitivity but decreased specificity and increased cost	Sensitivity and specificity of the automated algorithms were sub-optimal (cardiology 54.5% and 97.5% respectively and geriatrics 78.9% and 97.9% respectively). AF prevalence high with 35.6% and 36% in

			analysis per patient. No deviations from protocol.	cardiology and geriatric wards, respectively.
Evans et al. (15).	A total of 51 people in 2 weeks from 4 different clinical areas were approached with 50 agreeing to participate.	Exclusion was related to 2 disease groups (terminal or neurological disease) so affects generalisability. Low-resource settings (African region).	'Several' patients had to repeat the ECG recording due to artefact. Unclear ECGs were reviewed by a cardiologist. All healthcare users had access to mobile technology at their place of work.	Automated diagnostic analysis found 42 normal ECGs and 'possible' AF in 4 (8%) of ECGs.
Halcox et al. (16).	Not a feasibility study. Randomisation 1:1. 5726 individuals invited, 1004 recruited.	Minimal participant withdrawal (5 in total). Twice weekly recordings over 12 months were expected. All completed the screening study with 39/52 sending in the required twice-weekly ECGs. There was no difference between age groups, with age not being a barrier. Participants in the intervention arm were not at all or only	Complete data with statistical testing proposed and evident. The study co-ordinator could arrange ECG review within 48 hours of abnormal ECGs being uploaded.	ECG analysis using the automated algorithm with overreading of abnormal tracings by a cardiologist. 19 (1.84%) patients in the intervention group had new AF during the 12 months versus 5 in the study arm (hazard ratio 3.9, 95% CI 1.4-10.4, p=0.007).

		slightly anxious about using the device. The majority were confident in using AliveCor and extremely or very satisfied using the device.		
Lown et al. (17).	Recruitment through GP practices with single screening visit but using AliveCor as well as 3 other devices. Total of 879 were invited with 418 screened.	All who were recruited, completed the study visits. All screenings were undertaken with supervision, reflecting the limited number of repeated screening attempts needed.	Research nurses recorded the number of attempts required to obtain diagnostic readings. No missing data. About 10% of AliveCor recordings yielded unclassified algorithm results which would impose a high workload if all needed physician oversight.	Median number of attempts to obtain a diagnostic output was 1 (range 1-6). AF accurately detected with sensitivity 87.8%, specificity 98.8% and overall accuracy 96.6% (95% CI 94.4-98.1%). 79 AF cases diagnosed.
Lowres et al. (6).	Engagement and recruitment were high. A very small number (4/1000) of AliveCor recordings were uninterpretable due to artefact.	Participants who engaged were summarised as those more interested in their health, possibly underestimating overall prevalence.	Recruiting between community pharmacies differed between sites, dependent on pharmacist's availability and workload. Pharmacists were confident in the use of AliveCor	Pharmacists' interpretation of AF was high (51/67 new AF cases identified) without further diagnosis needed by supporting medical colleagues. Pharmacists' knowledge of AF

			without previous experience. ECGs taken when AliveCor was non-diagnostic were reviewed by a cardiologist.	increased significantly (mean test score of 49 ± 25% at baseline to 86 ±8% post-study (<0.001). Diagnosing AF was reliant on Pharmacists rhythm recognition as the automated algorithm was not available (this is widely employed now and has high sensitivity and specificity, reducing workload and improving workflow).
Lowres et al. (18).	Measured by acceptability and willingness to participate. 14/58 (24%) of patients declined, feeling 'overwhelmed'.	Participants felt 'empowered' when using AliveCor. Feasibility measured by participant compliance and ability to learn to use the device. This was high with 42/44 completing the intervention. 3-4 AliveCor recordings per day were requested for 4 weeks. AliveCor	Time to teach participants varied according to smart-phone familiarity and these patients did need a longer training period (20 mins teaching vs 5-10 mins). Age was not a barrier.	Participation enhanced AF knowledge through use of open- ended questions, an AF Knowledge Scale and participant interview. AliveCor was accurate in interpretation with 4% being non-diagnostic (interference, tremor, poor mobile reception in rural

		recordings were made for a mean of 29 ± 5 days and 86% sending recordings for ≥27 days. AliveCor was easy to use for 95% of participants.		locations). Sensitivity using the automated algorithm for AF detection was 94.6% (95% CI 85.1-98.9) and specificity 92.9% (95% CI 92-93.8%).
Soni et al. (19).	Not a feasibility study. Random sampling strategy of people in rural India with low resources and financially deprived areas.	Total of 354 people screened for 2 minutes for consecutive 5 days over a period of 6 weeks. A malfunction of the device prohibited the use in 120 participants.	Team of trained research co-ordinators and community health workers performed the screening with participants. A cardiologist analysed abnormal ECGs.	New AF in 12 people (5.1% prevalence, 95% CI 2.7-8.7). Only 1 person had AF in all screenings and 9 tested positive just once.
Soni et al. (20).	Not a feasibility study. Random sampling strategy, statistically representative sample calculated and achieved (2100, response rate 90.8%).	2074 screened in total, 80.5% were screened 3 times. Older participants were more likely to complete the full 3 screenings.	Uncomplicated in this study but transferability to rural communities without physician input less feasible (e.g., smart-phone availability, remote access affective transmission quality).	Automated analysis identified 'probable AF' in 88 (4.2%) and after clinical adjudication, 32 were confirmed to have AF. Overall AF prevalence of 1.6%.
Tarakji et al. (21).	The minimum sample size required was enrolled but just	All participants already had smartphones so were familiar	Minimal detail but not labour intensive for staff as screening	98% of participants rated the AliveCor as 'easy' or

	55 patients completed the study.	with this technology. Recordings made when symptoms presented or at least once a week, for 3 months. High number of recordings made but unclear if all participants fulfilled their requirement of the amount sent for the study time frame.	undertaken at home by patients independently.	'moderately easy' to use. Sensitivity for AF detection was 100% and 97% specificity.

Cost effectiveness.

Cost effectiveness of AF screening has been considered in research, including a cost effectiveness analysis by Lowres et al. who incorporated costs of AliveCor® ECG recordings, treatment, and outcome data according to the numbers incidentally detected as having AF (6) (see *Appendix 1C*). They concluded that the approach adopted in their study, whereby pharmacy customers aged ≥65 years were screened using the AliveCor® device, was cost effective. The estimated incremental cost-effectiveness ratio [ICER] of screening to prevent one stroke or to increase one quality adjusted life year [QALY], was well within the range fundable on a population basis (6,24). Their analysis incorporated calculations of anticoagulant prescription and adherence and identified improved cost-effectiveness with direct oral anticoagulants compared to vitamin K antagonists (*Appendix 1C*). This is significant, given the high risk of stroke and premature death identified in people with asymptomatic AF, the salutary effect of anticoagulants in reducing adverse outcomes and the cost effectiveness in stroke and thromboembolism prevention through the appropriate use of anticoagulants (25,26,27). Halcox et al. completed health economic evaluation in part, calculating a cost per AF diagnosis of £8255, according to UK NHS tariffs at their time of writing (16). This was calculated through evaluation of device costs, patient training, defective technology costs, overreading of ECGs where diagnostic clarity was needed and pathway coordination (16) (*Appendix 1C).* They did not complete analysis of cost effectiveness to stroke prevention in the community but suggest their conclusions align with other health economic studies (6,28,29).

In summary, feasibility metrics demonstrated that the AliveCor® device is an effective tool of choice in terms of process (response rate, ability to screen), resources (retention, compliance, suitability for the intention, minimal training) and management (adherence, equipment). Staffing impact was more intensive where further analysis of ECGs was required (management and scientific metric). Cost effectiveness analysis whilst not a primary focus, forms part of the objectives of this review in terms of overall considerations around the feasibility of implementation. AF

is costly in terms of healthcare consumption and the associated burden on wider society and utilising the AliveCor® device proved cost effective in the analysis in this review.

5.2 Validity of the AliveCor® device.

The sensitivity for AF detection varied across the included studies, ranging from 54.5% in the study by Desteghe et al., to 100% in the research by Tarajki et al. (14,21) (*Table 5*). Lowres et al., reported a 98.5% sensitivity for AF detection and 91.4% specificity with a further study indicating a sensitivity of 94.6% (95% CI, 85.1-98.9) and 92.9% specificity (95% CI, 92.0-93.8) (6,18). The majority of false-positive ECGs were associated with low-voltage p-waves and QRS complexes, atrial ectopy, and left bundle branch block.

Table 5. Summary of validity, representing sensitivity and specificity of eligible studies.

Research	Sensitivity	Specificity
Chan & Choy (12).	98%	29.2%
Chan et al. (13).	75% (95% CI 70-80%)	98.2% (95% CI 59.3-70.5
Desteghe et al. (14).	54.5% - 78.9%	97.5% - 97.9%
Evans et al. (15).	Unreported	Unreported
Halcox et al. (16).	Unreported	Unreported
Lown et al. (17).	87.8% (95% CI 78.7-93.9%)	98.8% (95% CI 96.9-99.6%)
Lowres et al. (6).	98.5%	91.4%
Lowres et al. (18).	94.6% (95% CI, 85.1-98.9)	92.9% (95% CI, 92.0-93.8
Soni et al. (19).	Unreported	Unreported
Soni et al. (20).	Unreported	Unreported
Tarajki et al. (21).	100%	97%

Evans et al. reported 84% of ECGs as 'normal' by the automated diagnosis, 8% 'unclassifiable' (all of which when later analysed manually by a cardiologist were deemed normal) and 8% as 'possible AF', which were later confirmed as AF by the cardiologist (15). In the AF screening study by Chan and Choy of 13,122 AliveCor® ECGs, 56 (0.4%) were uninterpretable and it is unclear in their publication if these were later reviewed and classified as normal or not (12). They did apply an age cut-off threshold of 60 years or above and when this was used, there was a 98% sensitivity and unexplained low specificity of 29.2% when detecting newly diagnosed AF. This poor ability to accurately identify patients who did not have AF potentially threatened the validity of the device in this study. In a separate study, the sensitivity using the automated algorithm was 75% (95% CI 70-80%) and specificity 98.2% (95% CI 59.3-70.5) (13). The positive predictive value was 99.5% (95% CI 99.4-99.6%). Of 11,574 AliveCor® ECGs, 839 (7.2%, 95% CI 6.7-7.7%) were uninterpretable and it is unclear whether these underwent subsequent review. In the study by Halcox et al., 76% of AliveCor® ECGs were reported as normal (out of a total of 60,440 ECGs over 12 months that were recorded in the intervention group) and none were later reclassified as AF by the cardiologist or physiologist checking the transmitted ECGs (16). Only 6 of the 21% of ECGs reported as 'undetermined', were finally confirmed to be AF. Soni et al. identified 4.2% (n=88) of recordings to have 'possible AF' according to the automated algorithm and after clinical adjudication, 32 participants were confirmed to have AF (20). One participant had feedback of 'unclassified' and this was later reviewed as being AF. The initial interpretation of AliveCor® ECGs in the study by Soni et al., identified 25 inconclusive transmissions (of 823 total screenings), later resulting in 20 negative screenings and five positives for AF (19). All AF diagnoses from the automated interpretation were confirmed as AF by the adjudication board. This data is summarised in *Table 5*, which also shows those studies where specific information relating to tool validity is omitted.

Desteghe et al. compared the use of the AliveCor® device to MyDiagnostick (Mydiagnostick Medical B.V), an alternative handheld rhythm screening device, demonstrating lower sensitivity from the AliveCor® device and slightly superior specificity when compared with MyDiagnostick (sensitivity 54.5-78.9 and specificity

97.5-97.9 with AliveCor® and sensitivity 81.8-89.5 and specificity 94.2-95.7 with MyDiagnostick) (14). Device patients (pacemakers or implantable cardioverter defibrillator) were included in the analysis and may have affected the results, as the AliveCor® device only had a 36.8% sensitivity in these patients. It is however, widely accepted that these types of devices are not appropriate in these patients due to inaccuracies with interpretation and detection of pacing spikes on the ECG (30). After the exclusion of device patients, the sensitivity and specificity for both devices improved with automated interpretation and physiologist analysis. Algorithm analysis of the AliveCor® device was 54.5% whilst manual interpretation by electrophysiologists reached 90.9% of AF patient recordings.

In the study by Tarakji et al., just seven of 831 recordings were uninterpretable (21). A normal rhythm was correctly identified in 97% of cases and AF 100% of the time, with 3% false-positive results. The AliveCor® device had a 97% specificity and 100% sensitivity. When the false positives were more closely examined, they were related to difficulty in assessing p waves making it problematic when detecting a normal rhythm in patients with pacemakers. Lown et al. also ran a comparative study between the AliveCor® device and three other portable devices, and when the automated algorithm was used, AF was accurately detected with sensitivity of 87.8% and specificity 98.8%, and an overall accuracy of 96.65% (95% CI 94.4-98.1) (17). The AliveCor® device yielded unreadable recordings from six participants with an average 3.3 attempts to obtain a diagnostic result. Low voltage ECG transmission accounted for two of the six unreadable recordings.

Variability in the sensitivity of the AliveCor® device could be attributed to movement artefact, interference and poor connectivity between the skin and electrodes, ectopic activity, and tremor (30). The AliveCor® algorithm and software is updated periodically, to enhance clarity over signal interpretation and reduce unclassified outputs, and therefore, if older versions had been used in some studies, this may have had some impact on signal analysis. These updates can for example, help distinguish between atrial ectopy and AF (30). Details around trouble shooting attempts are not always disclosed in the research papers, making it difficult to explain variation in device validity. Trouble- shooting can be facilitated when someone familiar with the

device assists with the screening and this might relate to the favourable sensitivity in studies by Lowres et al. study, where pharmacist led screening was undertaken (6), and Chan & Choy AF screening study where a researcher was present to instruct (12). The ability to hold the device securely might have impacted on the lower sensitivities observed in the study by Desteghe et al. which was undertaken in two in-patient hospital wards, one being cardiology and the other for older adults (14). Use in patients with implantable cardiac devices has also impacted on the sensitivity for detecting AF (14, 30).

In summary, AF detection rates ranged from 0.8% to 36% and this largely correlated to the study population with a wide age inclusion and mass / population screening representing lower AF detection. Recruitment from higher-risk groups (older age, targeted localities, presence of chronic disease) demonstrated higher numbers of people with AF. Further interpretation of ECGs was required with 0.4% to 4.2% of ECGs where a differentiation between AF and normal could not be made. Different durations of screening time resulted in varying rates of AF detection. AF was detected in 0.8% to 36% of the population during single-point-in-time screening and 1.6% to 24% AF detected through repeated intermittent AliveCor® ECG recordings.

5.3 Grading of evidence.

The GRADE quality of evidence assessment tool was used with a second reviewer assisting with the quality assessment of eligible studies (31,32). Assessing the quality of evidence is important and supplements the appraisal of methodological quality, facilitated in this review by employing the MMAT assessment tool (GRADE rating provided in the reference column of *Table 3*, to aid interpretation and discussion). Historical grading of evidence would impose a lower ranking on many of the eligible studies in this review, due to their observational design. Strengths in methodological approach and study design, however, enhance reliability in non-experimental studies. A summary of the quality analysis is displayed in *Table 6a* and *6b*. Overall quality reporting was moderate. All studies described the primary objective of the research and included a summary of the main findings. Detailed comorbidities of the study

participants were only adequately reported in some studies, but lack of this data was not always representative of a criticism and may simply not have been the focus of the research e.g., if feasibility was the study focus. Limitations were discussed in varying detail and there were no missing outcome data in any of the studies. Inclusion criteria including a non-selective sample of the population (e.g., all adults over 18 years of age) were evident in six of the eligible studies. The remaining research recruited a more selective sample, restricting age eligibility along with some other criteria (e.g., the CHA_2DS_2-VASc stroke risk stratification tool for patients with AF, where the risk score is ≥2 - Congestive heart failure, Hypertension, Age >75 years, Diabetes, prior Stroke/TIA/thromboembolism, Vascular disease, Age 65-74 years, Female sex) within their inclusion criteria (16).

When this quality of evidence assessment is matched against the MMAT quality appraisal, it is evident that those scoring highest in terms of GRADE assessment, rate similarly well in the MMAT quality appraisal. Four studies were awarded a 1B grading with Lowres et al. also meeting all the criteria in the MMAT assessment (6). Chan et al. (13) also scored highly with only one criterion from the MMAT being marked as 'unsure'. This was followed by Chan and Choy (12) and Halcox et al. (16) who missed one criterion each on the MMAT assessment ('is the sample representative of the population?' and 'are outcome assessors blinded to the intervention?' respectively). Two studies rated 1C on the GRADE assessment whilst meeting all the criteria on the MMAT appraisal (19,20). Two of the remaining studies rated slightly lower at 2B, meeting all the MMAT assessment details (18,21). Evans et al. also rated 2B but there were concerns with the small sample and sampling strategy when analysed using the MMAT (15). The study by Desteghe et al. was graded lowest with GRADE at 2C whilst meeting all the MMAT criteria (14). Overall quality reporting was moderate and appraising the grading of evidence is important when examining research from a range of methodological designs.

Table 6a. Quality assessment of each paper, detailing quality, consistency, and directness

Q = quantitative, des = descriptive, Ob = observational

Research	Design	Quality	Consistency	Directness
Chan & Choy (12).	Q, des, Ob	No serious limitations: large sample size, diverse screening centres across a vast city	No serious inconsistencies: strong analysis incorporating co-morbidity variables with univariate and multivariate analysis	No serious uncertainties: comparable to population screening and inclusive
Chan et al. (13).	Q, des, Ob	No serious limitations: large sample, 108 screening centres	No serious inconsistencies: >50 years inclusion, representing higher risk group	No serious uncertainties: consider voluntary nature of participants in community screening programmes
Desteghe et al. (14).	Q, non-rand, Ob	Some limitations: single site, 2 inpatient areas	No serious inconsistencies: wide inclusion criteria >18 years, but restricted recruiting locations, no information on co-morbidities (study focus on performance of screening devices)	Some uncertainties: high-risk populations screened so less generalisable to whole population but does relate to AF population (older, cardiac disease)
Evans et al. (15).	Q, des, Ob	Some limitations: single screening site, short study	Some inconsistencies: unclear if co-morbidities had an effect on the	Some uncertainties: short study period and small sample. Specific

		period duration and small sample size	outcomes, co-morbidities were reported but not accounted for in analysis (but primarily a feasibility study)	patient groups selected, affecting directness to wider population or high-risk groups
Halcox et al. (16).	RCT	Some limitations: lack of blinding and simple randomisation strategy	Some inconsistencies: Inclusion restricted to >65 years plus CHA2DS2-VASc ≥2 and this can vary according to risk and associated c-morbidities	No major uncertainties:
Lown et al. (17).	Q, non-rand, Ob	No serious limitations: 3 locations	No serious inconsistencies: >65 years, appropriate eligibility	No major uncertainties:
Lowres et al. (6).	Q, des, Ob	No serious limitations: variation in sampling maximised by incorporating 10 pharmacies in different regions	No serious inconsistencies: wide inclusion criteria with age restriction >65 years	No serious uncertainties: mostly representative of the wider population
Lowres et al. (18).	Q, des, Ob	Some limitations: small sample size, 2 neighbouring hospitals recruiting	Some inconsistencies: no other post-operative comparison studies included so difficult to estimate effects. Wide inclusion otherwise.	Some uncertainties: directness to this population but small sample size

			Secondary outcomes more likely to be affected by inconsistencies (e.g., co-morbidities data collected by not incorporated in analyses)	
Soni et al. (19).	Q, des, Ob	No serious limitations: systematic random sampling of participants and villages	No serious inconsistencies: age and gender detailed but confounders not considered (not objectives of this study)	No serious uncertainties:
Soni et al. (20).	Q, des, Ob	No serious limitations: large sample, random sampling, and allocations	No serious inconsistencies: any differences between age and gender and communities, accounted for by matching eligible participants until saturation	No serious uncertainties: more generalisable due to efforts taken to recruit random samples and age stratify within age and gender stratums
Tarakji et al. (21).	Q, des, Ob	Some limitations: single centre, small sample	Some inconsistencies: age restriction >18 years and ≤75 years excludes the older years who have a high-risk of AF. Effective for its purpose and study design	Some uncertainties: comparable to this intervention group (AF ablation) but no other studies in this review screening this sub-population

Table 6b. Grading and quality of evidence assessment.

Study	**Recommendation grade** Grade 1 Strong Grade 2 Weak	**Quality of evidence** A Low B Moderate C High
Chan & Choy (12).	1	B
Chan et al. (13).	1	B
Desteghe et al. (14).	2	C
Evans et al. (15).	2	B
Halcox et al. (16).	1	B
Lown et al. (17).	1	C
Lowres et al. (6).	1	B
Lowres et al. (18).	2	B
Soni et al. (19).	1	C
Soni et al. (20).	1	C
Tarajki et al. (21).	2	B

5.5 Ethical considerations.

Limited ethical detail was provided throughout the eligible studies. Chan and Choy, Evans et al. and Lowres et al. explained that consent had been sought from participants and that the research had been granted ethical approval (6,12,15,18). Only one study reported that all data was anonymised (15). Evans et al. provided a statement of ethical compliance stating consent proceedings, regulations of medical ethics and anonymity (15). Ethical considerations were incorporated within some checklists used for reporting systematic reviews, yet this detail was omitted from many publications. The complexity around systematic reviews includes the use and reporting of data intended for the primary research only. If the use of data is for a similar purpose, this poses less of a threat (e.g., if the primary study was concerning a screening tool and the objective of the systematic review was to explore types of screening tools). But if authors are contacted for additional unpublished detail (e.g., further details from the study participants that may not have been the primary

objectives), caution must be applied so this does not affect anonymity assured to participants.

5.6 Assessment of bias.

Assessment of bias in the reviewed studies (*Table 7*) has been guided by the Cochrane Handbook of Systematic Reviews of Interventions (33). Selection bias relates to studies that incorporated smaller numbers and the omission of accurate power calculations failing to offer statistical representation. The only studies that provided sample size calculations were Halcox et al. (16), Lowres et al. (6), Soni et al. (20) and Tarakji et al. (21). The speciality outpatient clinics and cardiology and geriatric wards will likely have involved patients with confounding risk factors, that could lead to imprecision over results. Patients who attended health screening days required voluntary participation and this could therefore bias outcomes according to the demographics of patients attending, localities, timings, and publicity.

Sequence generation and randomisation also relates to selection bias and some studies incorporated randomisation within their studies (16,19,20). Simple 1:1 randomisation was performed in the study by Halcox et al. for those who fulfilled inclusion criteria (16). Soni et al. strengthened the external validity of their studies by employing probability sampling, encouraging representative sampling and enhanced generalisability to the target population (19,20). Bias is more likely in the study by Chan and Choy whereby people volunteered to participate, and in the hospital or clinic-based research whereby patients were simply recruited if they fulfilled eligibility criteria (12).

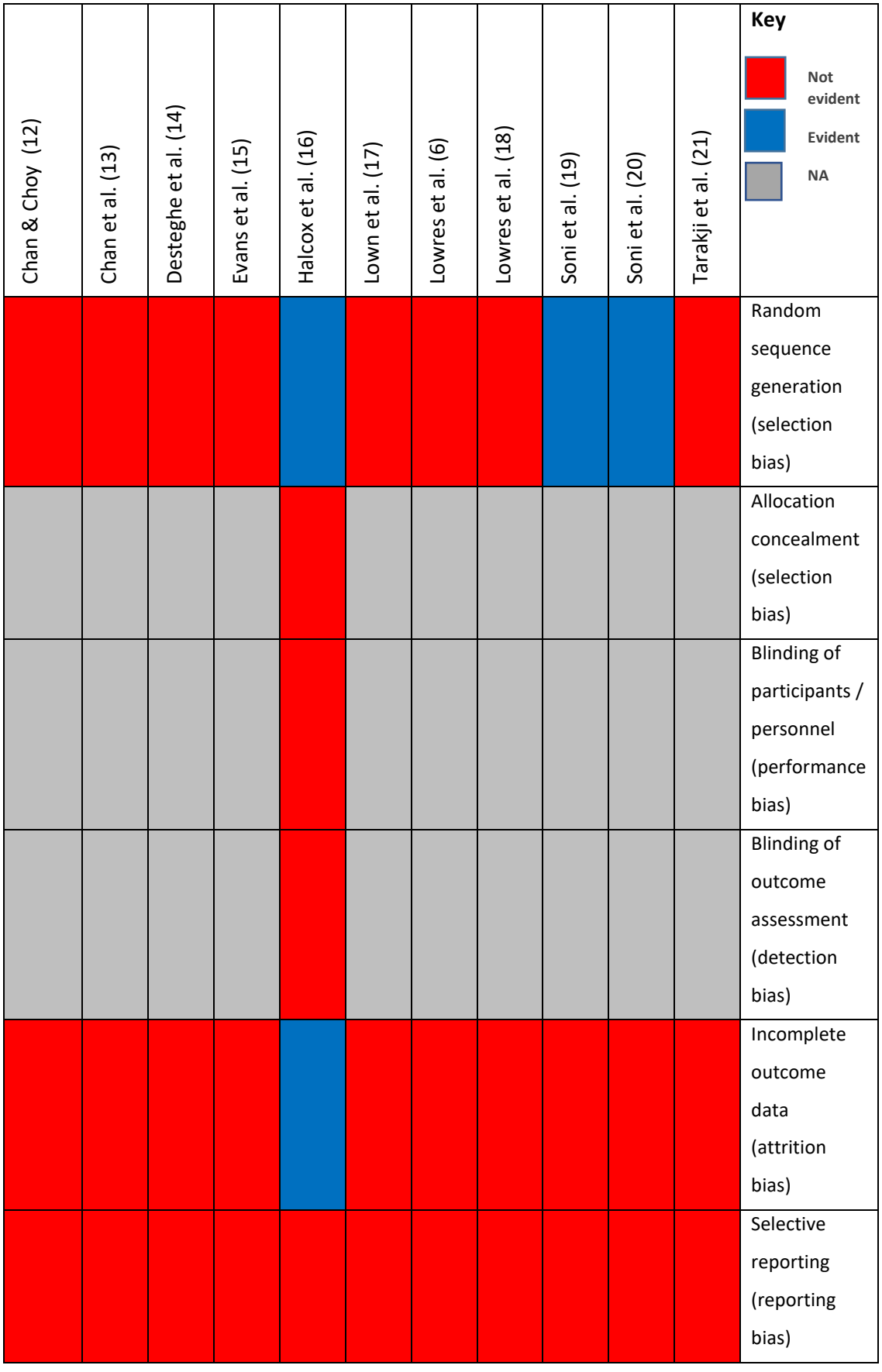
Information bias was less of a threat due to the validation of ECG applications. Ensuring studies are conceptually well planned can be evident through the use of pilot studies or detailed protocols, some of which were available in earlier publications and therefore limiting information bias (16,34,35,36,37).

Unmeasured confounders may also impact on results, for example, in the study by Evans et al., where the co-existence of additional comorbidities could have influenced outcomes (15). Although the medical history of the patient was taken, this was not factored into the analysis. This risk can be minimised by restricting inclusion criteria.

Furthermore, regression models were not used: potential confounders could have been incorporated into such the models as explanatory risk factors. This was however evident in the studies of Chan and Choy and Halcox et al. but represents bias within the results of the remaining screenings for AF (12,16). Some disease groups infer an increased risk of AF such as hypertension, heart failure, diabetes, and stroke (37,38). Older age groups, e.g., over 65 years and men also represent higher prevalence of AF, and this was not always factored into the analysis of results (28,39,40).

As the only randomised controlled trial within this review, the study by Halcox et al. was assessed for additional risk of bias in accordance with experimental trials (16). The importance of blinding of participants and outcome assessments is highlighted and whilst the study team employed randomisation via an external tool, non-blinding was evident. Indeed, the study team comment that close contact was maintained with participants, and this was more so in the intervention group, inferring a higher risk of bias. Furthermore, the authors recognise that their inclusion of allowing only people who could access the internet, and those who could use the device, likely excluding a proportion of those at high risk, and therefore selection bias.

Table 7. Risk of bias summary.



6. Discussion.

This study is the only systematic review that we are aware of that has specifically focused on the AliveCor® device as the screening tool for AF detection. This has enabled critique of the device in terms of effectiveness, utility, feasibility, and accuracy. As AF is the most common arrhythmia, this selectivity also enables further clarity by removing alternative arrhythmias and preventing confusion over accuracy of findings. Synthesis of the findings support the AliveCor® device as a convenient, valid, and effective tool for AF screening.

AF screening using the AliveCor® (the utility of the device for AF screening and clinical effectiveness).

Early diagnosis of AF provides the opportunity for early initiation of treatment, anticoagulation to reduce stroke risk and to reduce complications and hospital admissions associated with AF, and so an early screening tool could have a significant impact on both healthcare costs and quality of life. Screening tests should be low-risk, cost-effective and use accurate methodology to be worthwhile. The success of a screening strategy depends on prevalence and incidence of the condition in the screened population and accuracy of testing but use of known risk factors in identifying people who would benefit from screening is suggested to be effective and has also been demonstrated in this review. AF is multifactorial but ageing, prevalence of obesity and sedentariness are highly contributory (41,42,43), with age demonstrated as the strongest predictor of AF. A screening cut-off of ≥65 years has been recommended, on the basis of expert consensus (37,42,43), and this is supported by the prevalence of AF in the reviewed papers that specify older age in their screening studies.

Since its inception, the AliveCor® device has been used widely in clinical research and practice by health professionals and patients. Digital health technologies have changed health screening practices, not least within cardiology (44). The AliveCor®

device provides opportunities to be used as a single-point-in time screening tool or used repeatedly for intermittent screening, demonstrating the utility of the device. The latter can be initiated during times of symptoms experienced by the user, or at regular intervals as instructed by the researcher or health professional, as demonstrated in this review. The duration of monitoring has shown congruence with AF diagnosis and studies have previously demonstrated the effectiveness of single screening episodes in detecting AF (44,45). The largest systematic review combining data from thirty cross-sectional studies identified undiagnosed incident AF in low numbers, with identification being marginally higher in those aged ≥65 years, using single point in time ECGs via the AliveCor® device (46). Hence, this study has demonstrated that whilst using only brief singular recordings, AF can still be detected in significant numbers, most convincingly in older aged cohorts or those screened from higher-risk populations. However, the cost-effectiveness and appropriateness of screening people aged ≥18 years would be questionable in terms of low numbers and the value this would bring when resources, time and workload is considered (and further evidenced by the lower numbers of AF detection in corresponding studies in this review where age was not an exclusion to screened participants).

Previous studies have demonstrated enhanced AF detection by intermittent or continuous monitoring, suggesting that paroxysmal AF may be missed by single recordings. However, a systematic review of single point in time screening to identify unknown AF, demonstrated this still as an effective approach with slightly higher numbers of AF diagnosed in the older age groups (>65 years), supporting the evidence extracted from the papers within this review, where AF was seen in older populations (47). In the AF screening study by Svennberg et al., (28) twice-daily ECG recordings were made for two-weeks, and this proved slightly more effective in terms of AF detection rates. Their approach also highlighted the relevance of repeated recordings, evidenced by more AF being diagnosed on subsequent ECGs and this is also supported by findings within this review.

In this review, five studies adopted a protocol of intermittent monitoring using the AliveCor® device. Soni et al. identified AF in low numbers, but the majority were diagnosed on their first ECG (20). A similar study also implemented repeated screening over consecutive days and there were higher numbers of AF diagnosed (19). Repeated, intermittent recordings were also requested in Halcox et al. (16) and Lowres et al. (18) studies, the latter also requesting symptomatic activation. This therefore supports the use of intermittent ECGs where paroxysmal AF may be missed by single recordings, yet this approach relies upon the compliance of the individual to independently activate the device without supervision and make clear ECG rhythm recordings for analysis.

Screening approaches.

Screening approaches continue to be debated with strategies generally aligning with opportunistic or systematic screening (48-52). Both opportunistic and systematic screening increases the rate of detection compared to routine practice, but systematic screening is more expensive (48). Screening approaches varied across the studies within this review, including population-based screening akin to mass screening (13) and more focused screening, identifying higher-risk participants according to age (6,9,16,17,19,20) and the existence of co-morbidities (17). A correlation was seen with higher numbers of people having AF in the groups where the screening protocol was more targeted e.g., when the screening took place in hospital wards housing cardiology and geriatric patients (14) and where recruited participants had undergone cardiac surgery (6). Age was not always a factor as AF detection and prevalence rates varied across the studies where participants were recruited from older age categories. Furthermore, a systematic approach whereby studies incorporated intermittent or repeated screening, produced mixed results. However, the lack of homogeneity across reviewed studies here makes further comparisons more difficult as study locations, participants and eligible criteria varied.

This review has demonstrated a targeted screening approach to be more effective in AF screening studies. Screening approaches have been further explored in The Screening for AF in the Elderly (SAFE) study, this being landmark research comparing three strategies of AF screening in the over 65-year age group in primary care (49). Systematic screening of the target population with 12 lead ECGs was compared to opportunistic screening using pulse palpation in a target population by GPs and routine care. Opportunistic screening was more effective than routine care and more cost effective than systematic screening. Improvements in detection and subsequent care in the opportunistic screening group were also noted (49). However, Moran et al. added that systematic screening had higher uptake with a third of those screened opportunistically not attending for follow up (48). The Cochrane Collaboration analysed randomised controlled trials focusing on AF detection in over 65-year-olds, drawing similar conclusions to the SAFE study (48). The NNS in systematic screening was compared to routine practice and was marginally higher for systematic screening compared to opportunistic screening. There is further evidence showing an equivocal number of patients identified with either systematic or opportunistic screening over routine care (49-51), again supporting the findings from this review whereby screening approaches revealed more AF when screening was targeted to specific patient groups (older age, co-morbidities, inpatient, and cardiology localities).

In this review, evidence from screening cost-effectiveness modelling highlighted that screening strategies are less cost-effective in under 65-year-olds and those over 80 years, but still remain within acceptable limits (6,28,29). The studies within this review, whilst not selected for their cost effectiveness analysis, did provide details within two reports. They supported screening using the AliveCor® device, demonstrating cost effectiveness, but it is accepted that this was only critiqued in detail in one study (16). Furthermore, the cost of an AF related stroke is estimated to be significantly greater than a non-AF related stroke from a health outcome, economical and societal perspective (53). Background evidence has illustrated that AF related strokes are associated with an increase in inpatient costs compared to strokes unattributable to AF (54-59). Studies incorporating rehabilitation periods of recovery represented a significant increase in costs in AF stroke patients compared to non-AF

related strokes (54,58). Ali et al. estimated an adjusted independent effect of having AF on costs as an additional £2173 (53). Longitudinal studies estimated the costs of an AF related stroke to be considerably more at one year and similar findings were evident in the Berlin Acute Stroke Study (60,61). This is supported by a study focusing on the economic impact of AF-related stroke as well as a Swedish study whereby AF-stroke patients were followed for three years (62,63). These findings also demonstrated cost increases compared to non-AF related strokes.

Screening acceptability (considering the feasibility of the tool in wider research and clinical practice).

The feasibility of the AliveCor® device as a tool of choice in wider research and clinical practice is an important consideration when contemplating optimal screening approaches. The ease of use, immediate visualisation of the ECG and comfort have been rated favourably in this review and associated research. Within this review, the AliveCor® device was also rated the tool of choice and easier to access when compared to a transtelephonic monitor for making symptomatic recordings (30). Feeling empowered and having peace of mind and reassurance through self-initiated monitoring and feedback was also reported and supports the users' acceptance and willingness to comply with remote mobile monitoring devices (18). Patient education on how to use the AliveCor® device varied in the studies reviewed, from simple instruction incorporating up to ten minutes of tuition and practice to twenty minutes of guidance for those less familiar with smartphone or mobile technology. Importantly though, the less comfortable people were not deterred from using the device nor did it impede their ability to self-monitor. The mode of transmission, unlimited time of use, control of activation, societal adaptation to smartphone technologies and compliance, even when unsupervised, further supports the AliveCor® device as a feasible tool of choice in AF screening (17,18,20).

Patient perceptions were predominantly discussed in terms of device feasibility, but physician assessment was also shown to be important. Evans et al. surveyed physician

opinion relating to device access and internet connections in a remote setting and summarised this as a feasible tool for AF screening in a low-resource setting (15). Outside of this review, Godin et al. screened participants in Canadian Primary Care clinics and surveyed physicians relating to the clinical value, implementation, satisfaction, confidence, diagnostic ability, and accuracy of the AliveCor® device (64). Clinical value, ease of integration and likely acceptability from patients were rated most highly, further supporting the findings within this review.

Furthermore, the AliveCor® device has been used in disparate research designs including large community screening programmes and more focused high-risk groups. Populations have therefore been heterogenous with varied clinical, anthropometric, sex, age and geographical characteristics, thus, demonstrating the utility, feasibility, and wide applicability of AliveCor® as a screening tool, be it via an opportunistic or systematic approach.

Screening accuracy (how valid is the tool for AF screening).

The AliveCor® device incorporates an automated algorithm for the detection of normal or abnormal rhythms and accuracy of this has been analysed widely. The AliveCor® device has been awarded the accolade of being the most clinically validated screening tool (65). Most of the studies critiqued within this review, demonstrate high sensitivity of the device at >98% with similarly high sensitivities in research outside of this review of >90% (6,21,66,67). Lower sensitivities appeared related to the automated algorithm interpretation and once checked by a specialist, improved. Furthermore, sensitivities may be less favourable when troubleshooting is not optimised, for example, patients with a tremor or who are unable to hold the device securely can produce a less clear ECG recording. The AliveCor® device can be applied to the bare chest if this is a problem, but this does not always appear to be stipulated in the research. The exclusion of patients with a cardiac pacing device should be applied due to inaccuracies affecting automated interpretation. Specificity has also been reported highly with figures representing >99% (5,66,67,68) although this review

did also uncover lower specificity in one study (12), and specificity was unreported in four of the reviewed studies (15,16,19,20).

Further evidence continues to support the accuracy of the AliveCor® device as a screening tool both from research within and outside of this review, demonstrating favourable validity most notably after the exclusion of 'unclassified' recordings. Findings from this review are further illustrated by a supporting accuracy study by Koshy et al., where enhanced sensitivity and specificity (>95%) were demonstrated after removing uninterpretable ECGs (69). Similarly, William et al. calculated comparable sensitivity and specificity but note a quarter of ECGs recorded by the AliveCor® device were classified as 'uninterpretable' (70). No further information was provided on the uninterpretable ECGs regarding methodological reasons for this, just that participants were asked to place at least one finger from each hand on the electrodes. Brasier et al. also report a number of 'unclassified' ECGs and once removed, resulted in optimal sensitivity and specificity (71). Detail on whether steps were employed to improve ECG transmission were lacking, simply stating that the index finger and middle fingers were placed on the electrodes. Positioning of the AliveCor® device, tremor or stability of the device were not detailed. Diagnostic accuracy improved when AliveCor® ECGs were reviewed by practitioners experienced in rhythm analysis, compared to relying on the automated interpretation, in the studies examined in this review. This emphasises the relevance of having practitioner oversight when patients use such devices but should not deter patients from initiating use of the AliveCor®, but ensure they seek clarification over unclassified recordings. The interpretation of accuracy statistics must be appraised with caution and considered in terms of how this is presented. The frequency of unclassified or uninterpretable ECGs is significant when considering usability, as the necessity for additional adjudication when automated analysis has been non-diagnostic, imposes an additional workload on skilled health professionals required to further analyse the ECGs.

6.2 Limitations of included studies.

Limitations of the included studies include the lack of homogeneity between study protocols and the differences therefore between screening methods. Some focused on obtaining a single-point-in time ECG where other studies required repeated screening and over a varied length of time. This had an impact on the different rates of detection of AF and the likelihood of accurate identification. The AliveCor® device was operated by participants in some studies, with supervision or fully operated by research teams in others. Experienced practitioners would have more insight in terms of trouble-shooting poor transmissions and may be able to produce enhanced recordings. Populations also differed in terms of geography and clinical groups. India, Africa, Hong Kong, Australia, and the United Kingdom encompassed the countries within which AF screening studies were undertaken, all with diverse epidemiology and health status. Whilst this is not a limitation as such, it is noteworthy that the different locations and populations within these studies contributed to the heterogeneity between the research, leading to some differences in findings.

The coexistence of chronic disease, age and sex also differed. For example, some patient groups were targeted because of their co-morbidities (including older age), whilst other studies with fewer exclusion criteria, included younger participants who might have been less likely to have associated chronic disease. Eligibility criteria was set for older age groups in some studies but again this was not consistent among all eligible studies in this review. Some research was undertaken in the community, primary or secondary care. Community screening programs operated in pharmacies, community halls and GP practices. Hospital based recruitment took place in cardiology wards, general wards, geriatrics, and outpatient clinics, leading to higher numbers with a diagnosis of AF. Overall, these variabilities influence the patient groups recruited and the varying health status of participants may have impacted on outcomes e.g. where chronic disease and older age predominated, higher incidence of AF could result and this may not be truly representative of the population.

The analysis of ECGs from the AliveCor® device was diverse with some studies relying on the automated algorithm and others employing interpretation by the study team. There was however consistency between further analysis of abnormal ECGs by specialists within the teams.

A final limitation is that the populations within which the AliveCor® device was used may not always reflect the general population for which the device is intended and must be considered when applying results to the real-world. The context within which the devices were used for monitoring purposes must be considered when evaluating overall validity and suitability for the screening purpose.

7. Limitations and Recommendations.

7.1 Limitations of this review.

The PRISMA statement (www.prisma-statement.org/) and The Cochrane Handbook for Systematic Reviews of Interventions have been used as reference throughout this review, to ensure a methodical and rigorous approach (72). Cochrane suggests an international collaborative approach, not restricted by nationality or language and this was reflected in the inclusion criteria of this review. It is however accepted, that additional studies may exist that did not fulfil eligibility criteria. Results were presented through addressing the primary objectives and secondary questions, with overall outcomes summarised in accordance with effectiveness of the AliveCor device as a screening tool for AF detection in screening studies.

The limitations to overall findings from this review centre around the lack of homogeneity between study protocols and methods. Whilst the overall theoretical principles and study objectives have similarities (e.g., the studies are looking for AF using the AliveCor® device), the disparity between geographies, localities and

populations and screening protocols, results in difficulties when summarising such heterogenous studies. This does however demonstrate that the AliveCor® device is a tool of choice amongst diverse communities.

7.2 Recommendations.

National guidelines on AF screening suggest pulse palpation followed by an ECG when the pulse is irregular (4). NICE have also produced focused guidance on using the AliveCor® device as a tool of choice for AF screening (73). The European Society of Cardiology (ESC) 2016 guidelines and recommendations for AF screening suggest AF screening be undertaken opportunistically in >65-year-olds via pulse palpation followed by an ECG rhythm strip if indicated (42). The current UK National Screening Committee recommendation on AF screening in adults does not recommend systematic population screening despite acknowledging the benefits from doing so. They state there is a lack of evidence relating to the effect of treating people with AF identified through screening, so report no benefit (74). Conversely, a report by the AF-SCREEN collaboration, promotes world-wide implementation of screening for AF in all >65-year-olds (3). This review has shown that the AliveCor® device is an effective tool, evidenced widely through the findings within research undertaken utilising this mobile ECG device. Further research would be advantageous whereby methods of screening and protocols are more homogenous. Screening matched participants as in the randomised controlled trial by Halcox et al. provides the opportunity to identify the effectiveness of the AliveCor® device compared to either standard care or alternative screening devices (16). The majority of research involving the AliveCor® device has adopted an observational focus using cross-sectional design and this is not dissimilar to the design often implemented in arrhythmia screening studies.

It would seem appropriate following the findings from this review, to support age group screening where AF is more likely to be detected. Targeted screening of higher risk patient groups would also seem sensible, yet we must acknowledge that AF can still occur despite the absence of high-risk co-morbidities. Whilst repeated monitoring using the AliveCor® device has demonstrated favourable outcomes in terms of AF

being diagnosed on subsequent monitoring (e.g., not on the first AliveCor® ECG recording), this is more resource intensive and not always as feasible. Single-point-in-time use of the AliveCor® is still advantageous when screening opportunities present. Healthcare practitioner oversight is advantageous but the AliveCor® device is designed to be used by patients independently and offers the ability to self-record ECGs without professional involvement. Ensuring the patient knows how to refer on when unclassified ECGs are displayed, is important, and this can be through the availability of the interpretation service within the AliveCor® device or through external sources.

8. Conclusion.

In the growing digital health technology era, revolutionary tools allow new methods for screening including within cardiology for rhythm analysis. AF is growing in prevalence with a worldwide burden impacting on our increasingly ageing population, further affecting health outcomes, morbidity, and mortality. This impact is not only health related but has economical and societal bearing. The AliveCor® device offers a mobile, validated, and secure option for heart rhythm screening and is feasible for both patients and health professionals to use in hospital and the community. Evidence demonstrates effectiveness of the AliveCor® device as a screening tool in terms of validity and accuracy. This brings wider benefits in relation to early identification of AF, such as protection against thromboembolism when anticoagulation is initiated. Advancements continue within this field, with AliveCor® developing enhanced algorithms and modified wearable devices, with different lead configurations, offering the consumer more options in terms of suitability and selection.

AF is a condition that can benefit from screening and should remain a key focus within national screening programmes due to the significant burden this brings to patients, society, and healthcare. There are a number of tools designed to assist with AF detection, with the AliveCor® device offering a convenient and effective option. A mobile device that provides a platform for both the health care provider and patient

initiation supports screening programmes through its accessibility. This should however be considered alongside appropriate patient selection to optimise acceptability and accuracy, particularly if used independently, without healthcare practitioner involvement. Further analysis of ECGs may be required and contemplated when selecting the most appropriate tool. Furthermore, the AliveCor® device can be used in low-resource and diverse locations, demonstrated through the heterogenous studies included within this review.

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Chapter 3.

Methodology.

3.1 Introduction.

This chapter will examine the chosen methodology for the studies, along with the strengths and weaknesses therein. The aims and objectives of these studies will be discussed. The directional relationship between ontology, epistemology and methodology underpinning the research will be demonstrated. The broad theoretical basis of the research questions will be considered as it is recognised that research questions commonly direct towards the paradigm underlying the methods that will be appropriate to address the research question (Gough, 2015).

The focus for this research originates from an aspiration to explore the association between diabetes (type 1 and 2) and AF and whether diabetes increases the likelihood of developing AF. This information is useful from a public health perspective on disease prevalence and comorbidities and the associated detrimental outcomes that can result from these chronic conditions. Any negative impact can potentially be reduced by identifying through screening, people with AF and diabetes, with the aim to reduce compromise to QoL and overall health consequence through early treatment and advice. This interest originates from clinical practice and real-life experiences with significant patient numbers presenting with both chronic conditions together. There is variability relating to the connection between AF and diabetes, which may be attributed to a lack of homogeneity between study designs, methods, and analyses. AF prevalence has been explored in epidemiological and screening studies and outcomes have demonstrated varying prevalence data in this patient group. This variance, however, is complicated by the inclusion of mixed comorbid disease and not including patients with diabetes as the only targeted population. Findings therefore affirming or disregarding a connection between AF and diabetes within existing literature may therefore not be entirely representative to the diabetes group. Furthermore, the pathophysiological connections have revealed divergent

theories, with debate over a causal or correlational link suggested between AF and diabetes (see *section 1.1.1 and 1.1.2* and *Figures 9 and 10*) (Sun & Hu, 2010).

3.2 Aims, research objectives and the research questions.

Over-arching research question:

Should we be screening people with diabetes for atrial fibrillation?

Based on the overarching question, three studies were designed to answer the specific research questions set out within each study and include both quantitative and qualitative approaches. A research study (*Study 1, Chapter 4*), whereby people with diabetes are screened for AF, incorporates gathering of comorbid, demographic and health related data to determine predictors and prevalence of AF in this population. This study uses statistical analyses to answer the hypotheses. A study examining QoL (*Study 2, Chapter 5*) aims to determine if there is a difference between QoL scores across physical, emotional, and social health domains in people with AF and then people with both AF and diabetes. In this quantitative study, patients complete the respective survey [SF-36]. Responses are analysed adhering to guidance by the developers of the survey, followed by statistical analyses to answer the study hypothesis. A third study (*Study 3, Chapter 6*) adopts a qualitative, interview design and explores patients' views and understanding of AF, AF screening and the AliveCor® device used in the AF screening study. This provides a different perspective to the quantitative studies, thus adopting a mixed-methods approach. The combination of these studies aims to enhance comprehension around the coexistence of these two chronic conditions, whilst contributing towards recommendations around AF screening practice.

3.3 Research philosophy.

Ontology is the starting point of research, and a fundamentally important concept in the social sciences (Grix, 2002). Ontology is logically followed by the researcher's epistemological and methodological positions. The interrelationship between these building blocks to research are summarised in *Figure 6*.

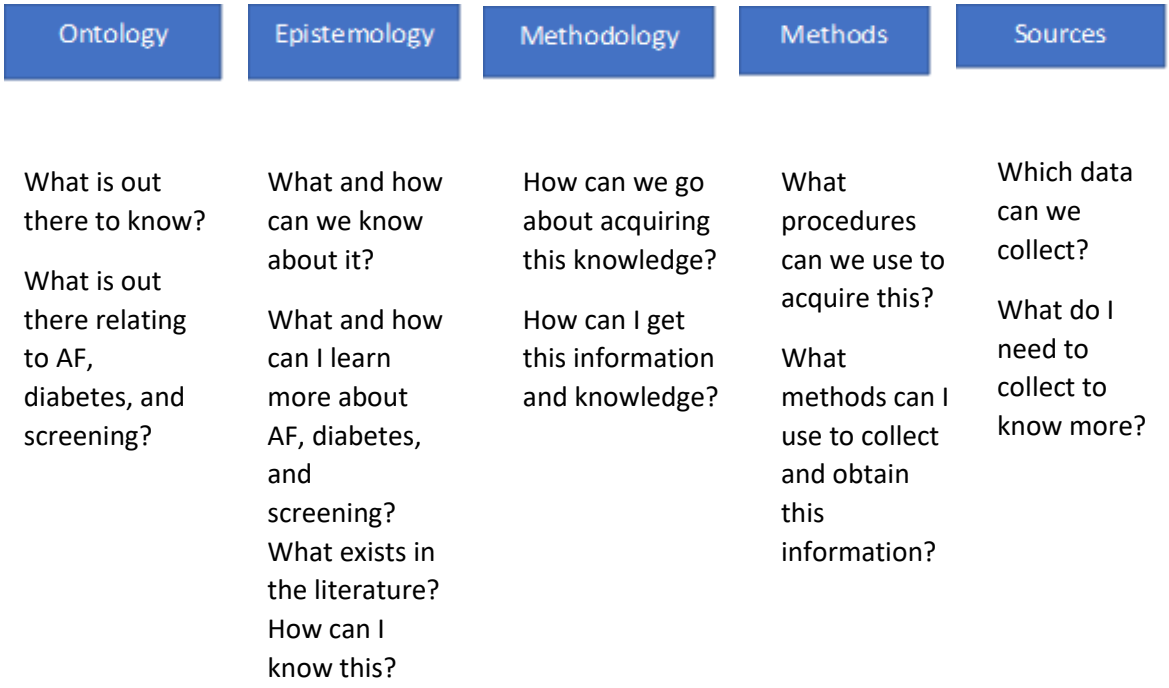

Figure 11.

The interrelationship and building blocks of research *(Adapted from Grix, 2002).*

The ontological viewpoint underpinning this research in *Study 1* (*Chapter 4*) and *Study 2 (Chapter 5)*, relates to positivism. This philosophical approach suggests that science is the only way to learn the truth with the research philosophy defining how data are collected and analysed (Žukauskas, Vveinhardt & Andriukaitiené, 2018). Factual knowledge is gained through measurements and these observations are trustworthy and valid (Dudovskiy, 2016). Positivist studies usually adopt a deductive approach

described as purely objective with minimal interaction (Dudovskiy, 2016). Deductive reasoning is normally based on a hypothesis (e.g., *if* duration of diagnosis is a significant predictor of AF, controlling for age, *then* duration rather than mere existence of diabetes is the risk factor). Screening for AF in a population with diabetes, aims to explain and predict. Where the data support this, the theory is supported (e.g., the theory is that diabetes increases the risk of developing AF). This approach is therefore contrasting to one where new theory is based on observations and generated using an open ended, exploratory approach (inductive). Survey based research within the QoL study (*Study 2, Chapter 5*) also follows this paradigm through the quantitative gathering of data from the specified population. It is however, anticipated that interpretation of observations in data generated through this research could lead to the development of new knowledge, therefore adopting a circular approach whereby deduction and induction are complimentary.

Whilst *Studies 1* (*Chapter 4*) and *2* (*Chapter 5*) align with a positivist approach, appreciation of theoretical principles underpinning alternative philosophies is necessary, to ensure an appropriate and considered approach to the study design. The values and beliefs of the researcher can have significant impact on the subsequent research. There has been a paradigm shift in medical and nursing research from the traditional quantitative design to inclusion of qualitative methods, narrative commentary, and mixed methods (Gough, Thomas & Oliver, 2012). Statistical evaluation has dominated through review of health and social interventions but Noyes, Popay, Pearson, Hannes & Booth (2011) recognise the important introduction of alternative methods which may contribute to addressing complexities of interventions. This is entirely representative of the value that both qualitative and quantitative methodologies bring to research and evidence-based medicine when considering the physiological, behavioural, psychological, and social aspects of AF management. This is multifactorial and cannot be evaluated in terms of outcomes by an objective measurement alone, for example, heart rate. Effects on left ventricular function require quantifying and this often dictates intervention. Similarly, patient symptoms require exploring along with treatment concordance, patients' experiences

and understanding in order to comprehend biopsychosocial approaches. Only then can we develop an understanding of the overall impact of AF. Helmer, Blumenthal and Paschen (2020) support this notion that not all information is reducible to means of measurement. Appreciation of alternative methodologies is therefore valuable in terms of supporting the quantitative science through comprehension of the effects of disease by facilitating feedback on behaviours and influences beyond measurable and statistical elucidation. *Studies 1* (*Chapter 4*) and *2* (*Chapter 5*) apply objective methods to answer the study aims and objectives but incorporating a qualitative study (*Study 3, Chapter 6*) is important for the gathering of information relating to participants' views and experiences of heart rhythm screening via semi-structured interviews.

The aim of the screening study (*Study 1, Chapter 4*) is to determine whether screening people with diabetes as a targeted population for AF is warranted and beneficial. It is therefore concerned with gathering objectively measurable data, with outcomes including the diagnosis of AF, determined by the presence or absence of the arrhythmia through ECG documentation. The notion that this is less influenced by 'social actors' has been considered, but it is accepted that many measurements are affected by external stimuli (accelerated heart rate due to stress, pain, or exertion). Whilst the AliveCor® device reveals a real-time ECG recording which cannot be manipulated, simply the selection of this tool rather than comparators, and the algorithms built within for aiding analysis, all contribute to the measurements and outcomes generated. So, whilst facts are uncovered and accepted as reality, explanations as to why and how things happen are justifiable through the application of correlation, measurements, and verification (Punch, 2005). Research concerning a medical diagnosis of AF cannot be construed by multiple interpretations of reality, this is simply by measurements and analysis of an ECG. It is accepted however, that people present with varied symptomatology representative of the arrhythmia that could be discussed in a qualitative-type approach. But whilst symptoms may be suggestive of AF, without ECG documentation, it is against the current medical model to make this diagnosis.

However, the belief that researchers can be purely objective is contested by supporters of post-positivism; reality cannot be entirely independent of the

experience, according to Khanna (2018). Observations gathered this way cannot be relied upon as they are subject to error and pure objectivity is impossible due to bias from cultural beliefs and experiences (Corry, Porter & McKenna, 2019). It is, however, anticipated that the quantitative studies were impacted upon minimally by personal goals or beliefs and the studies were designed in such a way as to minimise this. Nevertheless, the impact from a professional perspective as a cardiac nurse specialist will have influenced this research, as it was from this clinical inquisitiveness that resulted in the exploration between AF and diabetes.

Positivism is aligned with the empiricist view that knowledge stems from human experience and that observation should be the means of gaining new knowledge, not opinions or actions as for rationalists (Ryan, 2018). Knowledge is not static, and researchers need to be open and transparent to new ideas. Appreciation of complimentary approaches to gaining new knowledge, encourages wider acceptance and avoids being 'black boxed' into accepting existing approaches to knowledge growth. The notion that no single viewpoint can fully explain the subject of enquiry is supported by proponents of critical realism. Critical realists wonder how we can be sure of reality with certainty; post-positivist critical realists propose all observations to be fallible with error and it is all revisable. They therefore advocate triangulation as an approach to strengthen study outcomes through application of multiple measures and observations (Noble & Heale, 2019). And hence the application of three independent yet related studies, designed to enhance understanding around AF and diabetes through screening for AF prevalence with consideration of comorbidities, demographics, and their effects, alongside QoL of participants when these conditions coexist. This is enriched through the gathering of individuals' lived experiences of AF screening via interview feedback (*Study 3, Chapter 6*). This exploration adds to the data and more explicitly, triangulation of the results from these studies, guides, and informs recommendations around AF screening. In particular, triangulating QoL measurements with lived experiences from interviews of how the diagnosis has affected the participants, provides enriched data through combining research methods to validate findings.

Study 3 explores lived experiences of participants from *Study 1*, who were diagnosed with AF during their screening episode. Their views were explored through semi-structured interviews and this inductive approach enables theories to be generated from the research (as opposed to a deductive approach with positivism which is intended to test existing theories and guide the research with hypotheses via logical reasoning). Themes that emerged from this research help develop and enhance our understanding of the human element and behaviours around screening for disease. The generation of potential theories relating to screening preference and behaviours helps to develop ideas which can then be re-tested in practice. This oscillation between testing emerging theories, collecting data, and further developing theories, demonstrates the complementary nature of combining research strategies and reflects the growing maturity around research paradigms.

The ontological position linked to the qualitative research in this study, is described as constructionism. This implies that social properties are outcomes of interactions between individuals and the human world and are socially constructed and in a constant state of revision, rather than a phenomenon that is 'out there' (Bryman, 2008). Ontological constructivism claims the 'knower makes the world', that certain objects do not exist independently of the mind and rather are constructed by the mind, rather than discovered (Noyes et al, 2011). This position has been described as destructive, even lacking credibility as tests aiming at checking whether a hypothesis matches the facts it refers to, are dispensed with. Constructivism can also be cognitive, and the epistemological position shares some related characteristics and approaches to research with interpretivism. Here, participants' examination of the world leads to an interpretation and understanding of that social world (Bryman, 2008). Interpretivists believe in multiple realities and respect the subjective meaning of social action (Taylor & Medina, 2011). Consequentially, they understand social phenomena and interpret this further. Constructionists propose that knowledge is built through interactions between individuals and the real world and thus, knowledge is built socially. A single methodology to generate knowledge is opposed and it is felt that knowledge must be approached from multiple perspectives (Noble & Heale, 2019). This contrasts with the positivist approach where there is an emphasis on

explanation of human behaviour, rather than the *understanding* of human behaviour in social sciences.

The integration of qualitative research makes this thesis mixed methods, generating a principled, complimentary approach beyond one methodology. Mixed methods research [MMR] offers a flexible and adaptive conceptual framework for designing and conducting increasingly complex requirements of contemporary researchers. MMR elucidates several benefits through the integration of post-positivism and interpretative frameworks (Creswell & Plano-Clark, 2018). These benefits include the ability to combine two sets of strengths whilst compensating for weaknesses of each method. This leads to a greater assortment of divergent or complementary views, enriching understanding of phenomena (Johnson & Onwuegbuze, 2004). MMR can also help overcome the epistemological differences between quantitative and qualitative paradigms resulting in a principled combination of research findings (Lund, 2012). The results may then be more meaningful through the expansion of the study by allowing for greater breadth (quantitative) and depth (qualitative), leading to more rigorous conclusions. This was therefore replicated in this research, through the adoption of the quantitative studies whereby objective data was obtained to answer hypotheses about prevalence and predictors and perceived QoL scores, analysable through statistical testing. Sequentially, these outcomes helped design the follow-up exploration of participants' views, in order to understand more about screening from lived experience, resulting in greater insights to the phenomena around AF, diabetes and screening.

Using mixed methods, guided by the research problem and questions, demonstrates the application of pragmatism, a pluralistic approach that is not committed to a philosophical stance and promotes the application of 'what works' (Creswell, 2007). Forced choices between positivism or interpretivism for example, can be abandoned as pragmatism values objective and subjective knowledge to meet the objectives (Creswell & Plano-Clark, 2018). Similarly, the qualitative and quantitative divide can be eliminated, and this moves some way in ending the paradigm war (Feilzer, 2010).

3.4 Ethical implications of screening for disease.

The ability to screen for disease has progressed with enhanced methods and technology. Screening requires a considered approach, one that is cost-effective and uses an appropriately sensitive tool. Being ethically justified is important and in this scenario, screening for AF is low risk, has a clear benefit and the condition screened for can be managed. Many ECG-based cardiac screening programs exist internationally, usually with the objective being to perform a resting ECG in asymptomatic people for potentially life-threatening cardiac disease (Orchard et al, 2019). Screening for AF has been investigated with the rationale that anticoagulation has demonstrated efficacy in reducing stroke risk in people with AF (Orchard, Lowres, Neubeck & Freedman, 2018; Orchard et al, 2019). Targeted groups and approaches to AF screening varies and whilst it is generally accepted that people aged over 65 years are at greater risk (of AF and stroke because of the AF), recommendations vary. The European Heart Rhythm Association [EHRA] produced a consensus document on AF screening and highlight the importance of targeting the at-risk populations to increase screening efficiency (Mairesse et al, 2017). Screening effectiveness, they advise, depends on the target population, the diagnostic accuracy of screening and cost effectiveness (Mairesse et al, 2017). Opportunistic and targeted screening have been proposed as optimal approaches, compared to mass screening which may yield proportionally fewer cases of AF (Moran, Teljeur, Ryan & Smith, 2016). A report by the AF-SCREEN collaboration suggests worldwide implementation of screening to everyone aged 65 years or over, through a pulse check, handheld ECG device or BP monitoring system (Freedman et al, 2017). Screening that can be facilitated in daily practice, for example, via a simple pulse check during any consultation (GP visit, observations on a ward round, vaccinations) can identify an irregularity that can be validated by recording an ECG. This supports national and European guidance and recommendations by heart rhythm specialists (Hindricks et al, 2021; NICE, 2021).

Ethical issues have arisen as a result of screening for disease, and this relates to the process of screening or specific screening programs (Delatycki, 2012). Autonomy and informed consent are essential when screening for disease and this applies to the

entire process of screening, not just the initial encounter. When taking a patient's pulse opportunistically, the practitioner must inform the patient as to what could result from this intervention. The patient has the right to decide on a course of action with reasonable awareness of what is intended and any consequence (Bryman, 2008; NHS Health Research Authority, 2017). Deontological theory, an ethical theory that uses rules and universal moral laws to distinguish right from wrong, states that we have a duty and an obligation to fully inform patients or participants through honesty and it is immoral to coerce (Misselbrook, 2013). This categorical imperative in accordance with Kantian philosophy, contrasts with the utilitarian approach whereby the 'ends justify the means' (Abumere, 2019). Doing the greatest good for the greatest number defines consequentialism, where the act is morally right according to the consequences or the motive behind the act (Sinnott-Armstrong, 2021). This relates to screening for AF, whereby the process of screening aims to detect the arrhythmia and subsequently, reduce the consequences of missed diagnosis. The motive behind screening is to reduce negative health outcomes relating to AF, if not diagnosed.

Screening should promote the ethical principles of beneficence and non-maleficence, through identification of people with AF which can then lead to appropriate treatment to optimise both physical and emotional health. The act of screening for AF generally conforms to these ethical principles, but 'to do no harm' requires consideration. False-positives and false-negatives can impact significantly in AF screening, through inaccurate diagnosis leading to either missed AF or an affirmative diagnosis that is incorrect. The method, therefore, needs careful consideration and justification to ensure the most appropriate and valid device is utilised with high sensitivity and specificity, and in the correct manner. Practitioner involvement is fundamental in terms of analysing ECGs from screening and has been shown to enhance the sensitivity over automated analysis, making a vast difference in terms of diagnostic accuracy (Chan & Choy, 2017; Davis et al, 2012; Harris, Edwards & Mant, 2012; Svennberg et al, 2015; Turakhia et al, 2015). The lead researcher in the AF screening study (*Study 1, Chapter 4*), is experienced in ECG interpretation, and familiar with the ECG screening tool used. This enabled optimal ECG acquisition, thereby reducing the need for repeated recordings and clarification. Single point in time screening as

undertaken in *Study 1 (Chapter 4*), follows recommendations by most guidelines as opposed to continuous ECG monitoring, which may detect brief episodes of AF of questionable clinical significance (Orchard et al, 2018). However, it is recognised that paroxysmal AF can be missed by a single screening episode and therefore it is recommended that higher-risk populations have this repeated annually (Orchard et al, 2018).

The selection of populations for who might undergo this screening also need consideration in terms of "do no harm". For example, if AF is detected in low-risk groups (good health, younger, without concomitant health problems), their risk of complications such as stroke would be low in accordance with the CHA_2DS_2-VASc stroke risk scoring stratification and therefore would not require anticoagulation to reduce their risk of thromboembolism. They then may experience concern over this new diagnosis, which is not followed up with treatments and therefore, harm may have been caused. Wearable technologies provide challenges in this context as they are often worn by younger patients in whom the risk of stroke is lower in association with AF and may lead to mental anguish over a diagnosis where no treatment is indicated.

Similarly, screening for AF exposes otherwise asymptomatic people to tests and possible treatments which they might not have sought to explore. For example, yielding a diagnosis of AF through screening (irrespective of risk factors), might lead to anxiety, reduced QoL, employment compromise (AF is a notifiable condition for some jobs e.g., HGV drivers) or complications of treatments (Mandrola & Foy, 2019). Anticoagulation would likely be recommended but the patient might not be able to take this which could lead to further stress, knowing they might be at risk of stroke. Therefore, when considering screening programmes, there is a duty to explore all the implications and to demonstrate the potential benefits, before introducing a new screening initiative and the current consensus is that AF screening should be aimed at higher-risk populations (Orchard et al, 2018). This is therefore, explored in the screening study in this research (*Study 1, Chapter 4*) whereby prevalence and predictors of AF in people with diabetes are investigated, to determine if this is a high-risk population warranting screening. This is also investigated through seeking

patients' views around AF screening, having received the diagnosis and experienced the screening process first-hand (*Study 3, Chapter 6*).

3.5 Methods.

The methods used in this thesis are guided by the research objectives identified in the three studies, with the associated research paradigms and underpinning philosophies guiding the design. The following section sets out the justification for the research design used in each of the studies, including sampling, data collection methods and instrumentation and data analysis.

3.5.1 Methods for Study 1, AF screening research.

Research design.

Study 1 (*Chapter 4*) adopts an observational, prospective, cross-sectional study design, where people with diabetes are screened for AF and asked questions relating to their demographics and risk factors. A single point-in-time screening episode takes place, and this is a common choice of study design in AF screening studies (Chan & Choy, 2017; Chan et al, 2018; Desteghe et al, 2017; Kaasenbrood et al, 2016; Lowres, Neubeck, Redfern & Freedman, 2013; Lowres et al, 2019; Proietti et al, 2016; Rivezzi et al, 2020). Screening for AF via a single screening episode is valuable for detecting AF that is persistent or permanent. AF that is intermittent (paroxysmal), may be missed this way, but screening is still justified when considering the diagnostic yield of AF screening by this approach. In the Belgian Heart Week initiative (Proitti et al, 2016), AF was detected in 1.1% of the study population who were 20 years of age and over but up to 5.5% when people of 65 years and over were screened once, by their GP (Rivezzi et al, 2020). AF was identified in 1.4% of people over 65 years of age in another study, with higher prevalence in older age groups and in men across all ages, (Lowres et al, 2019). Of those who were in AF in Lowres et al (2019) research, 84% qualified for anticoagulation, due to their risk factor profile for thromboembolism and stroke. In another study where screening for AF was undertaken with a baseline and then

intermittent handheld ECG recording, AF was seen on the first ECG screening (day one of the screening protocol) in nine of the twenty-three patients identified with AF during ECG monitoring of this type (Hendrikx, Hörnsten, Rosenqvist & Sandström, 2013). It is, however, accepted that longer duration monitoring, be this through repeated screening episodes or via continuous ECG monitoring, could detect more AF. This does require more resources in terms of equipment and time, expense and a different study design that would prepare for patient follow up or tuition to make self-recordings. This was not feasible for this research as this was being undertaken by an individual lone researcher whilst working full-time and conducting this PhD on a part-time basis. Funds were unavailable to purchase additional ECG monitoring devices for patient use and time constraints meant inviting participants back for further screening was not possible. The COVID-19 pandemic also contributed to the time available to recruit and screen patients, along with the constraints of government enforced isolation.

Sampling.

A non-probability approach to sampling, whereby selection is based on non-random criteria, is adopted in the AF screening study (*Study 1, Chapter 4).* Participants with diabetes are invited in two ways. First, those who attend the diabetes centre are invited consecutively to join the research, if eligible for inclusion. Second, participating GP surgeries post a mailshot to patients on their database who have diabetes and then asked to contact the lead researcher for a screening appointment. Pre-arranged lists of scheduled patients' attending the diabetes centre is not permitted as some visits are unscheduled. It is also not possible to have access to the GP database for reasons of confidentiality and therefore, random sampling is not feasible in either location. *Study 1* (*Chapter 4*) adopts a convenience sample, whereby those invited at the diabetes centre are approached consecutively on various days and times the researcher can attend. The varying schedule aims to try and capture different groups of patients on different days (i.e., not purely new patients in the Consultants clinic, but those attending ad hoc or for dietary or podiatry advice). It is, however, recognised that this still does not represent a probability method and can impact on selection

bias, whereby the study population is not entirely representative of the target population to which conclusions are being extended. Patients from the GP surgeries self-respond but it is difficult to generalise findings or consider the entire representativeness as screening by self-initiation may represent the more health conscious and omit those who are less likely to seek healthcare. Health consciousness corresponds to self-awareness about health and wellness and evidence links this with an increased likelihood of seeking preventative health support (Espinosa & Kadić-Maglajlić, 2018). This is supported by evidence linking health consciousness with healthcare engagement and a positive approach to health information seeking (Basu & Dutta, 2008). Three GP surgeries were selected due to their central location and size, therefore reaching the optimal number of eligible patients. Again, various times and days were made available for patients to attend, but working patterns, patient demographics and social reasons (e.g., their ability to get to the screening location, reading the invitation letter, ill health) may interfere with outcome generalisability.

Previous AF screening studies have followed a non-random sampling approach and therefore this is not felt to negatively impact on the sampling method (Godin et al, 2019; Orchard et al, 2019; Wiesel et al, 2009). It is, however, acknowledged that negative aspects of non-random sampling could include sampling bias whereby some participants are more likely to be selected than others. The sample may be less representative of the population through this method and there is a lower level of generalisation of findings (Bryman, 2008). Attempting to overcome potential confounders was addressed through control variables in the regression models used within analyses (e.g., to determine whether the presence of diabetes predicts AF, logistic regression was applied, controlling for age and sex). In this research, whilst the presence of diabetes was known, existence of other comorbid conditions varied and was not factored into analyses.

Local figures suggest 4000 people have diabetes in Jersey, but this does not account for the presumed similar number undiagnosed (Public Health Statistics Unit, 2016). The sample size was calculated using this local data. Factors impacting recruitment here are commented upon in *Study 1 (Chapter 4)*. Further contributing factors may

include recruitment approach, particularly from the GP surgeries as this relies upon the patient making their own screening appointment, compared to the consecutive approach at the diabetes surgery.

Data collection and instrumentation.

Instrumentation within *Study 1* includes the AliveCor® ECG recording device, a blood pressure monitor, weighing scales, height measuring stick and a data collection sheet for the documentation of physiological measurements, demographic details, and risk factors.

It is recognised that the administration of research instruments can impose error and therefore validity of the tool is important (Higgins et at, 2020). Validity and reliability both increase transparency whilst reducing opportunities to insert researcher bias (Singh, 2014). The AliveCor® device is well validated, Conformité Europëenne [CE] marked, Food and Drug Administration [FDA]-cleared and approved by NICE for detecting AF (NICE, 2021; NICE, 2022). This therefore imposes less risk in terms of instrumentation or information bias (Higgins et al, 2020). Validity of research instruments helps ensure the tool is doing what it has been designed to do, enhancing the reliability by correctly measuring the concepts under study. Minimising bias is important as not only are we attempting to make sense of the level of rigour applied, comprehension around the completeness and reliability of outcomes is necessary when contemplating transferability and generalisability to practice. The AliveCor® device was selected due to the familiarity, availability, and effectiveness as an AF detection tool, as demonstrated in the systematic review (*Chapter 2*). The portability, device accuracy and ease of use with patients contributed to the utilisation of the AliveCor® device in the AF screening research.

Data analysis.

Study 1 (Chapter 4), as a quantitative research study, adopts the use of statistical testing. Analyses are conducted using the SPSS programme (Statistical Package for the Social Sciences Version 25 Inc. Chicago, Il, USA), and tests selected according to the

hypotheses. One database incorporates data from patients screened at both locations. This was necessary to collate and analyse within SPSS. Each patient was assigned an identification number and missing data and errors checked. Missing data were left blank as this represented a missing at random sample, that is, there were just a few data points where answers were missing, and these did not always apply to the same variable. This resulted in different sample sizes, for example, when looking at diabetes as a predictor for AF, analyses were undertaken on 274 participants as 27 contained missing data, leaving 91% of the sample available for analyses. Descriptive and inferential statistics were used depending on the objective of the research study.

Ethical approval.

The research complied with the Declaration of Helsinki and approval was obtained from the local Research Ethics Committee (Jersey) and Lancaster University Research Ethics Committee, prior to participant enrolment (see *Study 1, Chapter 4*). The study was conducted in Jersey, the lead researcher or research assistant discussed the study with the participants, allowed them to read the information letter, answered all questions pertaining to the research, and then gained informed consent if they agreed to participate. Identifying information from participants was not included in the write up of results, but their name and date of birth was recorded to enable access to their most recent HbA1c on a pathology report, and this was detailed in the consent form.

Study results have been disseminated through journal peer-review publication, local forum discussion and international conference presentation.

3.5.2 Methods for Study 2, QoL research.

Research design.

The use of surveys for collecting QoL data in *Study 2 (Chapter 5)*, was the most appropriate method for obtaining answers to the research objectives. The survey was made available through a popular arrhythmia website (available nationwide) with a wide user profile, regularly offering surveys for completion. It is acknowledged that having the survey only available online precludes completion by those without access to the internet. This design was still considered appropriate to reach participants more

widely than the researchers' geographical location which could impact on the generalisability of the findings. (Further details on the SF-36 and the justification for its use are detailed in *data collection methods and instrumentation,* at the end of *3.5.2*).

Sampling.

Study 2 (*Chapter 5*) also followed a statistical sampling calculation (using GPower®). The initial calculation resulted in 128 participants needed but when applying the appropriate test e.g., MANOVA for testing the difference between the two groups in the eight domains of the SF-36, the sample needed to be increased to 249 and this target number was reached. The surveys had clear signposting on the website to direct responders. More surveys were completed by people with AF alone than AF and diabetes and this may simply represent the higher numbers of people living with AF than the two diseases in combination.

Data collection and instrumentation.

Study 2 utilises the Medical Outcomes Study Short Form SF-36 Health Survey [SF-36], (Ware & Sherbourne, 1992) and a website, therefore requiring internet access and a device on which to view and complete the surveys. The eight subscales in the SF-36 include Physical Functioning, Role Physical, Role Emotional, Energy Fatigue, Emotional Wellbeing, Social Functioning, Pain, and General Health, and are complemented by physical and mental component summary scores. The SF-36 is selected due to its extensive validation, generalisability, and previous utilisation with people with AF and people with diabetes (Abbasi-Ghahramanloo et al, 2020; Aliot et al, 2014; Berkowitsch et al, 2003; Echouffo-Tcheugui et al, 2017; Engström et al, 2019; Jones, Taylor, hobbs, Bowman & Casadei, 2020; Kim et al, 2016; Lane, Langman, Lip & Nouwen, 2009; Raine et al, 2015; Reynolds, Lavelle, Essebag, Cohen & Zimetbaum, 2006).

The European QoL Measure [EuroQOL/EQ-5D] (EuroQoL Group, 1990) was also considered for use in this research due to the generic approach, previous use, and validation in QoL studies of chronic disease. There are correlations to the SF-36 with comparable effectiveness (Eker et al, 2007). However, physical functioning [SF-36] is

broken down into more items than the mobility and self-care components from the EQ-5D and the wording around emotional effects within the SF-36 was perceived as more appropriate for these patient groups, by the author for this study. There is also further detail within the social functioning domain [SF-36] versus usual activities [EQ-5D]. More specific scales exist which directly relate to diabetes or AF (see *Table 5 and 6*) but as their coexistence is under enquiry, a tool that can be utilised in both clinical populations, is preferred. Survey content should also be appropriate for the purpose and the SF-36 was chosen as this demonstrates content validity by asking questions relevant to the subject under enquiry within relatable domains, such as Energy Fatigue, Role Physical and Role Emotional, which not exclusively, but commonly include symptoms reported by patients, from clinical experience.

As these disease groups were in coexistence for one of the groups, a disease specific tool was not felt appropriate and rather a generic tool for its coverage across a range of physical and psychological domains was preferred. Furthermore, disease specific tools by design, focus on the areas felt to cause compromise and may therefore be less transferable to other disease groups. Symptom scales specific to the condition, similarly, might misrepresent symptoms or QoL compromise when comorbid disease exists. Some of the disease specific QoL tools have been developed for clinical trials and therefore appeal to that treatment or therapy specifically, but less so to the general population (with AF or diabetes). The QoL study in this research (*Study 2, Chapter 5*) explores QoL in the general population and this was therefore an additional justification for SF-36 selection. Time taken for completion is another important factor. The SF-36 is estimated to take about ten minutes to complete, whereas the AF Effect on QualiTy-of-Life Survey [AFEQT] survey for example, incorporates forty-two items in their original survey and so may take longer, potentially impacting feasible implementation.

Data analysis.

Study 2 (*Chapter 5*) involved entering responses to the SF-36 survey into an SPSS file whilst coding according to the measure's analytical guidance. This two-step scoring

process involves applying pre-coded numeric values, recoded as per a standard scoring key (Ware, 2000; Ware & Sherbourne, 1992) then items in the same scale averaged together to create eight scale scores. Missing data are not taken into account when calculating scale scores; the scores represent the average for all items in the scale that the respondent answered (Ware & Sherbourne, 1992). Having explored methods of analysing and interpreting data obtained from the SF-36, the mean and SD for each domain are calculated. This is despite the suggestion that this could be misleading for the domains that are categorical with differing coding scales (Torrance et al, 2009). Debate has resulted in the recommendation by the manual and interpretation guide (Bowling, Bond, Jenkinson & Lamping, 1999; Stewart, Hayes & Ware, 1988; Ware, 2000; Ware & Sherbourne, 1992) to adhere to mean and SD calculation to optimise the ability for easier comparisons of results across studies, and that the treatment of data as interval level has negligible effects on most statistical procedures. Some papers, however, report median SF-36 scores to describe the group average, floor, and ceiling effects (scoring 0 and 100 respectively), interquartile ranges and 5^{th} and 95^{th} percentiles, thus demonstrating the variation in tests and reporting of health outcome data using the SF-36, perhaps not always in the conventional way (Dunville, Lee, Smith & Fowkes, 2004; Smith, 2001; Torrance et al, 2009; Walters & Campbell, 2004).

Scores from subscales often have skewed distribution and it has been suggested that the use of parametric statistical testing for SF-36 may not be appropriate (Smith, 2001; Walters & Campbell, 2004). Torrance et al (2009) explored the variations in statistical approach between parametric and non-parametric tests, including bootstrapping methods, and concluded that despite the theoretical reasons why parametric approaches might not be the most appropriate, this approach is favoured in terms of simplicity and the ability to adjust for confounders, whilst facilitating comparisons with other datasets (Torrance et al, 2009). Confounders controlled for in *Study 1* were diabetes duration, diabetes control (HbA1C), age and sex.

Ethical approval.

Ethical approval was obtained from the local Research Ethics Committee and Lancaster University Research Ethics Committee. Through online survey completion, consent was given, and this was explained in the introductory page of the survey, before moving to the next screen where the survey questions commenced. No personal or identifiable details were requested, and the survey was therefore anonymous. The research complied with the Declaration of Helsinki. Participants had the right to withdraw from the research and this was explained during consent. Consent also explained that the study would be prepared for publication.

3.5.3 Methods for Study 3, Interview Study.

Research design.

Applying the qualitative study (*Study 3, Chapter 6*), incorporates semi-structured interviews to collect participants' views, thoughts, and experiences. Advantages of the semi-structured interview include the option for further spontaneous exploration, the amount of detail that can be generated, the flexible and sensitive approach and the reliability of information shared (Adams, 2015). The reliability, however, could be impacted upon by participant recall or reporting bias and the flexibility may lessen reliability. The open-ended questions can also present challenges with analysis compared to structured interviews with set questions, as they contain unstructured data making interpretation more complex. This approach, rather than unstructured, was still felt most applicable to this research as some questions required feedback that related directly to the research questions, whilst others allowed for further exploration. Interviewer sophistication, whereby the interviewer knows the subject under enquiry, has been suggested by Adams (2015) as an important component of successful and meaningful semi-structured interviews. In practice, this background knowledge and experience facilitates a free-flowing interview with conversational aspects incorporated. Interviewer knowledge, however, can have a negative effect where expectations can interfere with objectivity. Interviewer bias can impact the

dialogue by potentially not probing the participant as they assume to know the answers.

Sampling.

Participants interviewed in *Study 3* were selected from *Study 1*, when diagnosed with AF during the screening episode. This purposive sampling is justified as it is those with both AF and diabetes under enquiry. Purposive sampling is recommended by writers on sampling in qualitative research based on interview (Bryman, 2008) and entails an attempt to establish good correspondence between research questions and sampling (Bryman, 2008). Understanding patients' views around AF, the screening they experienced, and the screening tool used were discussed with this group. Using a wider group and including people who also underwent screening but did not have AF, was considered, but as the focus for the research questions was around AF specifically, experiences relating to those who had received this diagnosis was of particular interest and it is this, that was central to the research questions. Therefore, people with both AF and diabetes were included but it is appreciated, that seeking views from a wider group who just had diabetes without the AF diagnosis, might add another perspective to the findings from the interviews. For clarity around research aims, interview questions and response, the AF group were selected. Of the total group eligible for interview (n=16), not all were available to participate: two had died, four were uncontactable and one declined, and this may therefore affect findings.

Data collection and instrumentation.

Interview data for *Study 3* (*Chapter 6*) involves the researcher acting as the interviewer through conducting interviews in a semi-structured manner, whilst using a voice recording device to record the semi-structured questions and answers. Interviewing in this way allows for the objective comparison of participants' feedback whilst facilitating wider spontaneous exploration. A large amount of data can be generated, and this style can be flexible and sensitive and can be easier to analyse than unstructured interviews (Adams, 2015). Conversely, the flexibility afforded can impact reliability and the free-flowing aspect of this interview style can result in more

difficult comparisons within interviews, than the more structured approach (Adams, 2015). The semi-structured interview was selected for *Study 3 (Chapter 6)* as there were some specific aspects under enquiry where feedback was desired, yet deeper exploration was permissible.

Data analysis.

Thematic analysis involved reading each transcript carefully and repeatedly. Each interview was read line-by-line, annotating with descriptive labels, pen, highlighters, and paper. NVivo 12 Plus qualitative data analysis software (QRS International) was also used to support analysis. Text was closely examined to identify codes which were then refined, and themes and sub-themes developed inductively from the data.

Ethical approval.

Principles relating to good ethical practice were adhered to, as set out in the Declaration of Helsinki and participants received an explanation about the research and how this would be conducted. Informed consent was gained prior to data collection, and this included information about withdrawal of interview content. Consent also included acceptance that information may be used in publications or presentations, but personal information would not be included and nor would quotes be identifiable. Agreement was also given for the interview to be audio-recorded.

3.6 Theoretical and conceptual considerations of health screening.

Comprehension and consideration of theoretical background, approach, and concepts underpinning research can assist not only in research design, but in the appreciation of values and beliefs around the chosen paradigm and methodology. This consideration helps the researcher and reader understand the direction the studies have taken and the impact this could have on outcomes and interpretation.

For this chapter, the theoretical and conceptual underpinnings around health screening are considered as there are many aspects within this domain that can be related to other elements of this research. For example, theories behind AF are a topic

in itself – the pathophysiology, the causative or correlational link to lifestyle and behaviours, underlying values held by individuals and link to QoL, the diagnostic applications and management options – and indeed, the identification and screening approaches. Furthermore, diabetes and chronic disease, metabolic syndrome and multi-morbid conditions could be critiqued in terms of their association and underlying theories. Adopting mHealth and eHealth in modern healthcare could also be explored in relation to concepts underpinning their utilisation. Theories and concepts behind screening programmes therefore incorporate many of the multifaceted aspects within this research.

Health screening has increased dramatically over the last few decades through a need and desire to address the growing burden of disease (Andermann, Blancquaert, Beauchamp & Déry, 2008). This exponential growth has been partly achievable through innovations in digital technology and an ability to detect more conditions. A paradigm shift has resulted in a more proactive approach whereby detecting disease sooner, beyond the confines of clinically overt disease, is achievable. Surveillance medicine is a concept used to describe a new model of medicine where there is increased observation and surveillance of an apparently healthy population (Armstrong, 1995). Armstrong (1995) explains this breakdown of the traditional distinction between health and illness, whereby the population becomes 'potentially at risk'.

Health screening, according to the seminal work by Wilson and Jungner (1968), includes criteria that should be considered when implementing screening programmes (*Table 7*). The criterion states that the condition should be an important health problem with accepted treatment. The UK National Screening Committee [NSC] who are responsible for specifying screening programmes still draw, to a large extent, on these criteria (UK NSC, 2019). They specify that criteria around the condition, test, treatment, and programme should all be met before implementation of screening agendas. Contemporary updates to screening concepts include the economic implications, quality assurance and informed choice as well as equity and access of screening to the entire target population (Andermann et al, 2008).

Table 7. Wilson and Jungner's principles of screening.

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

Wilson & Jungner (1968).

It is however, not enough to consider the medical aspects of screening programmes, but also the social intervention that is fundamental within this debate. Medical screening within preventative medicine, raises important issues for sociological inquiry and this has been lacking, according to writers in this field (Armstrong & Eborall, 2012; Armstrong, 2019). This is important to understand, as screening is a social intervention as well as a medical intervention. Appreciation of societal influences that impact screening implementation and engagement along with sociological scrutiny can be insightful for developing and building successful screening programmes which contribute to social theory (Armstrong & Eborall, 2012). Underpinning work around the sociology of screening has developed beyond evaluating screening uptake and a more critical view can help understand important insights around health screening. This includes exploration of barriers to participation in screening and existing work

around the sociological impact of screening through cross-fertilisation from sub-disciplines is very important for wider application across screening programmes.

The success of screening programmes is multi-dimensional, and stakeholders' perspectives can influence planning, delivery, and outcomes. One approach will not necessarily fit all and from a realist perspective, what might work in one clinic for one patient group, might not work for others (the context). Theories around screening mechanisms would consider how screening might take place, the manner of recruitment and the method used to conduct the screening. These considerations will have implications on the feasibility of the chosen screening tool and its application. For example, methods used to record heart rate and rhythm vary significantly now with digital technologies enhancing consumer options. Many of these can be costly, making them less available across socioeconomic groups, and smartphone or tablet orientated devices may be inappropriate for people who are less tech-savvy. Screening initiatives that encourage patients to take ownership or require self-initiated monitoring may also impact on the accuracy or compliance, whereas programmes conducted by health professionals may assist with screening accuracy, yet prohibit as many screening episodes. Pulse taking or using handheld single-lead ECG applications is recommended by expert guidance with subsequent ECG monitoring where irregularities present (Hindricks et al, 2021; NICE, 2021). Traditional ECG monitors can be uncomfortable and impractical. Prior to advances in analysis, time taken to examine Holter monitoring results could be laborious but advances in technology have resulted time saving through automated analysis. Duration of wear may be incongruous with symptoms and monitoring methods should be considered in relation to demographic groups, socioeconomic status, motivation, individual needs, and abilities, and beyond the medical orientation.

Along with deliberation around screening method, should be consideration around the people who attend screening programmes, including reasons for attendance and associated components within theories around screening mechanisms. Motivation is key for screening engagement and the impact from screening advertisements should

not be underestimated. As well as motivation to attend, thought around screening promotion, public literacy and sociodemographic reach should be applied (Bish, Sutton & Golombok, 2000). In the AF screening study (*Study 1, Chapter 4*), motivation was in part, a pre-requisite for screening attendance, whereby participants recruited from the GP surgeries needed the initiative to make contact for a screening appointment. Public literacy was perhaps not given due attention as the mailshot sent out was a written letter without alternative media options for viewing. This is also relevant when considering screening advertisements, where they might be placed and how they can be viewed. Material about the offered screening should provide 'full information' but making this accessible to the public requires simplicity and selection over content, which may impact on how the information is presented (Armstrong & Eborall, 2012).

Participants recruited from the diabetes centre in *Study 1* (*Chapter 4*) perhaps had more sociodemographic variability, although detailed data relating to this was not obtained, as this is a free clinic and advisory service, which may attract patients who are less likely to see their GP where there is a fee. The socioeconomic link to screening attendance is well documented and there is evidence that those who might have the most to gain from health screening, are least likely to attend (Lang, Abel, Mant & Mullis, 2016). Screening uptake is poorer in areas of deprivation where there is greater risk of cardiovascular disease (Lang et al, 2016). There is also a well-established socioeconomic gradient evident in screening data across specialities, with occupation, education, and income level relevant to screening uptake (Lang et al, 2016; Young & Robb, 2021). Basic sociodemographic data was obtained from the screening study population in *Study 1* (*Chapter 4*), showing slightly more men than women participated, with an average age of 63 years. There were more men than women recruited from the GP surgeries and the diabetes centre. There are more men than women with diabetes in the population and therefore, this could relate to the proportion who participated. Wider research has shown that in general, men are less likely to undergo cardiovascular health checks, and this has aligned to differences in health seeking behaviours between men and women (Cheong, Khoo, Liew & Chinna,

2018). Another study suggested this was attributable to perceived drawbacks from the health checks for men although this was also observed to be contextual and related to socio-economic status (Galdas, Cheater & Marshall, 2005). This health seeking behaviour has been described by Lauver (1992) in his *theory of care seeking behaviour.* This was developed to understand why people do or do not participate in health promotional programmes and has direct relevance to screening attendance and adherence. This theory is based on constructs including clinical factors, sociodemographic factors, affects, beliefs, norms, habits, and external resources. This theory demonstrates that clinical and sociodemographic factors indirectly influence care seeking behaviour of screening participants through their psychosocial constructs (Lauver, 1992).

The *health belief model* (Rosenstock, 1966) is another health behavioural theory that can be applied to health screening in terms of beliefs, attitudes, acceptance, and compliance around health screening. The social psychologists who devised the *health belief model*, set out to investigate factors responsible for the failure of a free tuberculosis screening programme (Rosenstock, 1966). Since then, it has been applied to help explain health behaviours around other screening programmes and can be related to the AF screening study in this research (*Study 1, Chapter 4*) through associated components including 'perceived susceptibility' and 'perceived barriers' (Jones et al, 2015). Participants may have agreed to participate as they were targeted due to their diabetes, and this was explained prior to giving consent. They may have felt therefore, that they were more susceptible to having AF, through the participant information and invitation. Understanding barriers to screening, be this through personal health beliefs or perceptions, can also impact screening engagement according to the *health belief model* and understanding these perceptions is important when planning public health programmes. Interview feedback from *Study 3* (*Chapter 6*) seeks patients' views on AF screening and goes someway in addressing this component of the *health belief model* and is important when planning patient-orientated, public health programmes such as screening initiatives. Similarly, the *theory of planned behaviour* attempts to predict health behaviour by focusing on

beliefs and attitudes with constructs relating to social norms, perceived behavioural control and intention. The actual participation is determined by their intention to undergo screening (Ajzen, 1985) and again, this can be related to screening participation from the AF screening study in this research, particularly from those who responded to the GP surgery invitation. Participants who completed surveys for the QoL study (*Study 2, Chapter 5*) also did so through their own intention, without persuasion or coercion, by visiting the website that housed the surveys. This was voluntary and reliant on individuals navigating to the survey and following the commands throughout to completion.

Screening uptake may also be determined by individuals' understanding of the condition screened for, perceived risks, personal and peer related experiences and views around exposure to healthcare. These elements link to the health behavioural theories outlined, along with human factors that can influence screening engagement. The *theory of planned behaviour* suggests that attitudes are built up of behavioural beliefs whereby behaviours have an effect, combined with the motivation to achieve that effect (Ajzen, 1985). Understanding around the condition screened for may relate to how this is conveyed, publicity, language, and approach. Individual factors including underlying health beliefs, previous experiences, and peer influence can also be contributory. Feedback from participants from the interview study (*Study 3, Chapter 6*) demonstrated poor understanding around AF and this was after the screening had taken place, albeit in a small sub-group of the original screened population. Even though their understanding around AF was limited, this had not influenced their decision to participate, nor had it impacted their views that AF screening was worthwhile. This may, however, relate to their positive diagnosis for AF and asking people who did not have AF, might have yielded different responses.

The risks and benefits of screening will be perceived differently, and this may be based on previous experience, as outlined above, and from outcomes based on personal screening exposure. Along with consumer considerations, are debates around costs and this relates to healthcare organisations as the consumer, and patients. Cost featured heavily in the interview study feedback (*Study 3, Chapter 6*) with many participants mentioning the cost of screening appointments and the screening tool.

Cost analysis has also featured in research related to AF screening using the AliveCor® device, reaching favourable outcomes for AF detection with this method and subsequent stroke protection (Halcox et al, 2017). The screening approach is also impactful on cost with opportunistic screening favoured for AF screening due to cost efficiencies, when compared to systematic screening (Hobbs et al, 2015; Moran et al, 2016). Opportunistic screening is more ad hoc, perhaps when the patient presents to their GP for a medical check-up, then has a pulse or ECG check for abnormalities. There is no planned programme or follow-up strategy in contrast with systematic screening, whereby a target population is invited and screened. Systematic and opportunistic screening both detect more AF than usual care, and although equivocal, opportunistic screening is favoured due to the increased costs, labour intensiveness and more intrusive approach with systematic screening (Hobbs et al, 2005). Opportunistic screening though, by nature of its approach, may lead to concerns around informed consent, with misleading or inaccurate information being given prior to the screening episode. Screening for AF in this way, may not allow time for lengthy explanations regarding potential outcomes, stroke risk and the need for ongoing treatment. The harms of screening are not clearly explained, neither are the conditions being screened for or the harm that could be inflicted through misdiagnosis, or over or under-treatment (Gøtzsche & Nielsen, 2009). Principles around decision making and informed choice in relation to screening, has also led to the development of guidance by the UK NSC (UK NSC, 2021). They describe four broad principles that are key to screening programme implementation with informed choice as one of the essential components. This is accompanied by screening objectives that aim to improve the health and wellbeing of the population by maximising benefits and minimising harm, promoting equality and inclusion within screening agendas and utilising public resources proportionately and fairly (UK NSC, 2021).

Proposers of AF screening would envisage this as an opportunity to ‘do good’ and ‘no harm’ by identifying a treatable chronic disease, yet this diagnosis could impose harm by prescribing medicines that were not desired, impact on the patients’ QoL, cause side effects or induce anxiety. There are situations where AF is diagnosed,

anticoagulation advised, yet not tolerated or contraindicated in the individual, further adding to the patients' anxiety about a condition they may have had no symptoms or sequalae from. These risks and uncertainties around screening, have been described along with the impact screening can have on the individual and wider costs (Green, Thompson & Griffiths, 2002; Griffiths, Green & Bendelow, 2006). Potential problems might be highlighted as an outcome from the screening, such as another health concern that was not the purpose for that screening episode. This uncertainty has been a focus in research, including ways in which this uncertainty is managed (Green et al, 2002; Griffiths, Green & Bendelow, 2006). The moral obligation to act on this may contrast with the screening research and consent and subsequent action must be considered responsibly and in accordance with the code of practice.

Finally, theories relating to embodiment, citizenship and responsibilisation have been described within sociological screening narratives, where screening as a response to normative expectations prevails (Armstrong & Eborall, 2012; Griffiths et al, 2010; Howson, 1999). Good citizenship is described as acting responsibly by following the most sensible course of action e.g., by attending the screening on offer, and becomes a moral obligation (Bush, 2000). The way people act however, links back to the multifactorial aspects that connect behaviours, human factors, and underpinning attitudes towards screening. In the interview feedback from patients in *Study 3* (*Chapter 6*), these beliefs were reported as influential to decisions around medical care, with talk of their 'scientific and medical model beliefs' along with education, being central to their approach. To increase screening uptake therefore, it is important to consider these screening activity related theories from a sociological and medical perspective, to encourage engagement by understanding these potential barriers and use these sociological considerations to inform practice.

In summary, when screening programmes are designed, the multiple components that influence screening implementation require careful consideration, as depicted in *Figure 12*. It is important to consider how theories relating to health behaviours, beliefs, and their shortcomings, can impact on the design of screening programmes

and screening engagement, as this knowledge can be influential on uptake and the success of screening initiatives. Greater appreciation of underpinning sociological theories and their relevance to health screening might enable a more integrated and cohesive approach through facilitation of more effective programmes, whereby the background barriers are put at the forefront of the screening agenda. Designing screening initiatives which have an equivalent focus between sociological barriers and the medical agenda, should assist with movement towards more cohesive and effective programmes. Building sociological theory for use across all disciplines encourages a universal focus on which to centre screening initiatives.

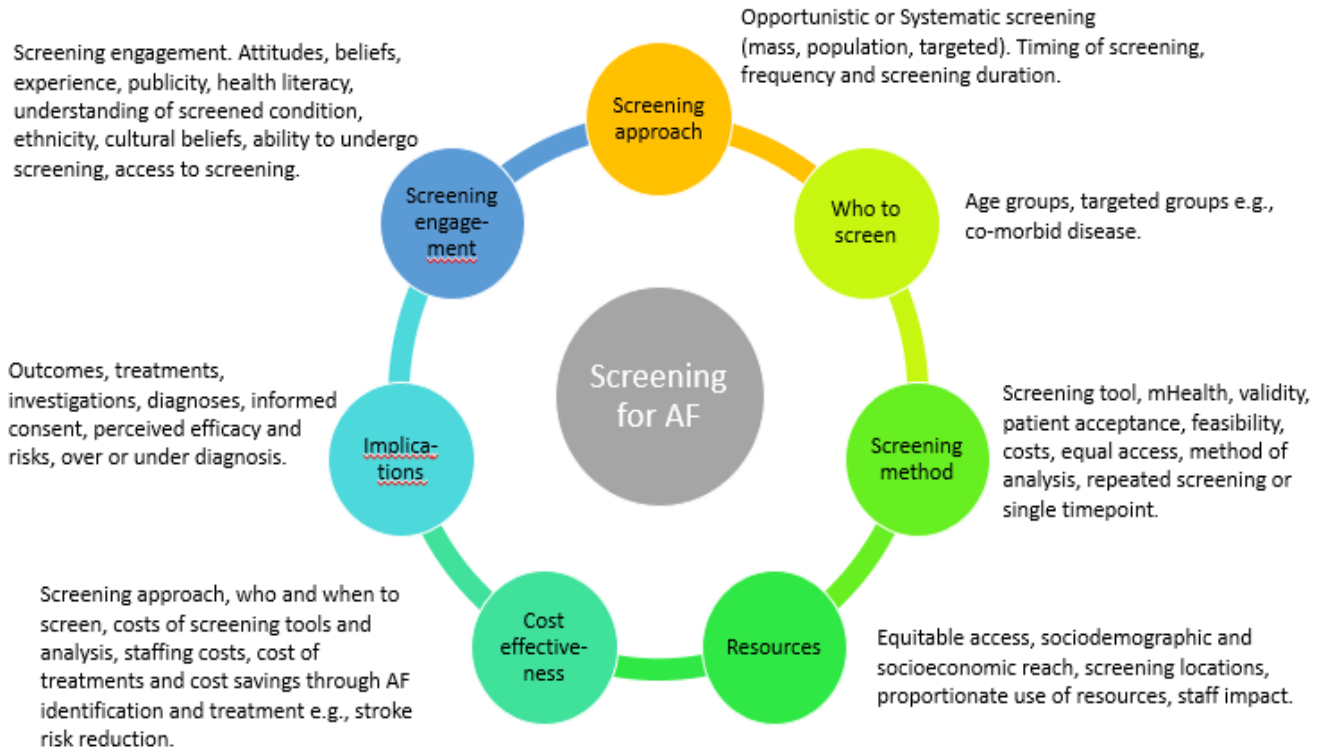

Figure 12.

AF Screening considerations.

3.7 Conclusion.

This chapter has provided an overview of the philosophical foundation that guided this research and the choice of methods used. This was delivered by reflecting on the researcher's ontological and epistemological perspective, which guided the methodology. A positivist approach was applied within the quantitative studies, and this aligns with empiricism where knowledge stems from human experience and observations. Mixed methods research [MMR] elucidates several benefits through integration of post-positivism and interpretive frameworks. The application of pragmatism, a pluralistic approach whereby objective and subjective knowledge is valued, arguably facilitates the optimal approach by answering the research objectives. Methods and procedures employed in each research study are summarised with justification for their choice. Ethical implications of each study are discussed along with appreciation of ethical principles and their application to AF screening. Theoretical considerations for AF screening as well as health screening, are explored along with appreciation of the wider multi-dimensional aspects that impact on successful screening agendas.

Chapter 4.

4.1 Atrial fibrillation prevalence and predictors in patients with diabetes: a cross-sectional screening study.

This cross-sectional screening study was designed to understand more about AF in people with diabetes, by exploring the prevalence and predictors of AF in this population.

AF screening studies to date have incorporated mixed comorbid groups, with diabetes often featuring. Analyses do not always consider the potential confounders or undertake multi-variate analysis and therefore, it is not always clear which comorbid disease has impacted AF prevalence. This study targets people with diabetes specifically, as the focus group.

Understanding of prevalence and predictors are important when considering target groups for AF screening. This can then assist with ensuring resources are channelled appropriately to the higher risk groups, where treatments offer the optimal benefits (such as anticoagulation, to reduce stroke risk).

The screening approach here is single timepoint, where one screening episode is performed using the AliveCor® device. Having scrutinised this tool in terms of scientific metrics and critiqued in relation to clinical effectiveness and feasibility, employing this beyond clinical use but within primary research, provides realistic application within a research study with a typical patient population.

Chapter 4.

This research aims to discover the prevalence of AF in a population with diabetes and whether screening here is feasible. Prevalence is further analysed in relation to age, sex, and risk factor variables. The hypotheses are:

Hypothesis 1: Presence of diabetes will be a predictor of presence of AF, controlling for age and sex.

hypothesis 2: There will be a difference between male and female patients in the frequency with which AF is identified.

Hypothesis 3: Screening patients with diabetes will detect a higher prevalence of atrial fibrillation than does screening in the general population.

Hypothesis 4: Duration of diabetes and level of glycaemic control will be more important predictors of presence of AF than diagnosis of diabetes alone, or age and sex.

Hypothesis 5: AF detection will vary between screening locations (an out-patient diabetes centre and patients recruited from GP practices) (see *Study 1, Chapter 4*).

4.2 Atrial fibrillation prevalence and predictors in patients with diabetes: a cross-sectional screening study.

Paper 2.

Page numbers within this thesis 182 - 207.

(Journal page numbers 1-6).

Published version of this paper can be found in Appendix 2N.

Chapter 4.

Atrial fibrillation prevalence and predictors in patients with diabetes: a cross sectional screening study.

***Short title*: Atrial fibrillation screening in people with diabetes.**

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Chapter 4.

Abstract

Introduction

The prevalence of atrial fibrillation [AF] and diabetes is increasing worldwide. Diabetes is a risk factor for AF, and both increase stroke risk. Previous AF screening studies have recruited high-risk patient groups but not with diabetes as the target group. This study aims to determine whether people with diabetes have a higher prevalence of AF than the general population and investigate whether determinants such as diabetes duration or diabetes control add to AF risk.

Methods

In a cross-sectional screening study, patients with diabetes were recruited via their GP surgeries or a diabetes centre. A 30-second single lead ECG was recorded using the Kardia® device along with physiological measurements and details relating to risk factor variables.

Results

300 participants were recruited, and 16 patients identified with AF (5.3% prevalence). This demonstrated a significantly greater likelihood of AF than the background population, p =.043. People with diabetes and AF were significantly older than those who only had diabetes. More people with Type 2 diabetes had AF than people with Type 1. Prediction of AF diagnosis by age, sex, diabetes type, diabetes duration and level of control revealed only age as a significant predictor (OR 1.089; 95% CI 1.025 - 1.158; p=.006).

Conclusion

These findings add to existing data around the association of these chronic conditions, supporting AF screening in this high-risk group, particularly in those of older age. This can contribute to appropriate management of both conditions in combination, not least with regards to stroke prevention.

Key words:

Kardia®, AliveCor®, atrial fibrillation, diabetes, screening

Competing interests: No conflict of interest has been declared by the authors.

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Key messages and impact:

- AF and diabetes are increasing in prevalence and are risk factors for stroke. Screening for AF can help identify and reduce stroke risk.
- Screening of people with diabetes rather than mixed high-risk patient groups has not been concentrated on as the lone, target group in previous research. This study also considers the impact of diabetes stability and duration.
- Identifying populations at high-risk can help when planning screening approaches and programmes in order to ensure they are effective in terms of cost and resource whilst reducing stroke risk.

Author contributions: Angela Hall was the lead author who devised the study, conducted the research, analysed the results, and prepared the paper. Andrew Mitchell was clinical supervisor, assisted in the design of the study and reviewed the manuscript and results. Lisa Ashmore and Carol Holland agreed the study design, and both acted as academic supervisors. Both reviewed the paper and Carol Holland assisted with statistical testing and review of results.

Abbreviations:

ANOVA	Analysis of variance	**F**	F test
HbA1c	Haemoglobin A1c	X^2	Chi-squared test
BP	Blood pressure	**df**	Degrees of Freedom
ECG	Electrocardiogram		
BMI	Body mass index		

Chapter 4.

1.Introduction

Prevalence of atrial fibrillation [AF] and diabetes is increasing worldwide (1, 2). AF is a common heart rhythm irregularity and prevalence increases with age. People with AF are up to seven times more likely to have a stroke than the general population (1) with risk increased further in the presence of diabetes (3). AF may exhibit no symptoms and go undiagnosed until patients present with sequelae, such as stroke or heart failure. Stroke secondary to AF is often avoidable with thromboprophylaxis and early identification could lead to stroke prevention.

Diabetes mellitus is a major risk factor for cardiovascular disease (4) and the frequency of AF is reported to be 1.4 to 2.1-fold higher in people with diabetes than without (5). The association between AF and diabetes may be through pathological determinants at a cellular and molecular level (6), or through shared risk factors (5).

Age-adjusted AF incidence and prevalence is larger among men, but women are older at the time of AF diagnosis (7). Men with AF have a larger burden of coronary artery disease, but women tend to have a higher prevalence of heart failure and valvular heart disease (7). Being male is also associated with increased likelihood of developing diabetes (8) and therefore, effects of sex on the presence of AF in the person with diabetes will be explored.

Finally, the health professional managing the patient's diabetes (GP or diabetes specialist) may not always relate to diabetes status. GP centres may attract the 'worried well' and those who voluntarily seek healthcare. A specialist may see the patient for other reasons e.g., dietary advice or podiatry. This study will consider whether there is a difference in AF prevalence between screening locations and any impact this could have.

Previous AF screening studies recruited high-risk patient groups but not with diabetes as the lone, target group (9-11). The aim of this study is to screen people with diabetes for AF using the Kardia® device (Mountainview, California, USA), to determine whether people with diabetes have a higher prevalence of AF than the general population. We also explore whether other determinants such as age, sex, diabetes

stability and duration impact AF prevalence in this patient group, or whether the existence of diabetes alone determines higher AF risk.

1.2 The Kardia® single-lead screening device

The Kardia® device, a smartphone-based heart monitor, is activated by placing fingers on pocket-sized metal electrodes, producing a single lead ECG. The device is a clinically validated screening tool, CE marked, and FDA cleared (12). Validity is high with sensitivities >98% and specificities of >90% (13, 14). A recent systematic review found it to be a convenient and feasible means of monitoring for AF, easily implemented into opportunistic and systematic screening (14). The Kardia® device is an event-type monitor recommended for use in England when episodes are more than 24 hours apart (15, 16).

1.3 Study hypotheses

This study aims to discover the prevalence of AF in a population of people with diabetes and whether screening in this group is effective. The hypotheses are:

- Presence of diabetes will be a predictor of the presence of AF, controlling for age and sex.
- There will be a difference between male and female patients in the frequency with which AF is identified.
- Screening patients with diabetes will detect a higher prevalence of AF than screening in the general population.
- Duration of diabetes and level of glycaemic control will be more important predictors of presence of AF than diagnosis of diabetes alone, or age and sex.
- There will be a difference between the proportion/percentage of people detected as having AF in the two screening locations.

If the null versions of the hypotheses are supported by the data, e.g., presence of diabetes is not a predictor of the presence of AF, then this would indicate that targeted screening is not indicated.

2. Methods

2.1 Design and Setting

This cross-sectional screening study screened people with diabetes for AF using the Kardia® device. The research was conducted in Jersey, Channel Islands (population approximately 100,000) in an out-patient diabetes centre and a central community clinic where GP patients attended.

2.2 Participants

2.2.1 Sample size

The sample size calculation estimated 351 participants to be representative of the island's population with diabetes (local figures suggest 4000 people) (17). This was based on a confidence interval of 5%, a confidence level of 95% and response distribution of 50%. Data collection was completed over fourteen months, with 300 participants recruited. Further recruitment was affected by delays incurred by the Covid-19 pandemic and low response rates from the initial GP practice, resulting in two further GP practices being recruited.

2.2.2 Eligibility

Inclusion criteria included people with an existing diagnosis of diabetes. This does not include disorders that can cause glycaemic dysregulation or insulin insufficiency due to interference with endocrine functions, such as conditions affecting the pancreas. People with pre-diabetes or undiagnosed diabetes with increased risk factors for the disease (e.g., through obesity), were not included and widening inclusion criterion to represent such groups could be considered in future research whereby diabetes is a focus. Patients were still included if they disclosed existing AF as this was relevant when calculating prevalence. Age inclusion was eighteen years or older, participants needed the capacity to consent and understand English as the researcher(s) could not speak other languages and funds were unavailable to accommodate translators. The

nature of screening recruitment from the diabetes centre also meant there was no time to arrange for translation services as patients were approached whilst they waited for their scheduled diabetes-related appointment. People were excluded if they were unable to get to the screening location when recruited from GP surgeries, as a central screening venue was arranged for this purpose. An exclusion criterion also existed if an implantable cardiac device including a pacemaker or internal cardioverter defibrillator was in place, having considered the guidance around the use of the Kardia® device and implantable cardiac devices (12). This is due to the short pulse widths transmitted being difficult to detect with ambulatory ECG machines, including the Kardia® device (12). The manufacturer guidance states the Kardia® device should not be used in people with an implantable cardiac device for these reasons, along with a lack of accuracy testing with the Kardia® device and paced-ECG recordings (12).

This is supported by research whereby weaker rhythm detection has been evident in patients with pacemakers, and lower sensitivity in detecting AF (18,19). Sensitivity and specificity increased in one study, once patients with implantable cardiac devices were excluded, through both automated and manual analysis (19). False positives were examined in another AF screening study and related to difficulties in assessing p waves (atrial activity) in participants with pacemakers (20). Ventricular stimulation via pacing resulted in an increased likelihood of misclassification by the Kardia® algorithm in another study (21). Many studies have therefore excluded these patients from their AF screening research (22,23,24,25) although this is recognised as a limitation, as an AF diagnosis could be missed, potentially underrepresenting AF prevalence in the populations screened. Other comorbid groups were not excluded as people with AF and diabetes often have coexisting chronic disease and therefore, the eligibility criterion for disease groups was not specified beyond these two conditions.

2.3 Screening procedure

The screening procedure is outlined in *Figure 1*. Patients attending the diabetes centre were invited to participate whilst waiting for their scheduled appointment, on the

days that the lead researcher was present, or days that the research assistant was on duty. Participating GP surgeries sent invitations to patients on their diabetes database and invited them to call the lead researcher to arrange a screening appointment. The exact numbers of letters sent was unconfirmed from the first two surgeries, despite repeated requests for this information (the researcher was not permitted access to the diabetes database for confidentiality reasons and therefore could not assist in this administration). The third recruited surgery sent 150 letters and forty patients responded, all of whom participated in the screening study. The three GP surgeries were selected due to their approximate registered patient numbers and central locations. Two of the biggest five surgeries failed to respond to the invite, resulting in the first, third and fifth largest GP surgeries recruited (as per information obtained from the Jersey Primary Care Body (2023) (26).

Patients were provided with an information sheet and had the opportunity to ask questions, their right to withdraw was explained and they were informed that declining participation would not affect treatment. If they agreed, patients signed a consent form.

The 30-second Kardia® ECG was saved to the user's phone then transferred to the lead researcher's phone for saving in an encrypted folder accessible through two passwords, then deleted. ECGs were documented as 'normal', 'AF' or 'unclassified'. All Kardia® ECGs were reviewed by the lead researcher and when 'unclassified', a 12 lead ECG performed. If this remained unclear, the Consultant Cardiologist was consulted. In the presence of AF, the patient was given an AF information sheet, a letter for their GP and a copy of the ECG.

2.4 Ethical approval

The study was approved by the University of Lancaster Faculty of Health and Medicine Research Ethics Committee (Ref: FHMREC18070) and the Health and Community Service Research Ethics Committee in Jersey. The research complied with the principles embodied in the Declaration of Helsinki. Participation was voluntary and written, informed consent was obtained. Participants were not identifiable in this research and their anonymity, therefore, upheld.

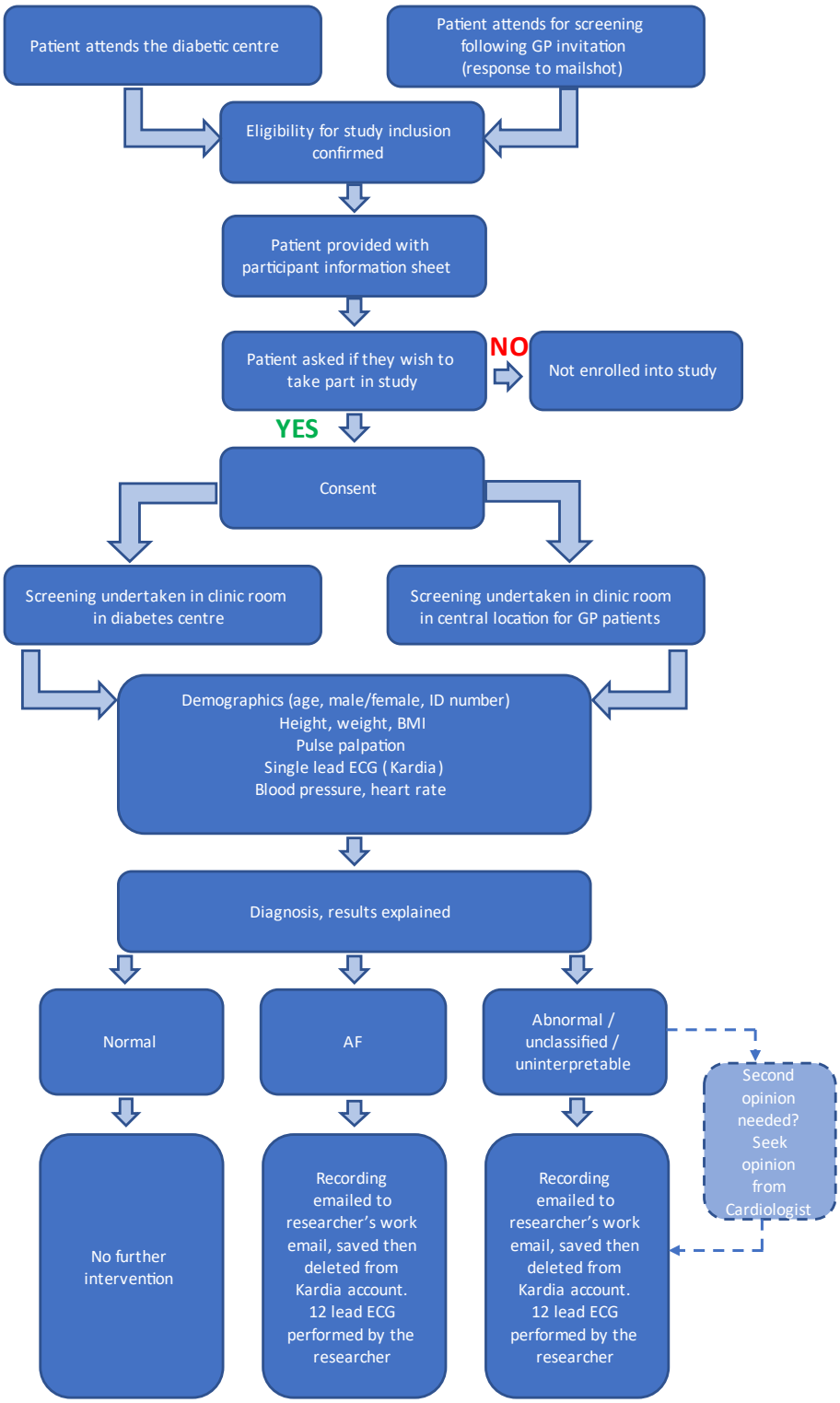

Figure 1.

Screening protocol and procedure for the AF screening study.

2.5 Statistical analyses

One-way ANOVA were used to determine whether there were statistically significant differences between groups (AF or sinus (normal) rhythm), for dependent variables age, BP, BMI, heart rate, diabetes duration, level of control (HbA1c). Group comparisons for categorical variables (diabetes type, sex) were analysed using the Chi-Square Test of Independence. This test was calculated on the total sample (*n*=300) and is sensitive to sample size (recommended for a minimum of fifty in the sample) (27). To determine whether the presence of diabetes predicts AF, logistic regression was applied, controlling for age and sex. To test whether screening patients with diabetes detects a higher prevalence of AF than screening in the general population, a t-test was used to compare the percentage of patients with diabetes between this study and the general population (previous AF screening studies). To examine whether duration of diabetes and glycaemic control were important predictors of presence of AF (in addition to the variance predicted by diabetes alone, or age and sex), these variables were incorporated into the logistic regression analysis. Finally, the Chi-Square Test of Independence was applied to examine differences in the proportion of people detected as having AF in the two screening locations.

3. Results

3.1 ECG screenings

Single lead Kardia® ECGs were recorded for the 300 participants (diabetes centre *n*=156, GP clinic *n*=144, one recording was not saved so this information is unavailable). The majority demonstrated normal rhythm via automated analysis (diabetes centre *n*=150, GP centre *n*=134), and sixteen showed AF (diabetes centre *n*=6, GP centre *n*=10), both confirmed on manual review (see *Appendix 2J*). The rhythm could not be accurately analysed using the incorporated algorithm in seven of the Kardia® ECGs and a 12 lead ECG was recorded for these seven “unclassified” cases. Of these, six were diagnosed as normal following manual review and just one remained unclear, requiring further adjudication by the Cardiologist.

Descriptive statistics and classifications are presented in *Table 1*. Interval data are presented as mean ± standard deviation and categorical data as numbers and percentages. Average age of participants was 63 years (± 13), and the majority were male (*n*=169). One way between subjects ANOVA showed a statistically significant age difference between groups ($F(1,298) = 8.928$, $p = .003$), with the AF group being older than the diabetes only group, and a difference in heart rate ($F(1,298) = 12.035$, $p = .001$) such that the diabetes only group (sinus rhythm [SR] in *Table 2*) had a lower heart rate than the AF group. There was a statistically significant difference in AF detection between diabetes types ($X^2 = 4.696$, $p = .030$) with more people having AF with type 2 diabetes. Based on a medium effect size of 0.5, a post-hoc power analysis showed that with a power of 0.90 and a significance level of p=0.05, n=300 participants were required in total.

3.2 Diabetes as a predictor for AF

A binary logistic regression analysis to investigate whether the presence of diabetes predicted AF, controlling for age and sex, was conducted. Block 1 contained the heart rhythm classification (dependent variable AF encoded to 1 and SR to 0). Block 2 contained age and sex as predictors. Analyses were undertaken on 274 participants (27 contained missing data, leaving 91% of the sample for analysis). The model was statistically significant, $X^2 = 12.58$, $p = .013$ with explained variation in AF presence being 14.1% (Nagelkerke $R^2 = .141$). Results demonstrate that age was the strongest predictor for AF (OR 1.089; 95% CI 1.025 - 1.158; p=.006) (see *Table 2*).

3.3 Difference between men and women in terms of frequency with which AF is identified.

AF was identified in 12 men (7.1%) and 4 women (3.1%). The Chi-Square Test of Independence showed no effect of sex on the frequency with which AF was observed AF (X^2 (2,299) = 3.641, p= .162).

Table 1. Comparison of demographic data from participants in the AF screening study.

Characteristics	**Total (*n* = 300)**	**AF (*n* = 16)**	**SR (*n* = 283)**	***F***	***P***
			Rhythm missing on 1 participant		
Sex					.125
Male, *n (%)*	169 (56)	12 (75)	157 (55)		
Female, *n (%)*	131 (44)	4 (25)	127 (45)		
Age, years (mean ± SD)	63 ± 13	72.4 ± 7.7	62.5 ± 13	8.928	.003*
Weight, kg	87.8 ± 19.9	90.5 ± 23.8	87.7 ± 19.7	.310	.578
Height, cm	169.3 ± 9.6	170 ± 8.5	169.3 ± 9.7	.347	.556
BMI	30.5 ± 6.1	30.8 ± 6.4	30.5 ± 6.1	.039	.843
SBP, mmHg	132± 16.8	130 ± 18	132 ± 16.8	.109	.742
DBP, mmHg	71 ± 10.6	74 ± 14.3	71 ± 10.4	1.718	.191
HR, bpm	71 ± 13.6	91 ± 22	78 ± 12.8	12.035	.001*
Diabetes type, *1 missing*					.030*
Type 1, *n (%)*	65 (21.6)	0	65 (100)		
Type 2, *n (%)*	234 (78.2)	16 (100)	218 (77)		
Diabetes duration, years (mean ± SD)	13.2 ± 11.1	12.9 ± 7.6	13.2 ± 11.3	.012	.911
HbA1C, mmol/mol (mean ± SD)	60 ± 1.3	55 ± 1.1	60 ± 1.3	1.473	.226
Hypertension, *n (%)*	178 (59)	10 (62.5)	122 (43.1)		.442
Smoker, *n* (%)	25 (8.3)	0	25 (8.8)		.216
Heart Failure, *n* (%)	18 (6)	1 (6.25)	17 (6)		.968
Obesity, *n* (%)	147 (49)	8 (66.6)	153 (54)		.677
TIA / CVA, *n* (%)	24 (8)	0	24 (8.4)		.789
PVD, *n* (%)	22 (7)	0	22 (7.7)		.248
Place of recruitment Diabetes centre, *n* (%) GP surgeries, *n* (%)	 156 (52) 144 (48)	 6 (37.5) 10 (62.5)	 150 (53) 134 (47)		

Kg: kilograms; cm: centimetres; mmHg: millimetres of mercury; bpm: beats per minute; SR: sinus rhythm; BMI: body mass index; AF: atrial fibrillation; TIA / CVA: trans-ischaemic attack / cerebrovascular attack; PVD: peripheral vascular disease; *F:* F statistic; *p:* significance probability where the p=<0.05 (*denotes a significant difference).

3.4 Screening patients with diabetes will detect a higher prevalence of AF than does screening in the general population.

AF prevalence was 5.3% in this study (n=16/299). Prevalence is expected to increase 2.3-fold between 2016 and 2060 (1) with an observed 0.5% rise seen over five years in England (2% in 2014 to 2.5% in 2019) (16,28). Therefore, 2.7% was selected as a test value to compare with our data for this diabetes sample. The diabetes population in this study showed a significantly greater likelihood of AF than the background population in the one sample t-test t(298) = 2.034, p =.043 (see *Appendix 2L*).

3.5 Diabetes duration and glycaemic control.

To investigate the role of diabetes duration (accounted for by the participant, since a diagnosis of diabetes was given) and glycaemic control (by most recent HbA1c, within six months) in the likelihood of AF being diagnosed, these variables were added to the above logistic regression in Block 2 along with age and sex. The model was statistically significant, X^2 = 12.58, p = .013. The explained variation in the dependent variable based on our model is 14.1% (Nagelkerke R^2 = .141). Neither diabetes duration (p = .649) nor glycaemic control (p = .349) added significantly to the model, with diabetes duration showing the least contribution (diabetes duration OR 1.012; 95% CI .962 - 1.064, diabetes / glycaemic control OR .775; 95% CI .455 - 1.321). Therefore, age was the only predictor of AF in this study (see *Table 2*).

3.6 Screening locations.

There were sixteen people with AF, six of these were detected from the diabetes centre and ten from patients recruited from GP surgeries. There was no significant association between screening location (diabetes centre and GP centre) and likelihood of detecting AF (X^2 (df 2, 299) = 3.641, p = 0.314).

Table 2. Logistic Regression including each independent variable and their statistical significance and prediction of AF.

Variables in the Equation									
								95% CI	
		B	S.E.	Wald	Df	Sig.	Exp(B)	Lower	Upper
Step 1[a]	Age	.086	.031	7.480	1	.006	1.089	1.025	1.158
	Sex(1)	.536	.630	.723	1	.395	1.708	.497	5.872
	Diabetes duration in years	.012	.026	.207	1	.649	1.012	.962	1.064
	Percentage value (HbA1c)	-.254	.272	.876	1	.349	.775	.455	1.321
	Constant	-7.517	3.248	5.358	1	.021	.001		
a. Variable(s) entered on step 1: Age, Sex, Diabetes duration in years, Percentage value.									

4. Discussion

Diabetes as a predictor for AF (controlling for age and sex).

Age was the only significant predictor of AF in this study. This study was open to people over 18 years of age (range 22 - 90 years). The mean age of people with AF was higher than those in a normal rhythm. Previous research shows that AF prevalence shows a strong age dependence varying from 0.5% in patients under 40 years, 5% over 65 years and 10% in octogenarians (1). Ageing is accompanied by atrial structural remodelling, and this is associated with conduction abnormalities (29). These anatomical changes along with comorbid conditions, enhances the risk of developing AF. These findings therefore support screening for AF in older age groups and can help focus screening resource and approach. Opportunistic screening in over 65-year-olds is recommended by clinical practice guidelines and expert consensus (1, 30, 31). A systematic approach whereby those who are older or at higher stroke risk are targeted, is an alternative recommendation (1). Therefore, if focus can be directed to people with diabetes over the age of 65 years, this might offer a feasible and effective approach to AF screening.

In this research, all patients with AF, had type 2 diabetes. Most participants recruited had type 2 diabetes (78%) and this predomination may reflect the prevalence of type 2 diabetes in the population. AF and type 2 diabetes share many risk factors such as obesity, hypertension, and cardiovascular disease. Pathological changes due to hyperglycaemia result in deviation to autonomic nervous tone (6). Chronic hyperglycaemia is a key modulator of atrial remodelling and thus, AF initiation. The loss of insulin production and signalling from type 1 diabetes can lead to atrial electrical remodelling and the mechanisms, therefore, between diabetes and AF initiation are complex (6).

Difference between men and women in terms of frequency with which AF is identified.

This research demonstrated no significant difference in the likelihood of men and women with diabetes being diagnosed with AF but a trend in that direction. Previous research has shown that AF is twice as common in men than women and men develop AF on average, 10 years earlier (32). Women however live longer and so the cumulative lifetime risk of AF is similar (32). The lack of significant difference in this study may be due to the small numbers with AF. Men may have a higher risk of AF because of higher risk factors, but in this population already selected for risk factors (diabetes), less difference may be anticipated.

Prevalence of AF in the diabetes screened population compared with prevalence of AF in the general population.

AF prevalence was 5.3% in this study compared to 2-4% in the general population. It is recognised that the recruitment target was not reached and therefore, may have impacted on AF prevalence and outcome data. Existing literature has shown between 5.2% and 47.1% of people with diabetes also have AF (11, 33). There are limitations to existing studies including lack of adjustment of common risk factors, smaller samples, varying methodologies or where prevalence may be underestimated through less

rigorous approaches to detection (34-36). Detection of paroxysmal AF is an issue when monitoring is of short duration, as in this research. A meta-analysis on over 108,000 patients indicated people with diabetes had a 40% greater risk of AF compared to those unaffected (37). The outcomes therefore in this study whilst higher than the general population, do not reflect the higher prevalence seen in other studies. This may be due to sample size, the voluntary nature of participation and missed paroxysmal AF. Performing larger screening studies with diabetes as the target group would be advantageous whilst utilising repeated monitoring through interval screening or consecutive home readings using a portable ECG application.

Diabetes duration and glycaemic control.

Neither diabetes duration nor stability were significant predictors for AF in this study. Duration of diabetes was specified by the participant and therefore, the accuracy of this may not be entirely reliable. Poor glycaemic control could also impact pathophysiological changes prior to an official diagnosis of diabetes so this window could also impact the progression to AF. The mean HbA1c was comparable in both groups. There were however only 16 people identified as having AF, so this could impact findings. The most recent HbA1c was obtained via pathology records, with the participants consent. The variability with when this was taken, was not specified e.g., was the test taken one week or six months before the AF screening. Diabetes duration has been suggested as relevant in the development of AF, with risk increasing by 3% for each year of treatment (38). The same study also highlighted higher AF risk with increased glucose levels. Higher HbA1c levels had a significant association with incident AF in prospective cohort studies but not in retrospective case-control studies (38). Poor glycaemic control has been further reported to increase AF risk in a recent sub-analysis of patients with diabetes and AF (39). Whilst this was not replicated in this research, it is worthy of consideration for future research with larger samples and where recruitment was not in part, dependent on patient initiation.

Numbers of people detected as having AF in the two screening locations.

There was no difference in the number of people detected with AF between screening locations. Patients from GP surgeries required motivation to attend an appointment, perhaps representing a more engaged approach to healthcare with less symptoms. Attending the diabetes centre is also free and seeing a GP in the study location incurs a fee. This may impact on patient attendance and the affordability for each patient. If additional tests are required, e.g., blood tests, an extra fee is applied as GPs operate as private practitioners. Primary care surveillance is important in diabetes management and socioeconomic status can impact on patients' health stability and longer-term outcomes, (40,41). When cost becomes a factor, this adds further stress and may restrict opportunities for monitoring the disease state. This may though, result in a more diverse population attending free services, such as the diabetes centre, where care can be provided without financial burden. The health needs of people from lower socioeconomic status are reportedly greater than people with higher socioeconomic status and can be a major determinant of health and chronic disease prevalence (42-44).

Participants from the diabetes centre were invited consecutively, on the days and times the lead and assistant researcher were available, and this direct approach may have influenced recruitment. Diabetes and health stability in these participants should be considered, but whilst this group were attending a specialist centre, screening times were random and reason for attendance varied (routine monitoring, podiatry, nurse advice, specialist input). This therefore may contribute to there being no significant difference in AF detection between the two locations. Furthermore, the latter part of screening recruitment occurred during a pandemic and involvement could have been influenced by other factors (isolation, health focus, availability).

5. Limitations

The study was under recruited by 15% as it became challenging to recruit further due to aforementioned reasons. This may have impacted on the results as a smaller sample size can reduce the power of the study and increase the margin of error. A

sample size that is too small increases the likelihood of a type II error skewing the results, which decreases the power of the study (45). Logistical reasons meant recruitment was hindered beyond the sample size obtained yet the study continued despite the potential for less conclusive results as it was still felt that relevant data and trends in this population could be identified, that could be developed in future, larger scale research. As a single point in time screening study, paroxysmal AF may have been missed, however this approach still offers value in AF detection for persistent and permanent. Prevalence was lower than some other studies where a higher prevalence of AF in people with diabetes has been detected (46-49). Differences between these studies and the current AF screening study include age for participant inclusion (e.g., higher prevalence of AF in people with diabetes when only people over 65 years screened (47), methods of screening (repeated, intermittent hand-held ECG screening (49) or continuous 24-hour Holter monitoring (47) and recruitment locality (e.g., a stroke unit (47). Contributing factors may also include recruitment approach between locations. Patients from the diabetes centre for example, were only recruited on days that the researchers were present for screening and therefore, other eligible patients may have been missed. Patients were excluded if they had a pacemaker or implantable cardioverter defibrillator, and this may have impacted on results by potentially underrepresenting AF prevalence. AF in pacemaker or defibrillator patients is not uncommon due to the range of conditions that required the implantation, for example, conduction abnormalities that promote AF development (50). Sinus node disease is an indication for pacing and is associated with AF development and the pacing mode can also impact on AF development, where for example, right ventricular pacing can increase AF risk due to associations with pathophysiological changes which reduce left ventricular function (51). As with the general population, in paced patients, ageing is a factor which may increase the likelihood of needing the cardiac implantable device, along with the increased prevalence of AF (50,51). Patient and public involvement was not included in the design of this study. Incorporating patients in future research relating to AF screening could help ensure the research remains relevant and appropriate, whilst promoting engagement and optimising outcomes.

6. Conclusion

Findings from this study have shown that age is the only predictor for AF in people with diabetes. There was a significantly greater prevalence of AF in this patient group, than in the general population. There was no difference in AF detection between recruitment locations or sex. This adds to existing data around the association of the two chronic conditions and assists in guiding the importance of AF screening in people with diabetes, particularly older patients. Larger screening studies would be advantageous to explore the variables within this study further. This can then inform and contribute to appropriate management of both conditions when in combination, not least with regards to stroke prevention. Up until now, research into screening high-risk patient groups for AF has been approached in combination, rather than as individual risk-factor groups. This can confuse findings, if not controlled for within analyses. Understanding more about the risks imposed by individual risk factors, is valuable when allocating resources for AF screening.

Data availability:

The raw data required to reproduce these findings are available on request, held on a saved file held by the lead author. This is therefore not available on a public repository.

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Chapter 5.

5.1 Quality of life among people with atrial fibrillation with and without diabetes: a comparison study.

Having identified a useful tool for AF detection and then screening to identify AF prevalence and predictors in people with diabetes, it is important to understand the effects AF can have in this population group. Fundamental to treatment and AF management, is understanding the impact this increasingly prevalent condition can have on QoL. AF and comorbid disease can cause emotional compromise, mental health effects and limitations to physical (e.g., daily activities, exercise, and work) and social roles. Comprehension around how AF and diabetes has bearing on individuals QoL can assist in developing the evidence around screening in this increasingly prevalent population.

AF is more prevalent in people with diabetes than the general population and the prevalence of both chronic diseases is growing. Therefore, the effects of these comorbid conditions, can be wide reaching and may be exacerbated when comorbid disease exists in combination.

AF is more than a physical problem for patients. AF affects all aspects of patients' wellbeing and therefore, obtaining information from patients directly through self-assessment, is important for QoL research and overall, in relation to patient management. Understanding how and where QoL is impacted more greatly can then assist with directing treatments appropriately in an individualised way whilst perhaps adding impact on the decision to screen for AF.

The SF-36 QoL instrument was selected to gather responses from people with AF and then people with AF and diabetes in combination, to see how the comorbid disease group compared to the AF alone group. This information adds new insights into QoL when these long-term conditions coexist and lower QoL scores may influence recommendations around screening and targeting specific populations.

Hypothesis 1: People with comorbid AF and diabetes have poorer assessed QoL overall as measured using the total SF-36 score.

Hypothesis 2: People with comorbid AF and diabetes have poorer assessed QoL in each of the eight domains within the SF-36 survey, than people with only AF.

Null hypothesis: Diabetes has no effect on QoL in people with AF, as assessed by the SF-36 overall score or eight domains.

5.2 Quality of life among people with atrial fibrillation with and without diabetes: a comparison study.

Paper 3.

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The published version of this paper can be found in Appendix 3G.

Chapter 5.

Quality of Life among people with atrial fibrillation with and without diabetes: a comparison study.

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Chapter 5.

Abstract

Introduction: Quality of life [QoL] is an essential consideration when managing the wellbeing of patients and assists in interpretation of symptoms, functional status, and perceptions. Atrial fibrillation [AF] and diabetes demand significant healthcare resource. Existing data demonstrates a negative impact on QoL as individual conditions, but there is less evidence relating to the impact of these disease groups in combination. This study therefore explores QoL in patients with AF and diabetes.

Methods: This cross-sectional, observational study required participants to complete the SF-36 survey via an online platform and was offered to people affected by AF alone and people with AF and diabetes in combination. The SF-36 provides a pre-validated tool with eight domains relating to physical and psychological health.

Results: A total of 306 surveys were completed (231 - AF group, 75 - AF and diabetes group). The mean and SD were calculated for each QoL domain, after re-coding in accordance with SF-36 guidance. MANOVA demonstrated an overall significant difference between the groups when considered jointly on the variables (Wilkes Λ =0.777, F(8, 276) = 10.113, p=<0.001, partial η^2= .227). There were significant differences between AF and AF / diabetes QoL responses in Physical Functioning, Energy Fatigue, Emotional Wellbeing, Social Functioning and Pain. In these domains, the mean was highest in the AF group. There were no significant differences in the Role Physical, Role Emotional and General Health domains.

Conclusion: This study demonstrates that diabetes and AF has a more detrimental effect on QoL than AF alone, in the majority of domains. Further research into the general AF population and where chronic conditions coexist is important to comprehend the true impact this disease combination has on QoL.

Keywords:

Atrial fibrillation, diabetes, quality of life.

Chapter 5.

Conflicts of interest and sources of funding:

None declared.

Key messages and what's new?

- Quality of Life is an essential consideration when managing the care of patients with chronic conditions. Whilst research has explored the impact atrial fibrillation can have on quality of life, this has not previously been explored when combined with diabetes – two common and increasingly prevalent long-term conditions.
- This study suggests that when atrial fibrillation and diabetes co-exist, quality of life is worsened in relation to Physical Functioning, Energy and Fatigue, Emotional Wellbeing, Social Functioning and Pain.
- This study did not show a significant difference in the Role Physical, Role Emotional and General Health domains between groups.
- Diabetes and atrial fibrillation often co-exist and awareness of the impaired quality of life as demonstrated in this study, should guide targeted management of both conditions in order to prevent a worsening to patient's quality of life.

Abbreviations:

AF	Atrial fibrillation
CHA_2DS_2-VASc	Congestive cardiac failure, Hypertension, Age, Diabetes, Stroke, Vascular disease, Age, Sex - stroke risk stratification scoring system (2 represents a score of 2 being assigned to the patients' risk for that category)
ECG	Electrocardiogram
QoL	Quality of Life

SF-36	Short Form Health Survey
MANOVA	Multivariate Analysis of Variance

1.1 Introduction

It is important to consider quality of life [QoL] when managing the health and wellbeing of patients as it assists in the interpretation of symptoms, functional status, perceptions, experiences, and patient expectations (1). Atrial fibrillation [AF] and diabetes are both long-term conditions that are increasing in prevalence. Both AF and diabetes can influence physical and psychological health and reduce QoL (1). Evidence has shown that in up to 40% of patients with diabetes, AF can coexist (2) and little is known about how diabetes can further worsen QoL in AF. This comparison study therefore explores the QoL in these often-coexisting long-term conditions.

1.2 Background

QoL is a subjective phenomenon, based on individual perception and developed through experiences and beliefs (3). QoL has also been referred to as the relationship between actual and desired health and functioning with interchangeable broader terms including health status (4). Thus, the inclusion of symptoms, functional status, control, autonomy, general life satisfaction and health perceptions are all important and reflect necessary components when assessing QoL, meaning multimorbidity may not simply equate to poor QoL.

Patients own assessment of their QoL is vital in treatment decision making as this may be incongruent with that of the health professional's judgement (4). This can be through informed discussions central to understanding the impact of interventions on patient's lives rather than just their bodies and medicalised outcomes.

QoL in AF

AF is the most common heart arrhythmia and has a significant impact on morbidity and mortality (2). Symptoms and complications can be debilitating as can side effects of treatments e.g., medication use. Rhythm control of AF is usually adopted to improve symptoms, yet evidence demonstrates that a heart rate control approach is often superior in terms of QoL (5). Furthermore, AF can induce anxiety, depression, emotional distress, and a decline in cognitive function (6). The accumulation of interventions, effects, or adverse outcomes, further compounds the overall wellbeing of patients with AF.

Most AF QoL studies have assessed symptomatic patients who are intolerant or refractory to anti-arrhythmic treatments, or who have undergone intervention, for example cardioversion or ablation (7, 8). Rate or rhythm correction has generally been the focus of QoL studies, and they have therefore been potentially biased towards selection of patients with symptoms or subgroups from clinical trials - baseline QoL scores have tended to be lower than the general population in these studies (1, 7, 9). AF stability can also impact on QoL scores, and this was represented in a study investigating the impact of paroxysmal AF, demonstrating an inferior QoL when uncontrolled (10). When AF is permanent, an improvement psychologically and physically is often seen due to less anxiety and treatment stability (7). There has been less focus on assessing QoL in the general AF population who may not be undergoing intervention.

QoL in diabetes

QoL in patients with diabetes has also been reported to be worse than that of the general population, compounded by older age, concomitant chronic disease, poor diabetes control and polypharmacy (11, 12). When diabetes coexists with other chronic illnesses, the effect can be worse (13, 14). Severe comorbidity (over five conditions) or the co-occurrence of two or more active health conditions that may or may not be linked by a causal relationship, has shown the greatest impact on people's wellbeing (14, 15).

1.3 Study aims and hypotheses

The purpose of surveying people with AF is to provide further information on QoL in the general AF population rather than, as many QoL studies have been focused, immediately after treatment or intervention. Surveying people with both AF and diabetes will provide insight into the effects of these chronic diseases in combination whilst informing directed treatment and supporting patients' wellbeing.

Hypothesis 1: People with comorbid AF and diabetes have poorer assessed QoL overall as measured using the total SF-36 score.

Hypothesis 2: People with comorbid AF and diabetes have poorer assessed QoL in each of the eight domains within the SF-36 survey, than people with only AF.

Null hypothesis: Diabetes has no effect on QoL in people with AF, as assessed by the SF-36 overall score or eight domains.

2. Methods

2.1 Design and Procedure

In this cross-sectional, observational comparison study, participants with a) AF alone and b) AF and diabetes completed a QoL survey via an online platform, using the SF-36 (16). This is a measure of functional health status, an important aspect of QoL, that relies upon patient self-reporting. It provides a pre-validated tool with previous application to both the AF and diabetic population but not specifically to these groups together. This tool includes eight domains relating to physical, social, and emotional functioning, pain, and general health; a high score denotes a more favourable outcome, that is, better QoL (16).

The survey was available online and clearly signposted on the Arrhythmia Alliance (www.heartrhythmalliance.org/aa/uk) and Atrial Fibrillation Association website (www.atrialfibrillation.org.uk). The website link opened the survey, with an introduction outlining the withdrawal procedure using a unique identification code that the participant added at the end of their survey. There were no external

advertisements relating to this and visitors to either website voluntarily elected to complete the survey at their convenience. Consent was assumed by the self-initiation of completing the surveys, without coercion, and this was outlined in the introductory section of the survey. The survey was available for as long as was required to obtain the sample size needed and this took approximately four months. QoL was measured once. No specific data was collected relating to participant demographics or the presence or type of comorbid disease; the study focused on exploring QoL in people with AF and diabetes, compared to AF without diabetes and it is the disease combination of interest here, more so than the potential confounders, and the relevance of impacted QoL from increasingly prevalent comorbid health conditions. It is, however, accepted that the relevance of such data is valuable in QoL research so the impact of such variables should be considered and incorporated in future research.

2.2 Participants

2.2.1 Sample size

A power analysis calculation was used (GPower®) to determine the appropriate sample size. A significance level of 0.05, a power of 80%, a signal: noise ratio of 0.4 (considered as 'medium') and testing differences between two groups, revealed a sample size of 249 participants when applying the appropriate test e.g., MANOVA. It was anticipated that approximately half the number of surveys should be completed by people with AF and half by people with AF and diabetes.

2.2.2 Eligibility

Eligibility criteria included participants who had a known diagnosis of AF or AF and diabetes, were eighteen years of age or older and could read and understand written English. This was important as participants completing the surveys needed to be able to interpret the set questions and answer these as accurately as possible. The surveys were only available in English due to the lack of immediate and adequate translation

ability. As the surveys were online, this excluded people without access to the internet and this is recognised in the limitations of this study.

2.3.3 Statistical analyses

Data were entered and analysed using IBM SPSS Statistics for Windows (Version 26.0; SPSS, Inc.). A p value of <0.05 was considered statistically significant. To make decisions on the treatment of missing data, the distributions of each domain were considered, such that the appropriateness of substituting the mean could be determined. Data were not normally distributed in all domains and missing data from unanswered questions were minimal with some variation across questions missed (i.e., it was not always the same question unanswered) and therefore, these were left blank, and the mean was not applied.

The study followed the SF-36 recommended analyses with scoring as a two-step process; first, pre-coded numeric values are recoded as per a standard scoring key (16). Items are scored and range from 1 to 100 - high scores denoting a more favourable QoL. Secondly, items in the same scale are averaged together to create the eight scale scores. Items left blank are not taken into account when calculating the scale scores (16). Means (illustrated in *Figure 1*) and SDs were calculated for the eight domains.

Scores from subscales often have skewed distributions but despite the theoretical reasons why parametric approaches might not be the most appropriate, this approach is favoured in terms of simplicity and the ability to adjust for confounders, whilst facilitating comparisons with other datasets. Distribution was explored using skewness and kurtosis as well as visually from histograms (*Appendix 3F*). Z scores were also calculated to measure where the data lies in the data distribution. Following a review of health related QoL research, MANOVA was applied to look for differences between the AF and AF and diabetes groups when considered jointly on the variables. To examine the hypothesis that people with co-morbid AF and diabetes have poorer assessed QoL than people with AF alone, a one way between participants MANOVA was conducted to compare the SF-36 scores in each of the eight domains between the two groups. This was then applied to the overall difference in SF-36 score between the

two groups. Variables e.g., age and sex, were not adjusted for in the MANOVA as this data was not collected.

2.4 Ethical approval

The study was approved by the Faculty of Health and Medicine Research Ethics Committee from the University of Lancaster (Ref: FHMREC18070) and the Jersey Health and Community Service Research Ethics Committee. The research was undertaken in accordance with the principles stated in the Declaration of Helsinki. Through online survey completion, consent was given. No personal or identifiable details were requested, and the survey was therefore anonymous.

3. Results

A total of 306 surveys were completed over a four-month period, in 2021 (231 (75.5%) with AF and 75 (24.5%) with AF and diabetes, perhaps reflecting the frequency of comorbidity).

Descriptive statistics

Descriptive statistics including means (illustrated in *Figure 1*) and SDs were calculated for the eight domains in both groups, suggesting a more favourable QoL outcome when people have AF alone rather than AF and diabetes combined, in every domain besides the Role Emotional scores (*Figure 1*). The domains which scored highest in terms of QoL for people with AF alone were Pain, Emotional Wellbeing and Physical Functioning respectively. The lowest scores and therefore, poorest QoL, came from the Energy Fatigue domain in both groups.

The distribution of scores illustrated the skewed nature of the domain scores in the two groups as anticipated for Role Physical and Role Emotional as these are inherently categorical and can therefore be misleading (see *Appendix 3E and 3F*). This was the same in both the AF and the AF and diabetes groups. The interquartile range was included in the descriptive statistics (*Appendix 3E*), along with the median score,

indicating a wide spread of the central portion of data in the Role Physical and Role Emotional domains in both the AF and the AF and diabetes groups.

MANOVA

The MANOVA demonstrated an overall significant difference between the AF and AF and diabetes groups when considered jointly on the variables, Wilkes Λ =0.777, $F(8, 276) = 10.113$, p=<0.001, partial η^2= .227. Tests of between subjects' effects provided individual differences between groups in each domain and where there was a significant difference, means were examined to describe the differences. There were significant differences between AF and AF and diabetes QoL responses in the Physical Functioning ($F(1,283) = 35.086$, p=0.001), Energy Fatigue ($F(1,283) = 4.989$, p=0.026), Emotional Wellbeing ($F(1,283) = 4.518$, p=0.034), Social Functioning ($F(1,283)$ 4.241, p=0.040) and Pain ($F(1,283) = 7.599$, p=0.006) domains. The group with AF and diabetes therefore, experienced more difficulty with physical functioning roles which includes tasks such as climbing stairs, lifting, or carrying items, walking on the flat or undertaking exercise. People with AF and diabetes also experienced more fatigue, more pain and poorer social functioning than people in the group with just AF. Their emotional wellbeing was also more compromised, encompassing considerations around how nervous, calm, low in mood and then happy they felt. In all these domains, the mean was highest in the AF group (*Figure 1*). There were no significant differences in the Role Physical, Role Emotional and General Health domains (all p values were >0.05). Of these, the mean was highest in the AF and diabetes group combined in Role Emotional. In General Health, the mean was higher in the AF group but not significantly so.

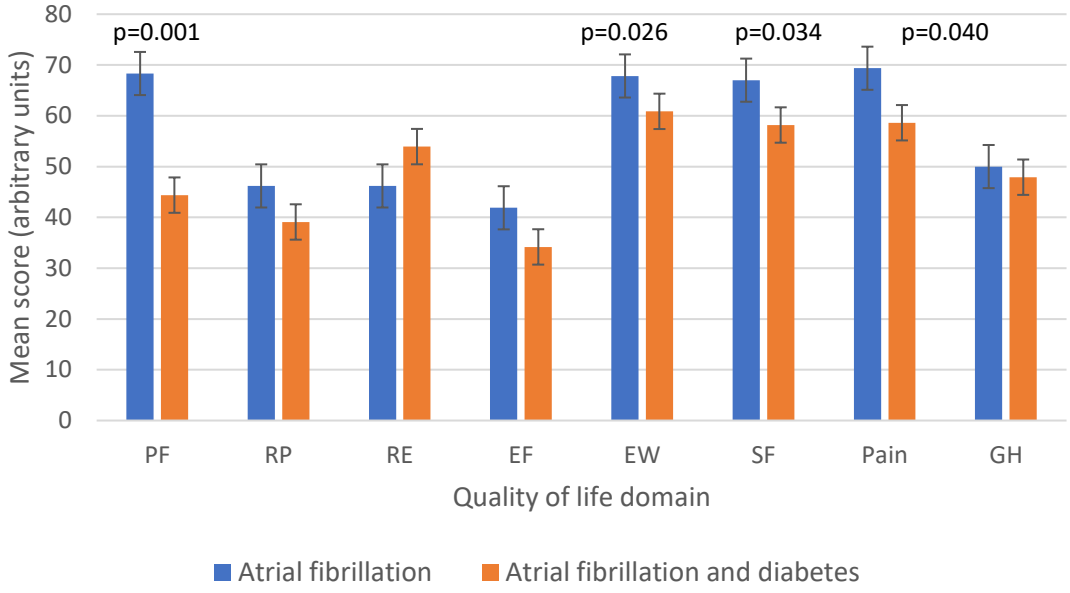

Figure 1.

Mean scores for each domain in the SF-36 quality of life measurement tool, *for people with atrial fibrillation and people with atrial fibrillation and diabetes.*

Data are reported as means +/- standard deviation. PF Physical Functioning, RP Role Physical, RE Role Emotional, EF Energy Fatigue, EW Emotional Wellbeing, SF Social Functioning, Pain, GH General Health.

Discussion

Overall, there was a significant effect such that the AF only group had better QoL than the AF and diabetes co-morbid group. There were no significant differences between groups in the Role Physical, Role Emotional and General Health domains. This therefore does not support the hypothesis that QoL would be lower in all domains between groups. The questions that encompass the Role Physical domain centre around being able to perform physical duties, limitations, and ability to perform work requiring effort. The means for Role Physical in both groups were not too dissimilar, albeit with a slightly higher mean in the AF group. The impact of diabetes on Role Physical may be related to other factors. For example, stability of diabetes can affect QoL and ability to function physically can be impaired where glucose control is more erratic. A study exploring QoL in people with diabetes alone (using SF-36)

demonstrated lower mean scores across almost all domains when diabetes was poorly controlled with the largest difference noted in Role Physical, General Health, and Energy Fatigue (17). Similarly, stability of AF can also negatively impact QoL, and this has been recognised in research outside of this study (10).

The lower QoL mean scores in the domains where there was a significant difference (Physical Functioning, Energy Fatigue, Emotional Wellbeing, Social Functioning, Pain) were when AF and diabetes co-existed. This supports the hypothesis in part and supports wider evidence whereby the coexistence of chronic disease results in a poorer QoL across physical and psychological domains (1, 7, 14), with AF and diabetes being linked specifically (1, 18). However, this study did not obtain information on the coexistence of other chronic disease, and this could have impacted results. Furthermore, age can impact QoL, but participants age was not recorded in this study.

Both AF and diabetes have been associated with anxiety and depression, and scores for Emotional Wellbeing and Social Functioning were lower when the conditions coexisted. Duration of diabetes has shown to impact QoL with the longer duration diagnosis being detrimental to QoL (13). This impacts Social Functioning also, and the significantly lower scores for the AF and diabetes group can be further explained through the assumed influence of complications and treatment stability. Conversely, duration of AF has shown contradictions in terms of psychological wellbeing (7), and this might in part, support the findings in this study. Longer duration AF has been shown to improve QoL in terms of emotional wellbeing and anxiety due to acceptance of the condition, fewer symptomatic episodes, less variation in therapies and reduced hospital visits (7, 19). New onset AF can negatively impact QoL due to anxiety around a new diagnosis and unfamiliarity of symptoms. Further research has shown that the earlier treatment can be initiated, the better outcomes patients have in terms of QoL (7, 10, 19).

This study has also highlighted that the Energy Fatigue domain scored lowest in both groups, and this is unsurprising when reduced energy and fatigue are commonly cited by patients with AF. It is also noteworthy that Pain scores in the AF group are not too disparate from the guidance mean provided by SF-36 (70.77) (16) but is scored

significantly lower in the AF and diabetes group. As with other domains, this may be representative of the comorbid conditions often in existence alongside AF and diabetes, therefore reflecting the poorer QoL when multi-morbidity exists.

Sociodemographic and clinical information was not collected on participants in this study, nor was information relating to psychosocial factors, health behaviours and prevalence of comorbid disease. These variables can impact QoL in people with AF and diabetes and the likely presence of comorbidities with existing cardiovascular and metabolic disease, may negatively impact QoL beyond the existence of AF and diabetes, alone. Evidence has demonstrated correlations between demographic factors such as increasing age and (female) sex (11,20), existence of comorbid disease (11, 13, 19, 20), psychological and emotional health (6, 21) and disease stability (22, 23) with both AF and diabetes. The absence of this information in this present study can be problematic as variables cannot be adjusted for within the available data.

Whilst this study did not incorporate a third group of people with just diabetes, it is important to consider the impact on QoL, before combining with AF. Making direct comparisons is difficult due to varying study designs, but it is apparent that QoL in people with diabetes does not appear to be assessed quite so poorly (with higher mean scores) compared to when AF is present or indeed when AF exists alone (18). And whilst statistical comparisons have not been made, it is acknowledged that QoL is negatively impacted in the presence of diabetes alone, but perhaps less so in Physical Functioning, Pain, and General Health (11, 17, 24, 25). It therefore appears that it is the existence of AF that has the biggest impact, whether as a lone diagnosis, or combined with diabetes.

Limitations

Patients and the public were not involved in the design of this research. The benefits of doing so, might have contributed to the implementation and engagement with this research and would be considered in future studies related to QoL and AF. It was anticipated that half the surveys would be completed by people with AF and the other half, by people with AF and diabetes. The distribution was not equal, with more

people completing the AF alone survey. Demographic data were not collected in this study and therefore contributing factors may not have been accounted for e.g., age or sex. Information on health status, coexisting chronic conditions or symptoms relating to either AF or diabetes was not obtained. Furthermore, duration of diabetes and type of AF was not asked, and this might have been beneficial to outcomes as both can impact on health related QoL. It is also acknowledged that the survey was only available online and therefore precluded completion by those without access to the internet. It is also noteworthy that those accessing an AF website who voluntarily complete such surveys, may be better informed about health, higher socioeconomic status, be more engaged, and more inclined to focus on symptoms with a perceived effect on QoL and thus, may have impacted the outcomes of this study.

Future research

Future research focusing on QoL in AF and diabetes as co-existing disease, or with other chronic disease combinations often prevalent with these conditions, is recommended following this study, with modifications to enhance comprehension around the impact from potentially contributory factors. These factors might include sociodemographic data, presence of other comorbid disease, duration, stability, and symptoms of the existing diagnoses. Alternative QoL measures could add value in terms of the data obtained from participants by including a disease specific QoL tool or considering the use of more specific tools for mood, anxiety, and emotional health. Accessibility to the QoL measures could also be enhanced by making these available on paper and via a Cardiology and Diabetes clinic, or via primary care.

Conclusion

This study focused on people with AF with and without diabetes and has suggested that the coexistence of diabetes and AF has a more detrimental effect on peoples' QoL than when AF exists alone in the majority of the domains. Both conditions are growing in prevalence and a negatively impacted QoL has detrimental effects on individuals, society, healthcare, and economy. Further research into the general AF population and where chronic conditions coexist is important to comprehend the true impact as it

is recognised that the ageing population will more commonly have combined comorbid conditions. In addition, understanding of QoL is also important to help inform and promote appropriate and targeted management of these patient groups both medically and psychologically. The appraisal and re-appraisal of treatment decisions for patients with AF (and diabetes) requires focus in terms of QoL and should be central to treatment options when caring for these patients.

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Data availability

The raw data required to reproduce these findings are available on request, held on a saved file held by the lead author. This is therefore not available on a public repository.

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Chapter 6.

6.1 Should we be screening people with diabetes for atrial fibrillation? Exploring patients' views.

Appreciation of patients' views within healthcare and patient orientated research is crucial to inform healthcare practices through elucidation of direct experiences in a way that incorporates evidence-based practice effectively. The two studies so far (the AF screening study - *Study 1, Chapter 4* and the QoL study - *Study 2, Chapter 5*) have adopted a quantitative methodology relating to AF prevalence and QoL data. The scientific metrics relating to the ECG screening device (the AliveCor® device) are presented in the systematic review in *Chapter 2*, and the tool implemented in practice throughout screenings undertaken in *Study 1* (*Chapter 4*). To further address the question of 'Should we be screening people with diabetes for AF?' and supplement these findings, this third study introduces a qualitative approach, adopting semi-structured interviews to gather patients' feedback about their understanding of AF and experiences of AF screening (in *Study 1*). Obtaining patient feedback is important when planning and evaluating care, to optimise outcomes and enhance care delivery. Elucidating patients' views in this research, can help address the areas where screening uptake may be compromised, explore the barriers to screening engagement and use this information to develop AF screening programmes, particularly in the presence of diabetes within which this research relates. Understanding beliefs and attitudes that patients' hold central to their willingness or avoidance to attend AF screening, means focus can be directed to these areas to promote engagement.

Comprehension around the behavioural and human factors that contribute to screening uptake is important, as this can help comprehend reasons prohibiting and encouraging screening attendance. Applying relatable theories including the health belief model and that of care seeking behaviours, can assist with understanding factors that impact on screening engagement. In this instance, where AF screening in people with diabetes is the focus, factors relating to underlying beliefs, perceived

efficacy and risks, knowledge around the conditions, intentions, external influence, and socioeconomic status, are all relevant. It is important to also consider age and how this might impact on screening involvement for AF, particularly when the evidence from the AF screening study (*Study 1, Chapter 4*) and wider research shows an increased prevalence of AF in older age groups. Efforts to increase participation and promote adherence to screening campaigns, particularly in older people, where risks associated with AF are often greater, would be appropriate and this might involve considered thought regarding, for example, screening environments.

This interview-based research identifies common themes from patients that impact AF screening priorities and can be used in conjunction with findings from the research within this thesis, to encourage and support active screening for AF. Obtaining feedback from patients on aspects of screening delivery means information is being delivered from those experiencing the intervention. This should be embraced and then screening and associated care, directed or co-created in partnership, accordingly. In the same way as views are received here from patient interviews, self-assessment of psychosocial and physical effects from illness or treatment, should be encouraged and this links with QoL outcomes, from *Study 2* (*Chapter 5*). It is the amalgamation of these inter-related components of screening and subsequent care, that can develop the evidence around AF and diabetes as comorbid conditions that deserve screening focus. Incorporating patients' experiences, offers further insight into the screening discussion, providing valuable and supplementary information regarding screening recommendations and public health initiatives. This qualitative study also explores patients' understanding of AF, their views on incorporating screening into routine care and feedback relating to the screening tool used in the screening study.

Research questions:

What do patients understand of AF?

What are patients' views on screening for AF, particularly when diabetes is an existing condition?

How do patients view screening tools for AF? Is this seen as a beneficial and tolerable approach?

6.2 Should we be screening people with diabetes for atrial fibrillation? Exploring patients' views.

Paper 4.

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The published version of this paper can be found in Appendix 4E.

Chapter 6.

Should we be screening people with diabetes for atrial fibrillation? Exploring patients' views.

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Chapter 6.

Abstract

Introduction

Atrial fibrillation [AF] and diabetes are increasingly prevalent worldwide, both increasing stroke risk. AF can be detected by many ECG screening applications, many being patient-led. Understanding patients' views around AF screening is important when considering recommendations and this study explores these views where there is an existing diagnosis of diabetes.

Methods

Nine semi-structured qualitative interviews were conducted with participants from a previous screening study (using a mobile ECG device), who were identified with AF. Thematic analysis was completed using NVivo 12 Plus software and themes were identified within each research question for clarity.

Results

Themes were identified in four groups: 1) patients' understanding of AF and its consequence; 2) patients' views on health screening and screening for AF; 3) patients' preferences and priorities on how screening can be incorporated into routine care and 4) patients' views on the screening tool.

Conclusion

Eliciting patients' views has demonstrated the need for clear and concise information around the delivery of an AF diagnosis. Screening initiatives should factor in location, convenience, personnel, and cost, all of which were important for promoting screening inclusion.

Key words

Atrial fibrillation, diabetes, screening, patients' views

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Key messages and impact:

▪ AF and diabetes are increasing in prevalence and are risk factors for stroke. Patients understanding of their AF is important for treatment concordance.

▪ Patients' views on screening for AF demonstrates this as an accepted and beneficial undertaking with screening tools and location important for screening attendance.

▪ Incorporating patients' views and experiences is essential within patient orientated practice and research and outcomes should be applied to the design of screening programmes.

Author contributions: Angela Hall was the lead author who devised the study, conducted the research, analysed the results, and prepared the paper. Andrew Mitchell was clinical supervisor and reviewed the manuscript and results. Lisa Ashmore and Carol Holland agreed the study design, Lisa Ashmore contributed to the interview questions and themes, and both acted as academic supervisors. Both reviewed the results and paper.

Chapter 6.

1. Introduction

There is an increasing prevalence of atrial fibrillation [AF] worldwide with a one in three lifetime risk of developing AF over the age of 40 years (1). AF is a leading cause of stroke and stroke risk is increased further in the presence of diabetes (2). Diabetes has also been recognised as a risk factor for developing AF and therefore, targeted screening for AF in such groups has been explored in combination with other comorbid risk factors (2).

There is yet to be universally accepted recommendations for AF screening. The European Society of Cardiology [ESC] recommend opportunistic screening in people >65 years and consideration of systematic screening when >75 years or in those at higher risk of stroke (3). The AF-SCREEN collaboration promotes world-wide implementation of AF screening in people >65-years (4). Furthermore, Public Health England incorporate AF within their 'ABC' [Atrial fibrillation, Blood pressure, Cholesterol] campaign for cardiovascular disease prevention with emphasis on nationwide screening for AF (5).

Opportunities for AF screening is enhanced through commercialisation of digital monitoring applications (6). Many of these can be patient-initiated and it is therefore important to understand patients' views of AF screening as little focus has been afforded here in AF screening studies. Rather, validity and feasibility of AF screening protocols has received greater attention with qualitative data obtained by exploring the views of health professionals on screening processes or screening tools (7, 8). The views of population groups likely to undergo AF screening is needed to inform screening recommendations relating to acceptability and engagement with implementation programmes.

This qualitative study therefore seeks to explore patients' views and understanding of AF. Patients' experiences of AF screening (from screened patients in the previous study), is also explored (9). Patients' views on how we can incorporate screening into routine care and the screening tool used to detect AF in the aforementioned research is also sought in this study.

1.2 Research Questions

The research questions for this study are:

What do patients understand of AF?

What are patients' views on screening for AF, particularly when diabetes is an existing condition?

How do patients view screening tools for AF? Is this seen as a beneficial and tolerable approach?

2. Methods

2.1 Study design and study materials

This study adopted a qualitative design, with one-to-one in-depth semi-structured interviews with patients who had diabetes and then a diagnosis of AF from the screening study. The interview schedule is set out in *Table 1*. The interview questions were devised to answer the research questions as appropriately as possible, and in response to the AF screening study from which the participants were recruited. The research and interview questions were developed from existing literature (1, 3, 4, 7, 10 - 18) and organisational guidance and recommendations around health screening (19 - 21). Obtaining views regarding their experiences of AF screening was important, along with participants' views on how screening might be incorporated into routine care. This information could then be used to inform how screening practices might be more appropriately implemented from the patients' perspective. The questions were designed to encourage conversation, in an open-ended style. The interview schedule was not altered throughout the course of the interviews.

Table 1. Interview schedule.

1. I'd like to ask you about the day you had the AF screening. What happened during the screening episode? What do you remember about the information given beforehand?
2. What is your understanding of atrial fibrillation?
3. What are your views about screening for health conditions in general?
4. What are your views about screening for atrial fibrillation? (Consider benefits and negatives of screening as prompts).
5. Before you took part in the first part of this study, had you considered the relationship between diabetes and AF? Can you tell me why you think this?
6. How do you think we could include screening into routine care?
7. What are your thoughts on the screening device used to record your heart rhythm (ECG) in the screening study? If this device was available to screen again, how would you feel about using this for further screening?
8. Did you have any reservations about taking part and if so, can you tell me a bit about them?
9. Do you have any regrets about taking part and if so, can you tell me a bit about them?
10. Is there anything else you would like to share about your participation in the atrial fibrillation screening study or your thoughts about atrial fibrillation?

2.2 Recruitment and sample

Patients were recruited from a previous screening study, all of whom were eligible for inclusion in this current study as they had documented AF during the AF screening research. Inclusion criterion for this study was participants who were eligible in the previous research, and this included people with diabetes, who were eighteen years of age or over, who could understand English, and had capacity to consent. People were excluded from the original AF screening study if they were unable to get to the screening location and if they had a pacemaker or internal cardioverter defibrillator.

The eligible participants were telephoned and invited into this study, then sent an information letter and consent form. After a two-week reflection period, invitees were telephoned again to confirm consent for interview. Consenting participants returned a signed consent form in a stamped addressed envelope and a time convenient to the participant scheduled for interview. Of the sixteen eligible participants, nine were

interviewed (two had died, four were uncontactable and one declined). Ethical approval was granted by the Faculty of Health and Medicine Research Ethics Committee at the University of Lancaster (Ref: FHMREC20156) and the Health and Community Service Research Ethics Committee in Jersey (Ref: 2021/HCSREC/02).

2.3 Procedure

Telephone interviews were audio-recorded with a voice recording device. Recordings were transcribed verbatim and anonymised (by assigning identification numbers). Interview duration ranged from thirty to sixty minutes. Interviews were conducted by the first author (AH), using the semi-structured interview guide (*Table 1*). Open ended questions were posed, allowing for new areas of conversation to emerge and explore.

2.4 Data analysis

Interviews were transcribed by the lead researcher (AH). NVivo 12 Plus qualitative data analysis software (QSR International) was used to support both inductive and deductive thematic analysis of the transcripts. Thematic analysis involved reading each transcript carefully and repeatedly, several times, identifying patterns and assigning codes (22). Initially this was through reading line-by-line, using descriptive labels, pen, and paper, highlighting text, and identifying codes and themes. The coding schema was then iteratively refined, and themes and sub-themes developed inductively from the data, focusing on factors participants spoke about in greater depth, rather than their prevalence (although there was some correlation). No triangulation was used, and data analysis was undertaken by the lead researcher (AH). When no new data, themes or relationships could be identified, no further data analysis was undertaken. As a specialist in the management of AF, the lead researcher (AH) had an in depth understanding of AF and tried to impose no influence during interviews but there may have been inference through phrasing, due to predetermined expectations.

3.Results

Of the nine participants, eight were male and the mean age was 69 years (range 53-86). One participant was female and the remaining three women who were eligible for

inclusion, either declined the invitation (*n*=1) or had died (*n*=2). Developed themes were assigned within each of the research questions with sub-themes where appropriate. (Numbers in brackets identify the participant).

3.1 Patients understanding of AF and its' consequences'.

***Sub-Theme*:** The concept of irregularity.

Patients were asked about their understanding of AF. All participants knew this related to their heart and some, but not all, mentioned that AF related to an irregularity.

'Well it's an irregular heartbeat.' (9)

'Well it's an electrical irregularity and I'm taking blood thinners for it.' (2)

'It's something to do with an irregular movement [of the heart valve].' (7)

'I know the doctor said your heart misses something…'. (8)

Varying descriptions demonstrated different levels of understanding including mention of double heartbeats, too much blood flowing through the heart, one side of the heart not running properly or at the right beat and the heart pumping too fast.

***Sub-Theme*:** Consideration of consequence.

Infrequently, blood thinning medications were identified as relatable to AF with two participants mentioning blood thinners as part of their treatment and another naming their anticoagulant. Nobody directly referred to stroke within their understanding. It was considered that AF was a consequence of stress, and another considered their high blood pressure was relatable to AF. A 'leakage of water' in the legs was also described which was considered to be connected with AF by either the arrhythmia causing the water leakage or vice versa.

'…I mean apparently I've had this problem for quite a long time and it was caused through stress and anxiety.' (4)

'…I'm taking blood thinners for it which makes it easier to be pumped round…' (2)

'I am taking it now…a medicine called Apixaban.' (9)

This varying recall of previously provided information was apparent, despite all participants being informed by the lead researcher [AH] at the time of screening and diagnosis, having an AF information sheet and also visiting their GP for follow-up. Some also had subsequent visits to the hospital for cardiac investigations and specialist clinical involvement.

3.2 Patients' views on health screening and screening for AF.

When asked for their views on health screening in general, patients were able to draw on experiences of screening for their heart, diabetes, eyes and prostate and their insights may therefore represent the demographics of this population. For example, some participants talked of relatable screening to their comorbid conditions including blood glucose monitoring and retinal screening.

Sub-Theme: Screening as a resource intensive initiative.

Patients reported various factors relating to resource including cost of screening and screening location. Age was also referred to with comments relating to who and when screening could be considered.

The majority of participants mentioned cost within their dialogue, referring to cost of a screening or even general appointment, cost of the tests and cost of even getting to the appointment. Cost saving was also talked of for longer-term benefits.

'*You gotta think of the cost… the amount of people, the number of appointments mucks the hospital up. I don't know what it costs for every appointment at the hospital. Must be a hundred quid.' (6)*

'Doesn't take any time and you'd err you'd soon see trends building up. It could save a fortune.' (2)

Views on screening location revealed that visiting the General Practitioner [GP] for this purpose was more favourable than the hospital with the majority preferring GP-screening, to lessen the ordeal of hospital attendance which was seen as having a

negative influence on screening opportunities. Besides GP-screening, other clinically relevant departments were suggested e.g., the eye department (for retinal screening) and diabetes outpatient centre.

'*Well I suppose the best, well, one way would be through your GP wouldn't it, if they had time'. (3)*

'I mean if I get a letter from the hospital saying we are doing XY and Z screening please make an appointment for screening, I throw it in the bin'. (9)

Without prompting, reference was made to the appropriate age of people to undergo screening, in general and in relation to AF.

'*Well maybe some of it could be when you get to a certain age maybe the doctors could do a bit of a screening could they? [The interviewer asked what age they thought would be appropriate]. Umm, say 50, 55 I suppose'*. (6)

'*…certainly if you're over 50 or whatever, you can do a lot of simple screening on your phone*.' (2)

***Sub-Theme**:* Fear of outcomes from screening**.**

Patients reported disparate expectations ranging from fear around screening engagement, to wider reaching benefits in relation to their own health. The 'need' to know and the 'necessity' of knowing about health conditions was reported. None of the participants regretted taking part and all preferred to know about their health and diagnoses.

'*Umm, I do like to know but I know a lot of people don't like to know. I like to know what I have…' (8*)

'*It if helps people find out about stuff, if you're not a guinea pig you might not find about cancer or things… That thing you did with me [referring to the AliveCor® heart rhythm recording], I wasn't worried about it. If you don't do it, you don't know.' (6)*

'…the benefits of that are you know your hearts not running properly so it could be put back into the right way, so it's running right again.' (6)

Follow up as a result of the screening including appointments, time off work and consequence, was included in responses, although these were from hypothetical scenarios, rather than personal experiences. One referred to an anecdote from a well-known politician.

'Well that is what I call the Ronald Regan approach… …doctors started to explain to him around his hospital bed about what they were going to do and what well, err, he started cracking jokes at them. And then he explained his attitude and said 'I don't care what you have to say, just cure me.' (9)

'…still too many people in the United Kingdom are afraid of discovering something is wrong. Umm, they're thinking there might be something wrong but it could be rectified. And umm, they're worried about taking time off work and the whole thing, they're worried about taking up the doctors time…worried they won't get an appointment and waiting lists… sort of universe of distracting concerns…' (9)

Sub-Theme: Expectations of screening reliability.

Lack of education around the positive benefits of health screening was shared by one participant, who felt that their own level of knowledge and scientific understanding resulted in their personal acquisition and desire for more in depth medical knowledge. The accuracy of ECG screening and monitoring was felt to be reliable by the same participant.

Reliability of the screening procedure or test was voiced with another patient wondering how accurate the tests are.

'…. And well, it doesn't always work anyway. Mine wasn't detected when I had a test in the UK. Yet I was nearly falling off a ladder.'

This was echoed by another patient, who recognised that things could change over time, with one screening episode not always being sufficient or accurate. Furthermore, a different patient reported that quite often, nothing will be detected but stressed the importance of the one occasion where something might be caught.

'Any form of screening is a good thing and because 99 err 90 per cent of the time umm nothing was detected then all of a sudden there's a change in the readings…' (2)

3.3 Patients preferences and priorities on how screening can be incorporated into routine care.

***Sub-Theme*:** The importance of screening convenience**.**

Again, location featured heavily. The viewpoint that healthcare is too centralised to hospitals was voiced and the need to decentralise by incorporating community GP based screening was emphasised. Access to busy hospitals was felt to be a barrier to screening programs, along with logistical difficulties, access, transport, and parking. One patient commented that they would not attend if invited to a hospital-based screening event.

'*…if I get a letter from the hospital saying we are doing XY and Z screening please make an appointment for screening, I throw it in the bin*.' (9).

Convenience seemed to directly relate to patient motivation to attend with attitudes towards health beliefs contributing to involvement. A dedicated screening service or screening centre was suggested as was a mobile, travelling screening unit.

Incorporating screening into existing appointments was suggested as an effective approach for encouraging participation. Several patients suggested when they attend their regular appointments for prescriptions, that relevant screening could be incorporated.

'*It's a good thing because as I say, I go for my three-month to see my GP and he checks me out and … they put all the machines on you*.' (7)

The patient and health professional relationship was felt to be relevant to the success of screening opportunities and if offered by the GP or another healthcare provider with whom they trust, might entice involvement.

'Well I suppose the best, well, one way would be through your GP wouldn't it, if they had time. You know at the same time, do some screening.' (3)

So, there is stuff that could be decentralised that GP level would probably be encouraged at greater use'. (9)

3.4 Patients views on the screening tool (a single-lead mobile ECG recording device).

***Sub-Theme*:** Technology as a barrier.

Familiarity and experience with screening devices was varied with some able to relay various benefits to health screening and self-monitoring, particularly in the presence of multi-morbidity. One patient explained the presence of diabetes and AF alongside respiratory disease and that this encouraged their use of home monitoring devices and associated technology.

'*Well I have a blood pressure monitor and a blood oxygen monitor and I have my blood sugar monitor and I use them*.' (9)

Technology know-how was reported as a potential barrier to screening tools, as was older age. Younger people and their familiarity around apps and mobile health was emphasised. This was considered important to encourage health monitoring, lifestyle, and behaviour modification with an overall proactive approach to modern healthcare. The focus on age was not however echoed across the group with many other participants stating their confidence with mobile phones and health related applications.

There was also existing familiarity with the AliveCor® device specifically with some reporting previous use or at least, visualisation of the device in the public domain.

'I go in that coffee shop and I can see people with that and their phone… when I go round shopping, I used to go to Marks and Spencers and the last time I see someone doing in Marks and Spencers.' (8)

***Sub-Theme*:** Feasibility of the mobile ECG recording device for screening.

The ability to use the device at home to make repeated recordings was suggested, with recordings then shown to the GP for surveillance along with for example, blood

pressure monitoring. The portability of the device was attractive, along with ease of use, convenience, portability, and comfort.

'There are simple gadgets and putting the app on the mobile phone means simple testing can be done in one's home.' (2)

'…you can keep it handy, put it in a drawer and do it once a week.' (6)

This ease and convenience were encouraging when frequency of screening was contemplated. Using the device once a week was suggested along with making 'regular' recordings at home. Nobody commented however on using it during symptoms, such as palpitations.

'*…you can keep it handy, put it in a drawer and do it once a week… Yeah, I suppose about once a week would be about right*.' (6)

One participant felt the device was good, as long as it was accurate. Another felt the accuracy was probably not entirely reliable but was good enough to detect a problem which could lead to further investigations for clarity.

4.Discussion

Previous research has shown that patients who have a good understanding of AF, report greater acceptance, fewer symptoms, greater control with enhanced coping mechanisms and less negative emotions related to the arrhythmia (23). Providing adequate information is therefore important to ensure treatment adherence (10). Patients' understanding and interpretation of AF in this study, which was limited in detail, content, and knowledge, is therefore relevant. All patients were provided with the same written information and asked to see their GP. The researcher (AH) explained the diagnosis of AF verbally to support the information provided and it appeared this was understood at the time, but not retained.

Stroke was not mentioned by any of the participants and just two stated the use of blood thinning medicines. Other heart problems were reported including blood pressure and the heart valves. This supports previous research regarding patients

understanding of AF, with many being unaware of the name of the condition (11). This, along with limited understanding of stroke risk, may be a factor in treatment adherence. Findings from a previous study have shown that patients had difficulty understanding the need for anticoagulation, particularly when advised as a life-long treatment (12). It may, however, be that the need was inadequately explained rather than related to patient comprehension. Patients' knowledge and engagement with healthcare and concordance with chronic conditions, has been highlighted in previous research (24). A study whereby patients were interviewed following a recent diagnosis of AF, highlighted 'knowledge deficit' two weeks after a new diagnosis of AF, relating to AF symptoms, reasons for medications and stoke risk (13). Another study considered patients understanding at the time of the Emergency Department visit and then three months later and concluded similar findings (14). This link with health knowledge and health status has been well documented and can result in under-utilisation of preventative resources including screening (25, 26).

Further considerations around this overall lack of perceived awareness could be in part due to the asymptomatic nature of their arrhythmia. None of the patients interviewed commented on or appeared to have problems or symptoms specifically relatable to their AF. None had needed hospitalisation or even specialist input from the cardiology team and were managed by their GP. In addition, when screening in the original AF study was undertaken, these nine participants were haemodynamically stable with normal physiological measurements (besides the AF heart rhythm tracing), exhibiting and reporting no symptoms at the time. It is possible that patients with symptoms of AF, requiring specialist intervention, complex medication management or sequalae of their arrhythmia would be more familiar with the condition and treatments, as opposed to those in this cohort who were stable. Whilst there is little evidence to support this in existence, experience of symptoms could impact understanding and so health literacy.

Recommendations regarding appropriate patient information for AF include keeping pathophysiological information basic, whilst using plain language (22). Learning how much the patient wishes to know is important, along with situating information within the contextual factors (social and psychological) that effect experience and

understanding of symptoms, physiological mechanisms, and psychosocial factors. Using a variety of media platforms can also be beneficial according to the patients' preferences.

Screening for AF was generally regarded positively in this research and all participants were pleased to have the knowledge of the arrhythmia. There was however acknowledgement that not everyone may be so open to accepting a new diagnosis or entering into screening programmes. Cost featured heavily in terms of resource and screening approach, but cost savings were also noted. Screening location was preferred at a GP practice or similar outpatient-based environment and hospitals were regarded as a deterrent to screening opportunities. As screening approaches evolve, an expanded role within primary care can be anticipated but this incorporation may place additional strain on already stretched systems (16). Evidence on the effective implementation of screening in primary care is required to ensure efficient use of resources, beyond consideration of the screening tool that has been a focus in heart rhythm screening research.

The ECG recording device used in this research was viewed positively by all participants with comments relating to ease of use, patient-led, portability, comfort, perceived accuracy, and convenience. Technology know-how was considered essential when patient-led, but not a barrier, with many reporting wide use of mobile phone and digital technology. This concurs with acceptance of screening devices by participants in large scale trials (17, 18).

Of the nine participants interviewed, eight were male. This research, therefore, largely represents the views of men. More men than women were included in the AF screening study (*Study 1, Chapter 4*) and this might be reflective of the prevalence of diabetes between the sexes. More men than women had AF also, and therefore impacted on the proportion of men and women eligible to participate in this interview study. Views around screening may be different for men and women, due to the differences between screening programmes applicable to either sex. Evidence also suggests that for decades, women have been underrepresented in cardiovascular research despite this being the leading cause of mortality for women worldwide (27 -

29). This has widespread implications in the overall stratification, management, and treatment of women with cardiovascular disease (30). Reasons for underrepresentation from women include patient willingness due to perceived harm from clinical trials (31), financial stability, sociocultural environment, patient education, patient engagement, and distrust of the healthcare system and medical research (32 - 34). In addition, decisions from women may be swayed by family members and social commitments, as well as influenced by altruistic motivations due to most women being caregivers (27). There is also evidence to suggest men are less likely to undergo cardiovascular health checks and have consistently underutilised preventative health care services compared with women (35). Reasons may be partially caused by the role of masculinity and social norms (36). Further explanations have been attributed to the more routine nature of women's engagement with medical services due to pregnancies, childcare, menstruation, and hormone related health checks (37). During these ongoing, routine opportunities, women are exposed to the availability of medical advice and may disclose health concerns or accept assessment. Whilst this offers some explanation regarding sex bias in cardiovascular research, the low numbers of women in this interview study presents a confounder on views here. Of the four women who had AF, only one was interviewed. This, therefore, impacted on obtaining additional views from women, but ways to optimise female representation should be considered when designing and undertaking future research within this field.

5.Limitations

Further research exploring patient views particularly in relation to associated health risks and risk factor modification would be beneficial. This research did not include questions around causes or symptoms. This study included patients who had AF during the screening study and only those who had agreed to participate in a screening programme who had diabetes and therefore may not be transferable to other patient groups. All but one participant was male and therefore female views were less represented. Female participants may have had different interpretations of screening due to female orientated screening programmes. All the interviewed participants had AF but widening this to groups had been screened but did not have

AF, or who had not undergone specific screening, might offer valuable data in terms of AF screening considerations. Patient and public involvement was not incorporated within the design of this research and by doing so, could have impacted on the questions asked and overall implementation and outcomes of the study.

6.Conclusion

This study highlights that patients' understanding of AF varies and AF consequence such as stroke, did not feature when exploring their views. Supporting patients to comprehend possible causes of AF, mechanisms, modifiable risks, and treatment options is imperative for adherence and working in partnership, to reduce sequela and improve quality of life.

Understanding patients' views of AF screening in terms of benefits and barriers, is important when contemplating and planning screening programmes. There was no perceived risk of AF screening according to participants in this study and this was reflected in their opinions of screening. Patient involvement is crucial for screening to be cost effective and feasible. Employing tools that are valid whilst easy to use offers further opportunity for AF screening.

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Chapter 7. Discussion.

7.1 Introduction.

This research aims to explore the association of AF and diabetes, two chronic conditions that are both increasing in prevalence, worldwide. The over-arching research question for this thesis is, '**Should we be screening people with diabetes for atrial fibrillation?'** This is addressed by the design and undertaking of four separate yet related pieces of research, focusing on specific aspects within the field of enquiry, whilst contributing data from different yet inter-related perspectives. The systematic review (*Chapter 2*) started by exploring the feasibility, validity, and utility of the AliveCor® device. AF detection in the critiqued papers showed some correlation to the study population screened with higher risk groups such as older age and coexistence of chronic disease, yielding more AF (Desteghe et al, 2016; Lowres et al, 2015). The AliveCor® device demonstrated effectiveness and a tool of choice for process, management, and resource metrics despite the heterogeneity between studies. Screening duration impacted on AF detection rates and the need for further ECG analysis beyond the AliveCor® ECGs and inbuilt algorithm was highlighted but offers itself as an appropriate tool for opportunistic and systematic AF screening programmes. The AliveCor® device was effective in identifying AF in all sixteen cases in the AF screening study (*Study 1, Chapter 4*) and was generally well received by patients when asked their views in the interview study (*Study 3, Chapter 6*). AF screening was felt to be a positive experience and one that brought no regrets from participants when asked during interview. Ways to coordinate AF screening including considerations around locality, costs, criteria such as what age to start screening, the frequency of screening and by whom. Outcomes in this research also demonstrated the need for clear and concise information around the delivery of an AF diagnosis as understanding around AF and consequences such as stroke risk, were variable. The AF screening study showed a higher prevalence of AF in the screened population with diabetes, compared to the general population, with age being a significant predictor. This, along with outcomes from the QoL surveys (*Study 2, Chapter 5*) showing a poorer

assessed QoL in five of eight domains when AF and diabete coexisted, adds support to the importance around screening and identifying AF in high risk populations such as people with diabetes. The poorer QoL and increased health risks from a physiological, mental, emotional and social perspective, demonstrate the importance of detecting AF so this can be treated appropriately, then reduce the potential negative consequences.

7.2 Contributions and originality of this research.

Contributions from this research come from each of the four papers. The systematic review is the only review whereby the AliveCor® device is critiqued explicitly. Other reviews exist whereby ECG monitoring devices are appraised (Duarte et al, 2019; Ramkumar et al, 2018), but synthesising evidence directly related to the AliveCor® device, with analysis of feasibility metrics and validity, delivers originality to the arena of ECG monitoring. This is suitably linked to the recently published NICE guidance on the AliveCor® device (NICE, 2022).

The AF screening study (*Study 1, Chapter 4*) is the only published screening study that targets people with diabetes specifically. Other studies incorporate at-risk groups with diabetes commonly featuring (Chan & Choy, 2017; Desteghe et al, 2016; Lowres et al, 2015; Samol et al, 2013; Sanmartin et al, 2013; Turakhia et al, 2015), but identifying diabetes alone, offers new insights into AF prevalence and predictors. AF and diabetes can pose a significant burden on individuals' health when they exist in isolation but when combined, health sequalae such as heart failure and renal dysfunction are more common (Heo et al, 2020; Magnocavallo et al, 2022). Stroke risk is considerably higher when AF and diabetes coexist, and AF related strokes are often more debilitating than strokes unrelated to AF (Patlolla et al, 2020; Xu et al, 2022). If AF can be detected in people with diabetes, an attempt to reduce poor health consequence by providing targeted treatment, might reduce the poor health cascade. Single-risk factor AF screening can also help determine those at truly high-risk of developing AF. When healthcare resource is so finite, careful planning is needed to establish and prove the beneficial intention. Identifying the high-risk populations therefore helps direct the

resource appropriately, whereby focus can be afforded in a way that brings optimal gain. This is also the only known study of its kind, whereby an island population has formed the sample. Therefore, assessing prevalence and variable related data from island residents, also offers originality. This provides useful information for local public health departments and outcomes relating to these burdening chronic diseases.

The current QoL study presents an original study whereby people with AF and diabetes were a focused group for obtaining QoL data, rather than related to clinical trials. Comorbid disease often exists beyond the presence of one chronic condition but designing a study whereby these two were specifically under enquiry, contributes to knowledge around AF and diabetes when they coexist. The impact they have on QoL, especially where detrimental, adds weight to the need for screening in these disease groups as the prevalence of AF and diabetes is growing, leading to further impact on other coexisting chronic disease. Screening can help by identifying these patient groups and then intervention may assist in reducing the impact they can have on QoL. Whilst QoL data is not the only factor to drive a screening agenda, the evolving importance of wellbeing, from the paradigm shift of purely physically driven targets, provides impactful evidence when considering screening and detection of a chronic disease that is growing in prevalence. Applying the SF-36 instrument to these groups in combination, offers a distinctive and diverse application of the SF-36 QoL survey. Accessing surveys via a nationwide website also offers a novel approach for obtaining this information on disease specific groups.

The qualitative interview-based study contributes originality by seeking patients' views and experiences of AF screening, specifically in participants who had been screened for AF and who had yielded an AF diagnosis. These views were also obtained from a sample of people who had diabetes as an existing diagnosis, and this has not been previously identified. Patients were also asked for their views on the AliveCor® device as a screening tool specifically, as opposed to monitoring devices in general.

7.3. AliveCor® as an AF screening tool.

7.3.1 mHealth and ECG monitoring.

There are a growing number of mHealth applications available for remote and mobile monitoring of cardiovascular disease (Varma et al, 2021). In heart rhythm management, the integration of devices such as the AliveCor® application, has demonstrated effectiveness as an AF detection tool through analysis of feasibility metrics and validity data, as demonstrated in the systematic review (see also *section 7.3.2*). Evidence from the systematic review reveals this is an attractive option for screening programmes and clinical practice and the portability encourages use in remote and low resource settings. This utility then means screening for AF in high-risk populations including people with diabetes, can be achieved in diverse settings and is relatable to screening criteria as outlined by Wilson and Jungner (1968), whereby there should be a suitable test and this test should be acceptable to the population.

The availability of ECG and non-ECG based devices for AF screening along with the constant evolution of digital technology offers opportunities, yet perhaps confusion, to the consumer over relevance and choice. Many mHealth devices have been subject to extensive validation and among these, are handheld and patch recording systems (Kwon et al, 2021; NICE 2020; Torfs et al, 2014; Rajakariar et al, 2019; Varma et al, 2021). Both ECG and non-ECG based systems offer valuable and alternative options for arrhythmia detection and the AliveCor® device is an example of this. With over 100,000 mHealth apps and over 400 wearable activity monitors available (Li et al, 2019), it is difficult to make comparisons, but the sensitivity and specificity of various options for AF screening have been presented in *Table 3 (section 1.1.4)*. Within the grouped examples in *Table 3*, there are differences in how heart rhythm recordings are acquired, and this can make a difference to ECG clarity. Some single-lead systems operate as standalone devices and the Omron HeartScan (Omron Healthcare Co. Ltd) is one such example. Evidence suggests that like the AliveCor® device, it is more likely to successfully diagnose AF, especially when the user has symptoms prompting additional recordings, than the traditional HM (Bansal & Joshi, 2018; de Asmundis et al, 2014; Kaleschke et al, 2009; Kearley et al, 2014). The MyDiagnostick Medical BV

(Maastricht, Netherlands), another single-lead ECG device, displays a red or green light if AF or sinus rhythm is detected and although the ECG rhythm is not visible in real-time, this alerts the user to a normal or abnormal result. AF analysis has shown 80-100% sensitivity and 93-99% specificity and a large AF screening study during flu vaccinations, found 1.1% of participants had new AF (Kaasenbrood et al, 2016). Total AF prevalence was 3.7% and the mean age of people with new AF was 69 years, having screened only people over 60 years (Kaasenbrood et al, 2016). The Zenicor Medical Systems AB (Stockholm, Sweden) is another hand-held device with no additional hardware (Zenicor, n.d.). A central display shows a lead I ECG, transmitted to a web based central database. An AF screening study identified 0.9% (95% CI 0.5-1.5) of participants with new AF when the population of 65-year-olds with additional risk factors for stroke (mean CHA_2DS_2-VASc score 2.8) were screened twice daily along with recordings during symptoms that could be attributed to AF such as palpitations (Berge et al, 2017). Another screening study that adopted a similar protocol but with participants who were 75-76 years of age, found AF in 3% of participants (Svennberg et al, 2015). This study found AF in 0.5% of the screened population on their first ECG and the use of this intermittently, increased new AF detection 4-fold, resulting in the total AF prevalence 12.3%, demonstrating the benefit of repeated screening (Svennberg et al, 2015).

Alternatively, the ZioPatch (iRhythm Technologies, San Francisco, CA, USA), also a single-lead device, aims to provide continuous rather than intermittent monitoring and therefore does not rely on patient activation. This may suit certain populations where dexterity may impede use of handheld devices and where disability may make self-recordings impractical. This water-resistant adhesive patch works similarly to a HM but with the advantage of recording for longer duration (14 days) (irhythmtech, 2022). The ZioPatch has a high diagnostic yield for total arrhythmia detection when compared to the HM and when 24 hours of monitoring was compared between the two methods, the HM detected more arrhythmias, yet the time to first recorded arrhythmia often occurred after 48 hours, demonstrating the importance of longer duration monitoring (Barrett et al, 2014). Comfort is an important consideration and impacts compliance and two studies reported this favourably from their cohorts

(Barrett et al, 2014; Kim et al, 2021). There are no loose wires across the precordium, meaning it is more discreet with potentially less interference and may therefore be more practical during hours of work and activity. The patch is well tolerated by users with good compliance and comfort rated favourably compared to the HM (Barrett et al, 2014; Tung, Su, Turakhia & Lansberg, 2015). Studies suggest it may have a higher diagnostic yield for arrhythmia detection compared to other ambulatory ECG recording monitors [Barrett et al, 2014; Schreiber, Sattar, Drigalla, Higgins, 2014; Tung et al, 2015; Walsh, Topol & Steinhubl, 2014). Similar outcomes were seen with the Wellysis S-PATCH which explored ease of use, comfort, efficiency, durability, and clarity of recorded signals, demonstrating this also to be superior to the traditional HM (Upadhyayula & Kasliwal, 2020).

Photoplethysmographic [PPG] technology is available within commercially available devices such as the Apple Watch (Apple Inc, Cupertino, CA) and FitBit but susceptibility to movement artefact especially in wearable clothing has been reported, and errors documented in 1.8 – 8.8% of PPG based devices (Shcherbina et al, 2017). However, iterations to wearable devices includes enhanced filters to optimise the clarity over signal acquisition and display.

Progress in technology also sees the amalgamation of PPG and ECG based systems and the Apple Watch is one such example, where a single-lead ECG can be acquired by placing one finger on the crown of the watch whilst another electrode connects from the back of the watch to the wrist (Apple, 2019a; Apple, 2019b). The Apple Watch has moved towards achieving both comfort and accuracy and the Apple Heart Study enrolled nearly half a million participants in their large-scale assessment of smartwatch identification of AF (Perez et al, 2019). This research aimed to measure the proportion of participants with an irregular pulse and demonstrated 2,161 had an irregular rhythm with 34% confirmed AF on subsequent patch monitoring (97.5% CI 29 - 39), the low sensitivity explained as unsurprising considering the intermittent nature of AF in some people (Perez et al, 2019). Among participants where an irregular pulse was detected, the PPV was 0.84 (97.5% CI 0.76 - 0.92) for observing AF on the ECG simultaneously with subsequent irregular pulse notification and 0.71 (97.5% CI 0.69 - 0.74) simultaneously with the tachogram (Perez et al, 2019). Where AF was not the

cause of rhythm irregularity, 40% showed other atrial and ventricular arrhythmias, mostly ectopic beats (Perez et al, 2019). They added that 84% of the time, participants with an irregular pulse notification were found to be in AF at that precise time and therefore, they were confident in the PPV (Perez et al, 2019). Beyond AF, additional arrhythmia classification was possible including the identification of atrial and ventricular arrhythmias, most of which were ectopic beats (Perez et al, 2019).

The Huawei Heart Study also recruited a large number, resulting in a low yield of AF diagnosis but 87% of those with 'suspected AF' were later confirmed (Guo et al, 2019). Of these, 95% were entered into an integrated AF management programme using a mobile AF application (mAFA). This demonstrates the added benefit of mHealth and eHealth support, beyond diagnosis and screening, but for ongoing monitoring, motivation, and guidance. This approach of reaching vast and non-targeted populations means more people can be screened in this way, perhaps including younger people and those who might be reluctant to seek healthcare or screening campaigns. This also has value as a health promotion opportunity beyond where there might be a normal screening outcome, and this is extremely important in prevention of onward disease. The disadvantages of this approach, includes accessing large numbers of participants, the intensive workload and resources that comes with managing such a project and the diagnostic prevalence which might be low especially with AF screening where it is acknowledged that prevalence is higher in older age groups.

BP monitors can also assist with AF screening and the Microlife Modified Blood Pressure monitor (Microlife Corporation) does this via the detection of an irregularly irregular pulse during the inflation of the automatic blood pressure cuff (Wiesel, Fitzig, Herschman & Messinea, 2009). The wide availability of BP monitors monopolises on this through ease of direct access and affordability, and evidence suggests this method may be more accurate than a pulse check (Wiesel, Arbesfeld & Schechter, 2014; Wiesel et al, 2009). This monitor was used in a study comparing its use to an alternative blood pressure monitor (Omron blood pressure monitor), demonstrating specificity of 90% or greater for both devices but with greater sensitivity for detecting AF in the Microlife monitor at 100% versus 30% with the Omron monitor (Wiesel et al,

2014). Cardiac implantable electronic devices provide remote monitoring, and this function is now recommended by major cardiology societies (Glickson et al, 2021; Slotwiner et al, 2015). Advantages include earlier detection of events and identification of device malfunction, permitting earlier intervention (Yao et al, 2019). Proactively identifying problems can enhance patient safety, reduce hospital admissions and readmissions and the ability to reach patients in rural areas whilst also reducing the footfall through hospital clinic departments adds to these advantages, along with the need for monitoring when there is clear evolution and improvement in the accuracy and efficacy of mHealth devices (Yao et al, 2019).

mHealth opportunities beyond ECG rhythm monitoring are plethoric, but include medication guidance and adherence aids, education, disease management and diarising of symptoms. Appointment reminders, research and lifestyle modification are also options featured within mHealth applications. mHealth ECG monitoring has widened the approach and resources for screening, encouraged patient-initiated monitoring and crucially, facilitates correlation of ECG recordings during patients' symptoms (Varma et al, 2021). This can be particularly beneficial in the context of AF, where the incremental costs for its use are relatively low (Iribarren, Cato, Falzon & Stone, 2017).

7.3.2 AliveCor® feasibility, utility, and validity for AF detection.

The systematic review focuses on the AliveCor® device in relation to AF detection and this can be used as a single timepoint screening tool, obtaining individual brief recordings, used repeatedly for intermittent screening, or initiated during times of symptoms such as palpitations. Variation with screening intensiveness is evident from findings from the systematic review. Most of the studies using repeated ECG recordings detected some cases of AF on the initial ECG, therefore demonstrating the utility of the AliveCor® device as a single timepoint screening aid (Halcox et al, 2017; Lowres et al, 2016; Soni et al, 2016; Soni et al, 2018; Svennberg et al, 2015).

Synthesis of the data from the systematic review showed that the AliveCor® device is feasible for AF screening implementation with ease of use quoted frequently in the

papers forming the review. Time to teach participants how to use the device for self-recordings was minimal, with ongoing acceptance and compliance. This was not unanimous though and instruction time varied according to smartphone familiarity with up to twenty minutes needed with some patients. Age was explored as a potential barrier, but this was not necessarily the case, nor was older age responsible for lack of protocol adherence when scheduled self-recordings were required (Halcox et al, 2017; Soni et al, 2018; Svennberg et al, 2015). There was also evidence that older participants were more likely to complete the full set of ECG recordings and submissions and perhaps this related to time availability and health conscientiousness whereby there was perceived gain through obtaining the ECG monitoring (Halcox et al, 2017). This finding has importance when contemplating screening protocols and barriers to digital health implementation.

The systematic review also revealed favourable feasibility of implementation as a screening aid, with a high proportion of participants in the critiqued studies adhering to study protocols using the AliveCor® device, low drop-out rates, and overall good compliance. When there was drop-out from study participation, this was not generally related to device use. Low resource drain (e.g., time taken to record an ECG, minimal staffing and workload impact, other equipment needed) and minimal barriers to use were also highlighted in the systematic review. One of the critiqued studies detailed difficulties with holding the device among older age patients (Desteghe et al, 2017). Usability was therefore lower in this study cohort. Comfort was also rated favourably in the review and more widely when compared to other screening devices and this is important when contemplating utility in practice (Lown et al, 2018). Training to use the device and compliance thereafter, when self-recordings were part of the study protocol, showed some correlation with educational level and smartphone familiarity (Lowres et al, 2016). Findings within the review have been supported by wider research and additional evaluations include the advantages through making symptomatic recordings and empowering the user (Lowres et al, 2015; Turakhia et al, 2015). Unlimited use, control over activation and societal adaptation to smartphone technologies has further supported the AliveCor® device for AF screening (Lowres et al, 2015; Lown et al, 2018; Tarakji et al, 2015). The clinical value, implementation,

satisfaction, confidence, diagnostic ability, immediate visualisation of the ECG and accuracy of the AliveCor® device, along with acceptability from patients, has been rated highly by health professionals, making this an attractive option, and further supporting findings within the systematic review (Godin et al, 2019; Hall, Mitchell, Wood & Holland, 2020; Tarakji et al, 2015). This links to the overall aim of this thesis by applying the AliveCor® device as a feasible option within AF screening programmes and for people with diabetes. Participants' views on the use of this device from the interviews conducted for the qualitative research included comfort, convenience and ease of use, supporting the relevance of these findings to the study aims.

Process, resource, management, and scientific feasibility metrics were explored in the systematic review and overall, these were presented favourably in the critiqued studies. The user-friendly technology interface along with the integrated algorithm within the software, provides guidance and rhythm interpretation. Synthesis of this data shows high validity of the AliveCor® device with sensitivities (the accuracy of identifying those who do have AF from the ECG) observed at over 90% for AF interpretation in four of the critiqued studies (Chan & Choy, 2017; Lowres et al, 2014; Lowres et al, 2016; Tarakji, et al, 2015). Similarly, a high sensitivity of greater than 90% for AF detection is evident from wider research beyond the systematic review (Lau et al, 2013; Orchard et al, 2016). Further adjudication over ECG interpretation increases sensitivity and specificity (the test's accuracy at identifying those who do not have AF) and again, this is evident within the review and additional studies employing the AliveCor® device (Desteghe et al, 2017; Halcox et al, 2017; Soni et al, 2016). Once 'unclassified' or uninterpretable ECGs are excluded, sensitivity has been reported beyond 96% (Brasier et al, 2019; Koshy, Sajeev & The, 2018; William et al, 2018).

Additional adjudication when automated analysis has been non-diagnostic imposes an additional workload on skilled health professionals required to over-read the ECGs. These data are not always clearly provided in research and similarly, efforts to enhance the ECG signal are rarely stipulated. Findings from the systematic review showed that manual interpretation increased sensitivity but increased cost per patient. This expert analysis did result in additional time demands with one paper detailing one minute per ten AliveCor® recordings (Chan, Choy, Chan & Siu, 2018).

Other studies within this review used health professionals proficient in ECG interpretation to review the unclassified ECGs, therefore imposing slightly less time than for all acquired ECGs (Halcox et al, 2017; Lowres et al, 2014; Soni et al, 2016; Soni et al, 2018). The current AF screening study demonstrated accuracy with ECG classification by the automated analysis with very few ECGs requiring closer inspection. This emphasises the relevance of having experienced members within a research team, especially at the time of ECG acquisition, so to obtain optimal ECG tracings. This is perhaps of greater importance with some patient groups whereby assistance for acquiring clear ECG readings is required, such as acquiring the best positioning or where physical difficulties preclude optimal finger placement. Independent use in these scenarios might result in unclassified ECGs where interpretation is difficult even with manual interpretation.

Furthermore, critique from the systematic review highlighted the disparate research designs including systematic and population screening, large community screening programmes and more targeted screening in hospital wards and healthcare clinics. Age group inclusion was wide-ranging, including participants from 18 to 65 years and over. Varying details were presented relating to risk factors and this population heterogeneity with diverse clinical, anthropometric, demographic, and geographical characteristics, demonstrates the utility, feasibility, and wide applicability of this device. The systematic review informed the empirical studies within this research through incorporation into clinical research beyond daily use in practice. This was also relevant within the target population of people with diabetes, in terms of feasibility of application for single ECG screenings in the study protocol design. This also led to the development of the interview-based research study, whereby participants views were sought relating to the AliveCor® device for screening.

7.3.3 Recommendations for remote and digital ECG monitoring tools for AF detection.

National and European guidelines have assigned favourable recommendations regarding the use of ECG monitoring devices, with NICE recently publishing their

guidance on the AliveCor® device (Hindricks et al, 2021; NICE, 2022). Here, they recommend this device as an option for detecting AF in people with suspected paroxysmal AF, who present with symptoms such as palpitations and are referred for ambulatory ECG. The European Society of Cardiology [ESC] advises that where digital screening tools are used and AF detected, a subsequent 12-lead ECG should be obtained or a further recording of 30 seconds or greater documenting AF, to confirm the diagnosis (Hindricks et al, 2021). They also suggest caution with the clinical adoption of some remote and digital monitoring tools due to the number available and lack of universal validation. Here, clinician guidance should help direct the tool of choice and evidence is favourable for the AliveCor® device. Summarising findings from the systematic review and the AF screening study, the AliveCor® device is recommended as a tool of choice for AF screening programmes. Acceptability, utility across diverse settings, comfort, ease of use and compliance contribute towards this recommendation. These factors are particularly important when screening or monitoring is designed as a repeated measure or patient initiated. The implications in these scenarios could impact participation due to difficulties accessing repeated screening appointments (mobility, transport, work, or family commitments) and motivation relating to health beliefs and intentions with ongoing screening visits. Where screening requires patient initiation, there needs to be some confidence that patients can implement the use of the screening device appropriately and independently, minimising barriers to obtaining clear and accurate ECG recordings.

Beyond this review, contemporary studies have evaluated AF detection using smartphones and smartwatches, opening new perspectives for AF detection. The KardiaBand®, an extension from the AliveCor® application that connects as a wrist strap to the Apple Watch, received FDA clearance in 2017 (AliveCor, 2017). As a wearable device, this offers immediate and discrete ECG recording. This immediate access enables rapid ECG capture during symptoms such as palpitations. Correlating ECG rhythms to symptomatic episodes is important when diagnosing arrhythmia and enables tailoring of treatments (see *section 7.3.1*).

It is however noteworthy, that whilst the opportunities available to patients and health professionals using the AliveCor® device, the KardiaBand® and other

comparators, are ever increasing, there should be investment into the demonstration of clinical utility, validation, and cost effectiveness (Varma et al, 2021). A collaborative statement on eHealth in arrhythmia management by expert international cardiology societies summarised, that formalising directions and recommendations cohesively, for the integration of mHealth into clinical practice, are difficult to currently make, due to the lack of consensus or coordination with design, use and implementation (Varma et al, 2021). Steps needed to standardise mHealth applications include comparable validation with ECG and PPG based systems and identifying care pathways (Varma et al, 2021). Impact on healthcare services, public health policy, cost effectiveness and promoting patient self-management needs attention. Cost modelling has shown that the AliveCor® device is cost saving compared with Holter monitoring in people presenting with symptoms such as palpitations (NICE, 2022). This is because of a reduction in diagnostic costs including the cost of the device (NICE, 2022). These are important considerations when establishing governance frameworks and corresponding responsibilities for manufacturers and consumers, and necessary for mHealth integration. Findings from the systematic review in this thesis, summarise some of these considerations including acceptability of the AliveCor® device as a screening tool with favourable feedback from physicians and added that the device would likely be acceptable to patients. This is then supported through findings from the interview study which seeks patients' views on the AliveCor® device, concurring with health professionals' assessment as a feasible approach to AF screening.

Integral within the feasibility assessment, is the evaluation of the impact digital and remote monitoring, including the AliveCor® device in terms of the impact such monitoring can impose on workload in relation to ECG analysis. Scientific metrics within the systematic review showed that the number of unclassified ECGs were less than those that gave a clear diagnosis, therefore avoiding the need for every ECG to be inspected. Therefore, although less laborious rhythm analysis is required with the AliveCor® device, some level of expert interpretation is likely to still be required. This is echoed in clinical experience where patients still often prefer the health professional to have oversight of their ECG recordings. This can, however, be done remotely (via email) and therefore lessens face-to-face appointments. Reducing the

footfall through hospitals is advantageous and whilst travel avoidance does not eliminate the environmental impact, this 'green' approach at least contributes to environmental sustainability. Reducing time in secondary care and encouraging primary and community-based care is in accordance with local government initiatives (Health and Community Services, 2019). The ability to reach patients in rural and deprived areas offers further benefit, as evidenced in findings in this current systematic review.

The psychological impact of using remote and digital ECG monitoring devices can be detrimental and whilst this did not feature within this review, there is evidence to suggest health anxiety can be a common problem with self-initiated monitoring, through overuse and reliance on devices (Cheung, 2021; Rosman, Gehi & Lampert, 2020). Psychoneurotic behaviour with smartphone apps where there becomes an excessive focus on the condition and loss of normal life capacity has been reported and this is supported through observations in clinical practice (Bocchiardo & Asteggiano, 2020). Self-diagnosis is a further problem which can result in self-medication. In the context of arrhythmia management, this can be dangerous where for example, paroxysmal AF is identified on the app and the patient then takes their anti-arrhythmic medicine inappropriately, leading to pro-arrhythmic risks (Valembois et al, 2019). Less focus has been given to the psychological effects of mHealth and eHealth, certainly in the arrhythmia arena and this is important when considering the appropriateness of such strategies and tools for patient use. Where this use is for screening purposes, within a structured and supervised programme or patient-led, the psychological impact of undergoing screening, can impede engagement. The qualitative interview-based study in this research revealed themes relating to patients' views of AF screening in people with diabetes, and within this, included 'fears of outcomes of screening' and 'expectation of screening reliability'. Whilst all participants had no regrets about taking part, and believed AF screening to be a beneficial endeavour, this demonstrates some of the emotions people feel when considering health screening. A review of the emotional impact of screening included concerns around receipt of the invitation, undergoing the test and awaiting and receiving the results (Collins, Lopez & Marteau, 2011). Screening by invitation was

reported as a reason to cause concern and anxiety over the reason for invitation and a likelihood of having the disease (Collins et al, 2011). This was not raised during patient feedback in the interview-based study but is worthy of consideration in targeted AF screening. Collins et al (2011) adds that where this causes distress, information processing could be affected, and this could impact on comprehension and retainment of advice given at the time. Any emotional or psychological distress however, that may be attributable to the screening encounter, is short-lived with effects not observed longer-term and therefore, should not be a reason not to screen (Collins et al, 2011).

A robust and individually tailored approach to mHealth and digital ECG monitoring is important to ensure optimal gains and limited disruption. A regulatory framework of these many consumer-grade devices used in a clinical context, supported through appropriate education regarding risks and limitations, is necessary to avoid inappropriate reliance and to ensure that medically approved ECG monitoring is used when appropriate (Bocchiardo & Asteggiano, 2020). The availability of digital ECG devices offers greater opportunity for screening by reaching higher numbers, people in remote areas and perhaps people less likely to attend screening programmes. There is also relevance to targeted patient groups who could undergo screening in this manner. Whether we should be screening people with diabetes for AF, includes how this screening might take place and methods to do so. These are important considerations when applying criteria for screening programmes to be effective and having a tool that is acceptable and fit for purpose, is one of these criteria (Wilson & Jungner, 1968).

7.4 Screening people with diabetes for atrial fibrillation.

7.4.1 Diabetes as a high-risk group and risk factor variables within this group.

The AF screening study revealed a statistically significant increase in the prevalence of AF in people with diabetes (5.3%) compared to the general population. This research recruited patients with diabetes as the target group. Previous AF screening research has included mixed groups of high-risk populations with varying research designs and

analysis, showing between 5.2% and 47.1% of people with diabetes also have AF and this is relevant when we acknowledge the growing prevalence of diabetes worldwide (Davis et al, 2012; Sanmartin et al, 2013). A meta-analysis of four case control and seven prospective cohort studies pooled data on over 108,000 patients, indicated that people with diabetes had a 40% greater risk of AF compared to those unaffected (Huxley et al, 2011). There are limitations with *Study 1,* along with relatable research whereby smaller sample sizes, varying methodologies, less rigorous approaches to detection and lack of adjustment of common risk factors are evident (Dublin et al, 2010; Krijthe et al, 2013; Nichols et al, 2009). Attempts to overcome the latter in *Study 1* were made by controlling for some of the variables within the gathered data. Prevalence may be underestimated also in the AF screening study due to the single screening episode, therefore potentially missing AF when of a paroxysmal nature. When ECG screening or monitoring is repeated or recorded for longer duration, AF detection may be greater (further discussed in *section 7.7*). The prevalence therefore in the AF screening study, whilst higher than the general population, does not reflect the higher prevalence seen in other screening or epidemiological studies or indeed from direct clinical experience. This may in part be due to the sample size, research design, availability of the researchers and the single rather than repeated ECG screenings.

In addition to the presence of diabetes, diabetes duration was considered, but along with diabetes stability, were not significant predictors of AF. Diabetes stability, measured by HbA1c, was comparable in people with and without AF in the AF screening study. AF was detected in just a small number of the total sample and therefore, could impact findings. In previous work, prospective cohort studies have reported a significant association with incident AF and higher HbA1c levels (Zhang et al, 2020). The risk of developing AF was also seen to increase by 3% for every year of diabetes duration (Zhang et al, 2020). Poor glycaemic control has been reported to increase AF risk in a recent sub-analysis of patients with diabetes and AF (Ahmadi et al, 2020). This is echoed by another cohort study exploring the risk of AF with diabetes, glucose control and renal function, determining the risk of AF to be increased with glucose variability (Ahmadi et al, 2020). The increased risk ranged from

1-4% per 1% higher from the mean HbA1c (Ahmadi et al, 2020) and although a modest impact, the cumulative effect on renal complications, brings further impact on AF development. A systematic review and meta-analysis (thirty-four studies and >10,244,043 participants) found a dose-response relationship between increased blood glucose and increased AF risk (Aune et al, 2018). Whilst glycaemic control was not a contributing factor to AF development in the current AF screening research, this prior evidence is relevant when designing larger studies.

Glycaemic control and diabetes duration may also impact on the anti-hyperglycaemic medication regime prescribed. This information was not obtained from patients in this research and is recognised as a limitation. The risk of AF can be associated with anti-hyperglycaemic drug use, and this risk can vary depending on the class of drug (Lăcătusa et al, 2019). One study exploring new onset AF showed that people with diabetes who took biguanides or thiazolidinediones were at a lower risk of developing new AF when compared with non-users (OR 0.81; 95% CI 0.71-0.95 and OR 0.72; 95% CI 0.63-0.83, respectively) (Liou, Yang, Chen & Jong, 2018). The positive effects of thiazolidinediones may be associated with anti-inflammatory and antioxidant processes, reducing atrial fibrosis, and suppressing AF inducibility (Liu, Korantzopoulos, Li & Li, 2008; Marfella et al, 2009). Several studies have reported a reduction in AF risk in people taking these medications (Chao et al, 2012; Gu et al, 2011; Korantzopoulos et al, 2008; Liou et al, 2018; Gu et al, 2011; Pallisgaard et al, 2017). Insulin use has been shown to increase AF risk and this may be due to longer diabetes duration, years of suboptimal glycaemic control, inadequate regimes with previous oral agents prior to commencing insulin and possibly compounded by the presence of comorbid conditions (Liou et al, 2018). An alternative theory may be that hyperinsulinism due to an iatrogenic component or insulin resistance, may be associated with an increased anti-fibrinolytic state (Asghar, Alam & Malik, 2012).

AF involves an inflammatory process, it increases oxidative stress and induces structural remodelling in atrial myocytes (Schotten, Verheule, Kirchhof & Goette, 2011; Wakili, Voigt, Kǫ̈b, Dobrev & Nattel, 2011). These mechanisms may assist with understanding how metformin, for example, presents a lower risk of AF, attenuated through lowering of blood pressure, oxidative stress, and an anti-inflammatory

response in people with diabetes (Chang et al, 2014; Fidan et al, 2011; Lachin et al, 2011). In a cohort study, monotherapy with metformin had the lowest incidence rates of AF in the first two years from diagnosis but faded afterwards (Chang et al, 2014). A 19% risk reduction of AF was observed during 13-year follow up (Chang et al, 2014). Other biguanides have also been associated with a lower risk of developing AF (Liou et al, 2018).

Other groups of drugs for diabetes management include dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter-2 (SGLT-2) inhibitors. Patients previously treated with metformin alone who then received combined therapy with a DPP-4 inhibitor, had a lower risk of AF compared to other drug groups as a second antidiabetic medication (Chang et al, 2017). In a case-control study, DPP-4s were neither associated with an increase nor decrease of AF (Liou et al, 2018). The GLP-1 receptor is found on sino-atrial cells and GLP-1 receptor agonists can induce an increase to heart rate due to either stimulation of these cells or in response to blood pressure reduction (Lorenz et al, 2017; Sun et al, 2015). An increase of the incidence of AF was observed in a pooled analysis of trials in the albiglutide and cardiovascular outcomes program (Fisher et al, 2015). A meta-analysis however, showed no increase in AF risk with these drugs (Monami et al, 2017). SGLT-2 inhibitors have a positive effect on optimising cardiovascular function through lowering of blood pressure and blood glucose, improving heart failure outcomes including hospitalisation and mortality, and metabolic actions including weight loss (Zheng et al, 2022). The cumulative effects, therefore, lower cardiovascular risk. A meta-analysis showed that treatment with SGLT-2 inhibitors was associated with a significant attenuation in the incident risk of AF compared with control (OR 0.82; 95% CI 0.72–0.93; p = 0.002) (Zheng et al, 2022).

It is also worth noting other groups of medications that patients might have been taking and the potential impact this could have on physiological measurements obtained, such as heart rate and blood pressure. Beta blockers and calcium channel blockers are two groups of medications that patients with cardiovascular disease including hypertension, could take. These have effects both on lowering heart rate and blood pressure. When blood pressure is optimised, the risk of arrhythmia is

reduced (Soliman et al, 2020). The dosage could also impact results as could that of additional medications including angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists, or angiotensin receptor blockers (ARB), used in the treatment of hypertension and heart failure (Makkar, Sanoski & Spinler, 2009). Evidence has shown that these drugs may reduce the incidence of AF recurrence by attenuating cardiac remodelling (Makker et al, 2009). AF activates the renin-angiotensin system (RAS), which can lead to atrial fibrosis, atrial structural and electrophysiological remodelling, and then subsequent AF recurrence (Shahid, Lip & Shantsila, 2017). Digoxin, a cardiac glycoside, is another medication that patients might be taking in the presence of heart failure, although used historically to reduce heart rate in the presence of AF (Ziff & Kotecha, 2016). Digoxin is a positive inotropic and negative chronotropic drug that decreases heart rate and increases the force of the heartbeat (Ziff & Kotecha, 2016). The anti-anginal drug ranolazine has been shown to assist in terminating AF episodes by inhibiting atrial sodium channels, although the accurate mechanism by which this works is not entirely understood (Kumar et al, 2009; Ramirez et al, 2019). Statins, cholesterol lowering drugs, which patients with diabetes are commonly prescribed to reduce the risk of cardiovascular disease, have also shown a reduction in incident AF through a number of studies (Bang et al, 2014; Hung et al, 2013; Pellegrini et al, 2009; Veronese et al, 2015), including a meta-analysis on ten cohort studies with coronary artery disease and observed a significant reduction in the occurrence of AF with statin use (OR 0.65; 95% CI 0.57-0.74; $p<0.0001$) (Zhou et al, 2013). Mechanisms may include the modulating effects of the inflammatory substrate responsible for AF, effects on endothelial function and altering the properties of transmembrane ion channels (Pinho-Gomes et al, 2014).

Beyond diabetes specific variables including medication usage, this current research considered the impact of age on AF prevalence. Age was the only significant predictor, with the mean age of people with AF higher than in people without AF. This echoes previous research where AF development shows a strong age dependence (Hindricks et al, 2021) but whether increasing age impacts on AF prevalence in people with diabetes, has been less explored. Adults over the age of 18 years was part of the eligibility criteria for the AF screening research as outcomes relating to age across the

years and not just older people, was of interest. Outcomes showed that in the presence of diabetes, increasing age was a contributing factor to having AF. Evidence beyond this current study suggests that more people with diabetes have AF across all age groups with one study demonstrating 8% prevalence even in 15-39-year-olds (El-Menyar, Albinali, Bener, Mohammed & Al-Suwaidi, 2009). The same study reported increased incidence of AF with increasing age in people with diabetes and up to 16% in 40-49-year-olds and 28% in people over 50 years (El-Menyar et al, 2009). Another study differentiated between age groups and reported increased prevalence of AF in older people with diabetes (Alwafi et al, 2020). There was also increased prevalence across all age groups over a fifteen-year observation period from 5.5% to 9.9% in people over 75 years, 3% to 4.3% in the 65-74 years age category and less of an increase although still in this direction, for people younger than 65 years of age (Alwafi et al, 2020). Evidence from the AF screening study shows that the people with diabetes who had AF, were older with the majority being over 65 years of age, and prevalence greatest in the septuagenarian and over age groups. This concurs with general AF prevalence data, and from diabetes related research whereby AF prevalence increases in older age groups. The population screened in the AF screening study were generally older but there was little representation from younger participants (e.g., below the age of 40 years).

Older age also presents a greater likelihood of multi-morbidity which can further increase AF risk (Heo et al, 2020; Magnocavallo et al, 2022). Data from Jersey (the location for *Study 1* and *Study 3*) relating to AF and diabetes prevalence, multi-morbidity, and age, shows numbers increasing for AF in people in their 60s along with a male dominance (States of Jersey, 2017a). Therefore, targeting older people in AF screening programmes would appear to be a sensible recommendation. Similarly, targeting screening to those with chronic illness (e.g., diabetes) would be recommended as there is a likelihood of coexisting, comorbid disease, thus impacting their likelihood of developing AF. Local data also shows that multimorbidity is common, with 37% of people with AF and 25% of people with diabetes having three of more comorbid conditions (States of Jersey, 2017b). Applying a screening cut off at 65 years of age might have produced different outcomes in the AF screening study, but

overall findings from this research and wider evidence lead to these recommendations, where resource can be directed appropriately.

The AF screening study also considered AF prevalence with differences between men and women and findings showed that more men than women with diabetes had AF, although this was not statistically significant. Men may also have had more AF due to having more risk factors, but when diabetes as a risk factor was already considered (as in these participants all had existing diabetes), less difference may be anticipated. Previous research has shown that men develop AF on average, 10 years earlier than women and it is more common in men than women (Magnussen et al, 2017). Women live longer and so the cumulative lifetime risk of AF is similar (Magnussen et al, 2017). Differences have been explained through sex-specific analyses, identifying genetic disparities in ion channel expression and biological differences in autonomic control of the cardiovascular system with sympathetic-mediated responses predominate in men (Pothineni, Shirazi & Mehta, 2016). Structural remodelling is greater is women and contributes to the highly complex pathophysiological processes involved in arrhythmogenesis (Pothineni et al, 2016). Atrial fibrosis has been described as more pronounced in women and this mechanism may be either due to an inherent differential expression of fibrosis, related genes, and proteins or due to the age of the men and women when AF exists (men often being younger when AF is detected) (Pfannműller et al, 2013). Oestrogen also plays a role in attenuating fibrosis and this process of adverse remodelling, but other mechanisms through which sex modulates structural atrial remodelling remains unknown (Pfannműller et al, 2013).

Body weight and BMI was measured in the current AF screening study, with the mean weight slightly higher in the AF group, with comparable BMIs. Again, the small numbers with AF may be contributory to these results, as it is accepted that increasing body weight is a risk factor for both the development of diabetes and AF. AF risk increases in obesity with an associated 50% increased incidence and a 4% increase in AF risk per one unit increase in body BMI (Wang et al, 2004). Diabetes and obesity often coexist and have synergistic effects on the development of AF (Asghar, Alum &

Malik, 2012; Grundvold et al, 2015; Kim et al, 2019; Lee et al, 2020). Common pathological pathways seem to be present in people with diabetes, AF and obesity and links may be in part due to electromechanical and structural remodelling (*Figures 9 and 10* in *Chapter 1*) (Bohne, Johnson, Rose, Wilton & Gillis, 2019). The coexistence of other risk factors may also be present in these populations such as hypertension, coronary artery disease and heart failure, and this can further accentuate the biochemical and pathological changes (as in *Figure 9 and Figure 10*, *Chapter 1*). BMI was not found to be associated with having or not having AF in the current screening study, and this lack of differentiation may relate to previous studies that showed such an effect in non-diabetes specific populations. As obesity is a risk factor for diabetes which had already been selected for, there may be less variance in BMI than in a non-diabetic population.

Overweight and obese men have been reported to have more than a 2-fold risk of AF compared with men of normal weight (Wang et al, 2004). Higher BMI and cardiovascular risk correlate with the increased risk of AF in men, based on evidence from epidemiological studies (Asghar et al, 2012). However, evidence regarding sex differences in the association between diabetes with AF remains conflicting. While men with AF have larger burden of coronary artery disease, women with AF tend to have a higher prevalence of heart failure and valvular heart disease (Asghar et al, 2012). Age-adjusted AF incidence and prevalence is greater among men, but women seem to be older at the time of AF diagnosis and have a higher risk for AF-associated adverse outcomes (e.g., mortality and stroke) (Asghar et al, 2012). AF prevalence was slightly higher in men and in participants who were heavier in the AF screening study, but this was not statistically significant in analyses. Again, the sample who were diagnosed with AF was small in this research (with only four participants with AF being women) and whilst risk factor information was obtained (e.g., do they have hypertension, heart failure, or a previous stroke), it was difficult to draw conclusions from this. A key aspect here is that the sample was pre-selected of people with diabetes, and this may therefore have a bearing on outcomes generated.

The accumulation of comorbidities explored within the AF screening study contribute to the development of AF. Whilst increasing age was the only significant predictor of an AF diagnosis, supporting research has shown the relevance and importance of other risk factors to the development of AF and are relevant when contemplating AF screening targets. Ongoing research should continue to focus on risk factor groups as their contribution to AF prevalence can help direct AF screening initiatives and help address questions around who we should be targeting for AF screening and why.

7.5. QoL in people with atrial fibrillation and people with atrial fibrillation and diabetes.

7.5.1 The impact of atrial fibrillation and diabetes as chronic conditions on quality of life.

The overall difference between QoL in people with AF and people with AF and diabetes in this research was significant, with the disease combination having significantly lower QoL. Outcomes demonstrated that QoL was lower in six of the eight domains assessed for people with both AF and diabetes. There were significant differences between the two groups in the Physical Functioning, Energy Fatigue, Emotional Wellbeing, Social Functioning and Pain domains, with lower scores evident when AF and diabetes coexisted. This supports the hypotheses from this study, whereby the coexistence of chronic disease leads to poorer QoL across physical and psychological domains. The lowest scores from participants were among the Physical Functioning, Role Physical and Energy Fatigue domains. The Energy Fatigue domain scored lowest in both groups, and this is a common symptom for patients with AF. The lower scores in the Pain domain may reflect chest discomfort that is sometimes felt by people with AF (particularly during paroxysmal episodes) although the nature of participants pain was not explored. Pain when AF and diabetes coexist was scored lower than by the group with AF alone, and this might be due to an accumulation of comorbid disease that can exist when chronic health conditions present in combination.

This research assessed QoL in the general population with AF and diabetes, rather than within clinical trials or following targeted treatments. Most of the research relating to QoL and AF has focused on heart rate control or rhythm control intervention. This has often been as part of a clinical trial or in patients who have symptoms, rather than the general population living with AF. Evidence from existing research demonstrates the negative impact AF has on the physical, emotional, mental, and social health aspects of patients' overall wellbeing (Thrall et al, 2006) and this is echoed in findings from *Study 2 (Chapter 5)*. Results from the QoL study show the lowest SF-36 domain scores from AF patients were in the Role Physical, Role Emotional and Energy Fatigue domains, reflecting the compromise, both physically and mentally, AF brings to the general AF population. Anxiety and depression have been previously associated with AF and diabetes and results from the QoL study support this, revealing lower scores for Emotional Wellbeing and Social Functioning when these conditions coexist. Duration of disease can also impact QoL, and this is evident from research relating to duration of diabetes and also AF. Treatment stability can also influence QoL, but information relating to disease duration and stability was not obtained from participants in this research and is recognised as a limitation. Duration of disease has been shown to impact mental and emotional health with longer duration diabetes exacerbating this (Trikkalinou, Papazafiropoulou & Melidonis, 2017). Conversely, longer duration AF where this may be persistent or permanent, has shown a lesser impact on anxiety (Peinado, Arribas, Ormaetxe & Badia, 2010). This may be due to rhythm stability, where treatments assist by limiting the erratic and unpredictable paroxysms that impact QoL (Peinado et al, 2010). However, even when the rhythm remains paroxysmal, a better QoL can be achieved when assigned an effective pharmacological regime (Guedon-Moreau et al, 2010). Paroxysmal AF has also shown to enhance levels of anxiety with an observed correlation between AF paroxysms and visits to the Emergency Department due to associated symptoms, also worsening anxiety (Guedon-Moreau et al, 2010; Peinado et al, 2010; Thrall et al, 2006). However, there has been limited research relating to people with AF who are less symptomatic or within the general AF population who may not be seeking healthcare. The QoL study within this research therefore attempts to address this, by

exploring the effects of QoL on the identified populations. This information, showing the reduced QoL in most domains, adds support to the argument for AF screening in people with diabetes as when these conditions are identified, efforts can be made to intervene to optimise health and wellbeing. Further information relating to participants' AF status would be useful (e.g., stability, symptoms, and duration), as this could help develop further research in specific areas with outcomes leading to focused patient management where most appropriate. Employing more targeted management for these patient groups from an early stage of disease, through medical therapies or other physiological support, may help reduce the burden on QoL. Being proactive when one disease exists, through emphasis on lifestyle advice e.g., smoking cessation, exercise, and weight control, is important to prevent the cascade of comorbid conditions that can result. Given the evidence from this thesis on the detrimental effects AF and diabetes have on QoL, coupled with the knowledge of increasing prevalence for both conditions, promoting identification of AF through active screening is advantageous, in that physical symptoms can then be managed, support for the emotional and mental strain from both conditions can be instigated and then, negative health consequences can be minimised. If AF is not detected, and screening is not encouraged or facilitated, the comorbidity cascade could progress whereby other comorbid disease could develop and further impact QoL. AF diagnosis should then be explained in a clear and concise manner, so to manage expectations and understand possible consequences, which may help reduce further negative influence on QoL.

The impact of diabetes on QoL has been well explored and has shown lower patient assessed scores across the domains of health, with the mere presence of diabetes deteriorating a persons' QoL (Trikkalinou et al, 2017) and this, therefore, reflects the worsening scores seen in results from *Study 2* (*Chapter 5*) when coupled with AF. Factors relevant to the stability, treatment and duration of diabetes were not captured in this QoL study but are relevant when considering when and why diabetes impacts QoL. Complications from diabetes including coronary artery disease, renal failure, the use of insulin and being of older age, have shown to affect QoL in a negative way. (Timar et al, 2016). Lower scores were seen in the QoL study in domains including Social Functioning and Emotional Wellbeing. This may relate to the

impact of having diabetes on social activities and there is evidence that psychological wellbeing is negatively impacted particularly in younger people with diabetes, which has been reported to contribute to destroying social relationships (Bronner, Peeters, Sattoe & van Staa, 2020). When AF exists alongside diabetes, whilst more prevalent in older populations, this might contribute to the difficulties experienced socially when perhaps physical symptoms exist from the arrhythmia, further impacting on the desire or ability to function socially.

7.5.2 The importance of measuring quality of life and the impact of comorbid disease.

Chronic disease, whereby there is some restriction to the individuals' ability to live and function as they would like, can lead to worsening general health, limited physical and emotional abilities, reduced health related QoL and increased healthcare costs (Fortin, Dubois, Hudon, Soubhi & Almirall, 2007; McPhail, 2016; Megari, 2013). Measuring QoL also helps with understanding outcomes of intervention. In AF management, QoL studies have been applied to patients with symptomatic AF to assist with understanding how their symptoms impact (Aliot et al, 2014; Guedon-Moreau et al, 2010; Thrall et al, 2006). QoL has also been assessed following interventions to try and improve or correct the arrhythmia, be it with medicines or procedures (Bubien et al, 1996; Duff et al, 2003; Gupta et al, 2020; Thrall et al, 2006; Tse et al, 2004). QoL however, is important at all stages of a patients' journey and should be measured in various ways and times both within the acute and chronic phase.

Commonly, QoL is assessed during an acute phase of treatment or intervention only, but it is important to measure beyond the clinical trials. The QoL study within this research was a one-time measure for this population. With the increasing burden of chronic disease, in particular AF and diabetes prevalence, measuring QoL in disease combination can assist with understanding the effects they have, beyond the single disease focus but by applying a more holistic approach. With the growing numbers of people living into older age, there will likely be an ongoing cascade of chronic comorbid disease, and moving towards patient assessment in this way, might

encourage a more relevant approach to the physical and psychosocial needs of each patient.

This accumulation of comorbid disease, or multimorbidity, is described as having two or more chronic conditions (Bao et al, 2019). This is compounded by the increasing aging population and through this, a major epidemiological shift is being observed with more people surviving with more chronic and comorbid disease (Farooqi, Gerstein, Yusuf, Leong & Biostat, 2006). Deficit accumulation states that as people age, they accumulate health deficits, and that more deficits confer greater risk (Rockwood, 2016). AF affects more people of older age but is not exclusively an older age problem. AF and diabetes though, are often in existence alongside other comorbid disease and local figures identify that 37% of people with AF, have three or more comorbid conditions (States of Jersey, 2017b). These multimorbidity figures also identify that in Jersey, 24% of people with diabetes, have three of more chronic conditions (States of Jersey, 2017b). A health related QoL study in multimorbidity, showed that diabetes and hypertension were the most paired chronic disease, followed by hypertension and dyslipidaemia (Bao et al, 2019). Another study found hypertension and dyslipidaemia to be the most prevalent chronic disease pairing, followed by hypertension and coronary heart disease (Wang et al, 2015). AF, hypertension, cardiovascular disease, diabetes, and renal dysfunction are disease groups commonly seen in coexistence and knowledge of multimorbidity patterns could provide more targeted measures to assess and improve QoL. Disease interactions can worsen QoL, as identified in the QoL research, and this is supported by research where these effects were explored in people with cardiovascular and respiratory disease, demonstrating the detrimental effect on the physical functioning aspect of QoL, when in coexistence, rather than in isolation (Fortin et al, 2007).

The increasing count of comorbid disease, with one condition often being a catalyst for the development of another, highlights the effort that is needed to identify preventative health measures to reduce the impact and likelihood of further accumulation of chronic illness. Screening for concomitant disease may then help with disease prevention and result in reducing the subsequent negative impact comorbid

disease can have on QoL. The implications of QoL appraisal as an outcome within healthcare can also help educate patients through anticipation of symptoms and understanding of potential consequences from their diagnosis and treatments. This may be facilitated through enhanced patient-physician communication, which has been reported as an additional benefit from QoL assessment (King et al, 2016).

Applying clinical practice experience along with these findings, leads to the suggestion that it would seem appropriate to measure QoL throughout the disease trajectory. QoL has prognostic importance and can be a predictor of treatment success and this prognostic ability suggests there is a need for routine assessment beyond clinical trials and symptomatic groups. QoL assessment might also highlight other problems that have not been disclosed during healthcare consultations that could lead to onward disease management, targeted health promotion, and appropriate support beyond the physical needs. Yet, despite awareness and research demonstrating the importance of QoL assessment, there remains barriers to routine implementation. The expectation that healthcare providers will routinely incorporate QoL measures into clinical practice seems yet to be fulfilled on a mandatory or routine basis. Barriers to implementation include lack of familiarity of QoL measures, perceptions regarding the utility and availability of instruments, methodological concerns, and logistical and practical considerations (Davis & Cella, 2002). The choice over QoL tool can be complex due to the number available, including generic and disease-specific options. The tool should be reliable, consistent, valid, and user-friendly and should be appropriate to use in clinical practice (Giesinger et al, 2009). QoL assessment does not appear to be promoted in the same way that other aspects of healthcare afford, for example, when new equipment becomes available to assist in a surgical technique, or novel pharmacological options to optimise symptom control or slow disease progression. Other barriers include existing workload and time constraints within often brief consultations, that preclude the application of adequate QoL assessment (Giesinger et al, 2009). Relentless performance targets, documentation, guideline adherence and waiting time pressures all add to the burden on the healthcare provider, making the implementation of additional work, challenging. Ways to make QoL assessment easier and more feasible, have considered the use of computer-based

methods (Giesinger et al, 2009). Studies using this method have demonstrated this to be an acceptable and effective method for obtaining QoL information, enabling real-time data and immediately available results for the clinician (Giesinger et al, 2009). Time and interpretation of the outcomes of assessment are still needed and perhaps having this available prior to planned appointments, might help overcome some of these remaining constraints. It may be however, that a shift in how healthcare scenarios or consultations are approached, is required. When a fifteen-minute appointment is scheduled, it is incredibly challenging to include a completely holistic assessment of the patient when they may present with pain or breathlessness, for example. Focus and relevance to the complaint is required when time pressures preclude further exploration. Consultation models and symptom assessment checklists exist to guide the practitioner in completing thorough and accurate patient assessment and incorporating QoL assessment within these models might assist with ensuring QoL assessment is completed as part of essential patient-centred care. An alternative approach within an AF clinic might be to address the patients' QoL within the initial part of the consultation, alongside symptoms and before talking in detail about the diagnosis and next steps. This way, a complete patient assessment is undertaken, learning the areas of biggest compromise for that individual. Where this is perhaps easier to negotiate, is when care is provided by a service where there is continuity and when the visits are recurrent, allowing for the assessment and re-appraisal of QoL as an outcome parameter. Despite these challenges, and the focus of biomedical outcomes resulting in being disease free, life prolonging or reaching recommended health targets, the implementation of QoL assessment is vital to ensure strategies implemented to meet these targets are done in the right way, for the right patient and at the right time. The challenge to implementing systematic QoL assessment remains and is compounded by the focus that effective healthcare may be judged on meeting (clinical and financial) targets. Incorporating patient outcome measures into meeting these targets, may go some way in promoting this essential assessment (King et al, 2016).

7.6 Patients' views and understanding around atrial fibrillation and screening.

7.6.1 Psychosocial aspects around screening and motivation.

There is limited research relating to the impact psychosocial aspects have on cardiovascular or AF specific screening and the impact screening has on psychosocial aspects of health (Asif et al, 2014; Holland, Cooper, Shaw, Pattison & Cooke, 2013). The aim of the interview-based study was to explore patients' understanding of AF and their views and experiences of AF screening, having used the AliveCor® device, in the hope this can inform screening practices through elucidation of lived experience relevant to this debate. Findings demonstrated most participants had a poor understanding of AF, yet an overall agreement that screening for AF was beneficial. Understanding around AF and stroke risk was low, but despite this, self-motivation to attend the screening (from the GP invitees) resulted in about half the sample of participants. Health screening overall, was regarded as a worthwhile activity among participants and interviewees expressed their preference over being aware of health diagnoses.

Interview questions related to how, when and where screening should take place. The preferred screening location was primary care or community-based settings, with the hospital seen as a deterrent to screening attendance. The GP surgery was preferred and considered the most appropriate environment and this, as an approach to screening, has been shown to be more effective than screening in the community in a meta-analysis of AF screening effectiveness and its determinants (Petryszyn et al, 2019). Screening methods were also considered, and patients' spoke of the convenience and ease of using the screening tool (the AliveCor® device). This is important for optimising screening participation, where risk, discomfort and inconvenience are minimised. This is supported by wider evidence presented in the systematic review, where the AliveCor® device was compared to other forms of ECG monitoring (Desteghe et al, 2017; Lown et al, 2018). This was, however, in relation to diagnostic accuracy and performance rather than user experience, but it is noteworthy

that the ability to hold the AliveCor® device was compromised in some patients where motor function caused some difficulty (Desteghe et al, 2017). When health professionals were asked for their feedback on the AliveCor® device, feasibility was rated favourably in a low resource setting where internet connection and device access was considered (Evans, Shirk, Muturi & Soliman, 2017). In a review outside of this research, physician opinion regarding the AliveCor® device was positive regarding clinical value, ease of interrogation and likely acceptability from patients (Godin et al, 2019).

Questions relating to costs for AF screening highlighted concern over wider implementation of the AliveCor® device, as the example, with some participants' considering cost as prohibitive for self-purchase and general use. Findings from the interview-based research showed that patients were mindful of the costs involved with screening. Considerations around cost included the screening appointment and the cost for the person to perform the screening along with the screening method. There was deliberation over how much the screening tool might cost, then surprise when the amount declared. The additional requirement of a smartphone or iPad device for connection, was also considered a possible deterrent when the purchase of the device would also be needed. This affordability can cause a divide in availability and access to digital ECG screening devices. Remote, wearable devices which provide wider opportunities for ECG monitoring in rural and low resource settings, are less available due to the health economy and expense of items including the iWatch and smartphone applications. The socioeconomic gradient has relevance to screening uptake and where there is greater deprivation, lower screening participation is apparent (Vrinten, Wardle & Marlow, 2016). Social norms, stigma and environment have also been suggested as relevant to screening uptake (Nuche-Berenguer & Sakellariou, 2021), with environment reflected in findings from this research. Attitudes and beliefs are among the motivational aspects also recognised as influential on screening outcomes and methods (Michie, Dormandy, French & Marteau, 2004; Young & Robb, 2021), and this supports feedback within the patient interviews, whereby thoughts on screening in general and AF, perhaps reflected their desire to proceed with the earlier AF screening and subsequent interviews. This also links to health

behavioural theories as introduced in the methodology chapter, including the *theory of care seeking behaviour* and the direct relevance to screening attendance and adherence to health promotional activities (Lauver, 1992). Emotions, perceived efficacy, risk, and intentions are influential on screening outcomes and the screening method (Michie et al, 2004; Young & Robb, 2021). When the individual has greater efficacy beliefs about the screening, uptake is also greater (Miles, Rainbow & von Wagner, 2011). As well as these underlying beliefs, decisions to attend screening also relate to access, availability, location, transport, and literacy.

Equitable access to those who are eligible for screening can cause societal division whereby some groups may be less able or motivated to cooperate. Age is an important factor here, particularly in relation to AF screening, where prevalence increases with older age, and as seen in the AF screening study, also applies to the population with diabetes. Age may not be a contributing factor for all, but consideration is needed with respect to the location and access, the ability to comprehend and retain the information for screening consent and then the risks associated with a diagnosis of AF, whereby ongoing tests and medication might be recommended. Age may also be a relevant component when contemplating ECG screening methods and application of digital technology, although there is evidence to support findings from the interview-based study, that age may not preclude engagement with growing technology for ECG monitoring. A recent report states that 75% of people aged 75 years and over, use a mobile phone and 49% use the internet (Ofcom, 2020). The growing usage has implications for health monitoring and the scope to incorporate digital ECG monitoring into the wider population, offers opportunities for AF screening. The impact of globalisation, development and implementation of technology and health inequalities also impacts on the sociological contribution to health screening and the evidence around mobile technology across sociodemographic groups shows a divide in regular usage of mobile phones but more so, internet use (Ofcom, 2020), although the cost of wearable ECG watches and similar portable devices does impact the affordability and availability in these circumstances.

There is some association between findings from the patient interviews research and results from a meta-ethnography of qualitative research relating to influential factors around cancer screening attendance, where three primary themes were identified (Young et al, 2018). These themes included ‘relationships with the health service’, ‘fears of the screening’ and ‘experiences of risk’ (Young et al, 2018). Similarly, factors relating to knowledge (language used, translation and knowledge of the benefits and harms), mental and physical capabilities and health literacy were felt to be relevant in screening uptake (Young & Robb, 2021). Themes from the patient interviews include ‘fears from outcomes from screening’ and this is where education and clear promotion with simple messages can assist with alleviating concern and dispel assumptions people may have about screening.

This complex combination of patient factors demand elucidation to develop optimal, evidence-based strategies to increase participation. Behavioural interventions including reminders for screening invitations, fixed appointments rather than open invitations and modifications to traditional testing, have been suggested (Young & Robb, 2021). Publicity, support around the campaign to dispel myths, endorsement from a trusted health professional and diversity over locations may go some way in addressing reasons for non-attendance or low participation. Social networks also appear important in screening participation, with isolation, social exclusion and family and friends influence affecting attendance (Lagerlund, Sontrop & Zackrisson, 2014; Zackrisson, Andersson, Manjer & Janzon, 2004). The distribution and awareness of health and screening facilities along with public health campaigns are relevant (Wakefield, Loken & Hornik, 2010; Young & Robb, 2021). Myths and acceptance of the screening procedure are also important (Bongaerts et al, 2020; Chorley et al, 2018; Kolthoff, Hestbech, Jørgensen, & Brodersen, 2016).

7.6.2 Enhancing patient comprehension and concordance around atrial fibrillation management.

Communication around health diagnoses can be complex, inaccurately presented and misunderstood. Patients were asked about their understanding of AF in the interview-based study. This was following receipt of this diagnosis during the AF screening research. Overall, understanding around AF was limited. All patients knew this related to their heart with some aware of an irregularity. Knowledge relating to stroke risk and anticoagulation was minimal. The health professional performing the screening and advising of the AF diagnosis was experienced in this role. A patient information leaflet was provided (from a national arrhythmia website) and patients were asked to visit their GP. Contributory factors underpinning participants' understanding may relate to how the information was delivered, the communication style, level of detail and approach. It may also be relevant that communications had not been designed with the input of patients to ensure understanding. The time between AF diagnosis and interviews (which was many months for some) may also have impacted. Participants interviewed were well with no overt AF related symptoms and neither by majority, were they subject to ongoing investigations or hospitalisation. This may impact on the desire or want of further information.

Open communication, avoiding the use of medical jargon and not assuming the patient has understood, are important. Encouraging questions and repeating key health messages, can assist with meaningful consultations (Graham & Brookey, 2008). Providing an environment where there is suitable privacy and time, can help foster a more conducive conversation. A technique shown to foster more conducive and meaningful communication is 'Ask Me', a communication tool created by the Partnership for Clear Health Communication which specifies three essential questions that patients should be able to answer after health care encounters: 1) *What is my main problem?* 2) *What do I need to do*? 3) *Why is it important for me to do this*? (Partnership for Clear Health Communication, 2007). This approach can be beneficial, regardless of intellect and 'health literacy'. Using posters and brochures to compliment information provided, can reinforce messages given verbally. This

encourages discussion and verification over their understanding, thereby helping to correct any misunderstandings before that meeting ends.

'Health literacy' has been well documented and described as the degree to which people have the capacity to obtain, process and understand basic health information along with services needed to make appropriate health decisions (Nielsen-Bohlman, Panzer & Kindig, 2004). The entire health care system relies on the assumption that patients can understand complex written and spoken information, but this is a fundamental problem affecting health status, outcomes, healthcare use and costs (Weiss, 2007). Patients are expected to navigate a complex medical system and then manage more of their often, complex care at home. This is further compounded by the introduction of eHealth and mHealth which for many, is too much to contend with. Findings from the patient interviews demonstrate that despite undergoing AF screening, receiving a diagnosis for AF, with subsequent medical review and written information, patients' understanding was limited, or perhaps never entirely understood. This may have related to information retention, as the time between screening and interviews were many months. Patients were also asked if they have considered any connection between their existing diabetes and new AF diagnosis, and by majority, they had not.

Results from the patient interviews demonstrate infrequent mention of stroke, stroke risk or anticoagulation. This is in keeping with the paucity of knowledge that exists around stroke risk, and risks and benefits of anticoagulation (Lane et al, 2015; Lane, Ponsford, Shelley, Sirpal & Lip, 2006; Lip et al, 2007). Recent experience of stroke has been shown to significantly influence patient values and preferences regarding AF and willingness to accept treatment such as anticoagulation (Lane et al, 2018). Supporting evidence demonstrates that when patients were asked about their preferences around anticoagulation, stroke prevention was the most important attribute (Andrade et al, 2016; Frankel, Parker, Rosenfeld & Gorelick, 2014). Educational intervention around anticoagulation in the context of AF has shown to be beneficial through an increased understanding after brief intervention (Lane et al, 2006). Effects of an educational intervention programme showed that prior to the intervention, just half

of the patients were aware that AF predisposes to thromboembolism and a non-significant increase was noted in patients' understanding of risks related to AF and relatable components e.g., that anticoagulation helps to prevent blood clots (Lane et al, 2006). Level of awareness seems to relate to individual circumstances, current health status and personal experiences, and not necessarily educational level (Lane et al, 2015; McCabe et al, 2011).

Evidence suggests that regardless of health literacy, memory for medical information is limited (Selic, Svab, Repolusk & Gucek, 2011), with 40—80% forgotten immediately (Sherlock & Brownie, 2014). The more information given, the lower the proportion correctly recalled and nearly half of that retained information, is incorrect (Kessels, 2003). Ley's model on effective communication in medical practice depicts this by demonstrating where there is understanding, there is greater satisfaction and adherence and recall (Ley, 1988). This recall then results in greater satisfaction and adherence (Ley, 1988).

Factors affecting information recall include age, anxiety and distress around the encounter or information given, the perceived importance of the information and how this is delivered. There exists a moderate inverse relationship with age and information recall from health consultations. Increasing age can result in an increase in variability in cognitive function and this may impact on the amount of information retained (Kessels, 2003). This has been described as either due to defects in encoding and storage of information, cognitive impairment and memory relating to specific events (Glisky, Rubin & Davidson, 2001; Kessels, 2003). What seems more apparent from clinical practice, however, is not attributable to age necessarily but rather attitudes, engagement, and motivation from the individual in relation to their care. Consistency of information with personal theories have been recognised to have an important impact, where new information that goes against a personal assumption about the condition or disease, is more likely to be forgotten or misinterpreted (Okun & Rice, 2001). Clinicians might therefore adopt the communication tool '*Ask Me'* as detailed above, to ensure patients have understood the consultation and where there are deficits, alter their communication style or delivery of information about their

health. Recall is also better when information is provided in simple language, and this applies verbally and via other mediums. Where written information is used, basic language, bullet points and white space has been shown to be advantageous, as have pictograms and animation (Brotherstone, Miles, Robb, Atkin & Wardle, 2006; Graham & Brookey, 2008). Furthermore, the impact of anxiety and distress can affect information recall, and this would relate directly to the work within cardiology, where from experience, the 'heart' leads to stress and worry if this is where the disease impacts. Even before progressing to full consultation, the patient may perceive this to be a stressful scenario where their heart is the organ of focus. Many patients anecdotally, think they are more likely to have a heart attack, despite AF being related to the electrophysiology of the heart, rather than the coronary arteries. This often leads to heightened anxiety which requires competence and knowledge to provide accurate explanations and reassurance, before discussing the presenting arrhythmia, for example. This is supported by research looking at health related QoL, depression and anxiety in AF patients (without co-morbid disease) which found anxiety to predominate (Lane, Langman, Lip & Nouwen, 2009). Along with AF, brings the necessity for stroke risk assessment and again, a similar connotation may be held by patients who hear 'stroke'. This anxiety can lead to attention narrowing, described as peripheral information such as treatments, appointments, and tests, which are less well stored and processed (Kessels, 2003). When talking to patients about AF, ensuring their perceptions regarding symptoms and medications are managed at diagnosis, can have a positive outcome on their physical trajectory (Lane et al, 2009).

7.7 Limitations.

Limitations relating to the AF screening study (*Study 1, Chapter 4*) centre around the design whereby recruitment was via letter invitation to people with diabetes from three GP surgeries and consecutive invitation face-to-face at the diabetes centre. No age category was specified besides being over 18 years, and this perhaps impacts the overall yield of AF diagnosis. The age range was 22-90 years, mean age 63 years in the

total sample (median age 64 years), and mean age 72 years in the AF sample (median age 72 years). Letter invitations relied on the patient to be motivated to call for an appointment and be able to attend the screening centre. Only one location was used for the GP participants, although various times and days were offered. The letter was written in English and the unavailability of translation may have precluded wider participation. The screening episode occurred once only and this was due to researchers' availability, time constraints preventing repeated screening and longitudinal design and resource and funding limitations preventing purchase of additional AliveCor® devices. Ownership of a smartphone or iPad device would be needed, so would have needed consideration within the research design (but then potential exclusion of those without access). The emergence of the global pandemic also hampered recruitment to a point where the total sample size was unachievable and therefore had to be accepted as slightly below the calculated statistically representable size. Furthermore, the study design did not incorporate people without diabetes to compare AF frequency with and nor did the research design allow for inclusion of a sample of people with known AF, in whom diabetes was assessed for. This limitation precludes comparisons between AF and diabetes in relation to the existing diagnosis and where, for example, prevalence and predictors differ if diabetes or AF, is the existing condition. Risk factors may differ in an AF group, without diabetes, where AF can exist as a singular condition in athletes for example, without associated comorbidities, which may be more prevalent when diabetes is an existing condition. If diabetes was screened for in an AF population, further analysis could include blood glucose measurements (e.g., HbA1c), risk factor profiles and renal function along with potential repeated measures over time, to explore changes to disease stability, predictors, and disease prevalence. Omitting patient medications within the data collection was a further limitation as drug effects can impact on the development and incidence of AF. Gathering this information should be considered in future studies exploring AF risk and incidence as this would help comprehend why medications used to treat diabetes and cardiovascular disease, are confounders of the data.

The QoL study was available online only, via an arrhythmia focused website, meaning only those accessing this website would locate the survey for completion. This therefore restricted the outcomes and generalisability by prohibiting people without internet access or information technology competence. The survey was not publicised beyond the website's 'available surveys' tab. This was also only available in English as there was not sufficient translation available due to cost limitations in arranging this. The QoL surveys also did not collect information relating to comorbid disease, medications taken or demographic details. Ethnicity data was not requested, although epidemiological studies and clinical trials consistently show a lower incidence and prevalence of AF in ethnic and racial minorities. Obtaining this information in future QoL surveys would be advantageous to help explain the impact of other chronic disease and demographics on QoL outcomes. Absence of this information might have meant the outcomes were not entirely representative of AF and diabetes, but rather the presence of another co-morbid disease. Multi-morbidity is important when exploring chronic disease and information relating to co-morbidities should be collected in future research regarding QoL and AF. Similarly, demographic such as age or ethnicity might have enabled alternative analysis within the data, to determine what relevance these factors might have had on QoL outcomes.

The use of the SF-36, a generic QoL assessment tool, was used for its relevance to AF and diabetes QoL based research along with previous utilisation in these disease groups alone (Abbasi-Ghahramanloo et al, 2020; Aliot et al, 2014; Berkowitsch et al, 2003; Echouffo-Tcheugui et al, 2017; Engström et al, 2019; Jones et al, 2020; Kim et al, 2016; Lane et al, 2009; Raine et al, 2015; Reynolds et al, 2006; Wukich et al, 2016). The questions within the SF-36 were felt appropriate to capture information relating to the physical, emotional, mental, and social aspects of wellbeing. Having appraised other generic and disease specific tools for the assessment of QoL, it is accepted that using an alternative tool might have provided different findings. Combining a generic and disease specific tool might offer an alternative approach to obtaining a more complete assessment of QoL, especially when chronic disease co-exists, but where symptoms perhaps predominate from one condition specifically.

Interviews with patients regarding their understanding of AF and their views on AF screening included a small sample of participants who had undergone AF screening in the screening study. This was designed to capture feedback on their experiences. The time between the screening episode and interview varied but was in the region of eighteen months. This may therefore have impacted on information recall. The patients were well with very little awareness of the arrhythmia or intervention relating to AF during this time, and this may have lessened their awareness or focus on their AF diagnosis. Only one woman was interviewed, and this could have impacted on feedback relating to overall screening enquiry and relevance (for example, different perception due to screening orientation differences for men and women). Feedback from women relating to AF screening were underrepresented and this presents a confounder on views. Only interviewing people with AF from the AF screening study and obtaining their views directly from the lived experience of AF screening and AF diagnosis, brought the perceived benefit of direct feedback from patients affected. Obtaining views from people who had undergone screening but were not diagnosed with AF, might have offered an alternative perspective, but to answer the research questions defined, the views of those with an AF diagnosis was most relevant. Reaching a wider group with a range of AF stability and symptoms, might be useful to gain further insight into patients' understanding and views. A focus group might also add interesting information with wider discussion around AF screening approach, location, and method.

There are therefore limitations within each of the three research studies and addressing these in future research could add insight to outcomes and existing evidence. Some of the limitations might have been improved by incorporating patients and the public within the design of the studies. Patient involvement can improve the quality and relevance of research, bringing an alternative perspective to the study whilst helping to ensure the research questions are focused and appropriate (Minogue, 2021). Contribution can be at various stages of the research journey from designing, implementing, disseminating knowledge, and evaluating the impact (Minogue, 2021). Using methodologies that patients are more likely to engage with is also an important consideration.

Incorporating a balance of research methodologies and study designs, provides different perspectives to a central research theme – that is, should we be screening people with diabetes for AF? The screening study, supported by QoL data and patient feedback provides a critical and analytical approach to understanding the impact, prevalence, predictors, and views of patients on this important global health problem.

7.8 Why, how, and when to screen for atrial fibrillation.

7.8.1 Optimal atrial fibrillation screening approach.

Screening approaches generally fall into two strategies – opportunistic and systematic. Screening can also be described as targeted, population or mass screening. The screening protocol adopted in the AF screening research followed a systematic approach, whereby patients with diabetes were specifically targeted as the high-risk group under enquiry. Results showed an increased prevalence in this group and thus a beneficial screening approach. There are however caveats to this, and larger studies would be recommended to gain further insight into the optimal strategies for AF screening. Increasing age has a significant effect on AF development, so this might be a relevant addition to screening criteria that helps direct resource for the greatest benefit.

There remains a lack of universal consensus regarding the optimal method, but opportunistic screening is favoured in recommendations made by expert consensus groups. The ESC recommends opportunistic pulse palpation or ECG in people over 65 years (Class I, level B recommendation) and consideration of systematic AF screening in people over 75 years or at high-risk (Class IIa, level B recommendation) (Hindricks et al, 2021). The European Heart Rhythm Association [EHRA] endorse the primary prevention screening recommendations from the ESC (Mairesse et al, 2017). The National Heart Foundation of Australia and New Zealand include the same recommendations for those over 65 years and add their recommendation for screening for AF through interrogation of cardiac devices (Brieger et al, 2018). NICE

also recommend this in people presenting with symptoms of AF (NICE, 2021). A global push to screen all over 65-year-olds is being driven by an international collaboration (AF-SCREEN) who propose national screening programmes to lower the risk of catastrophic strokes (Freedman et al, 2017). For now, the United States Preventative Services Task Force and the UK National Screening Committee [NSC] do not recommend AF screening, largely based on insufficient evidence on stroke reduction efficacy of AF screening and the lack of data on stroke risk of shorter asymptomatic episodes (UK NSC, 2019; US Preventive Services Task Force, 2022). This is contested by organisations including the British Cardiac Society [BCS], the British Heart Rhythm Society [BHRS], the Arrhythmia Alliance and AF association who oppose the NSC position and fear the detrimental effects this could have on preventing catastrophic strokes and physical and psychological sequalae from AF. There are however supplementary NHS health check programmes and Public Health England [PHE] initiatives that are designed to assess health risk for heart disease, type 2 diabetes, stroke, and chronic kidney disease (Waterall, 2010). The 'ABC' campaign by the Cardiovascular Disease Prevention team at PHE is designed to encourage the identification and treatment of AF (A), blood pressure (B) and cholesterol (C) (PHE, 2019) within primary care settings. The AF Toolkit (Academic Health Science Network, 2016) advocates the 'Detect, Protect and Perfect' motto within their campaign and resources, aimed at increasing awareness, identification, and management of AF.

Opportunistic screening uses existing structures within healthcare, and therefore less expenditure is needed to establish specified screening programmes. It could be argued that those at higher AF risk are those more likely to see their healthcare professional on a regular basis and therefore, have a higher probability of being offered appropriate opportunistic screening. This also applies to ventures such as flu vaccinations whereby older and high-risk populations attend, therefore offering an ideal opportunity for screening. An existing rapport may also encourage screening when offered by a known healthcare professional. Outcomes from the patient interviews study showed that patients considered their GP or an existing health professional as the most relevant to undertake screening tests. It was also suggested

that this would be most appropriate during regular health checks for medications or surveillance and as such, fit within a routine three or six-monthly visit. However, in this scenario, patients have not attended their appointment primarily for AF screening and therefore this needs to be clearly explained with patient agreement. There runs the risk that patients do not know in detail, what they are undergoing and the consequences. A new AF diagnosis would likely lead to further investigations and possible treatments, not to mention the emotional burden of a new diagnosis. How this is communicated, is pivotal. This can incur more time and may constrain the opportunity for thorough explanations and counselling. It has been reported that many healthcare professionals are not confident in ECG or rhythm interpretation, and this can be a further deterrent to screen beyond a pulse check (Engdahl & Rosenqvist, 2021).

Systematic screening targets the entire population or a stratum of the population and provides a complete coverage of the screening intervention. This can apply to all ages and when screening for AF, we see a higher yield in the older population, yet this group may have more difficulty with participation. This has been evident in screening studies inviting participants by age group where an inverse relationship has been identified (less screening uptake in older people), between uptake and screening yield (Hobbs et al, 2005; Svennberg et al, 2015). Participation from screening invitations sent to a mass population could also introduce bias whereby socioeconomic status and comorbidities could impact. Travel distance, time, transport, literacy, and disability can affect the individuals' ability to comprehend an invitation or reach the screening location. Therefore, flexibility is important by making the invitations available in various mediums and using different locations. Re-inviting has also been shown to increase the uptake of screening initiatives (Duffy, Myles, Maroni & Mohammed, 2017).

Self-initiated screening has opened other opportunities for AF detection. Site-less digital screening could improve uptake by limiting the need to attend screening localities, but the mSToPS trial showed that uptake was lower than corresponding conventional screening studies (Baca-Motes et al, 2019). Many of the digital recording devices however use PPG technology rather than ECGs and therefore, when AF is

highlighted, in accordance with guidelines, this would still need clarifying with an ECG (Hindricks, et al 2021). Such devices still do not offer 100% specificity, despite efforts to constantly evolve these algorithms, and thus provide false results. This can result in anxiety, unnecessary tests, and increased expenditure. The AliveCor® device with inbuilt algorithms for AF detection, is one such example and is available for self-purchase. The AliveCor® device has high validity and as detailed in the outcomes from this research (the systematic review, the AF screening study and patient interviews), is well accepted as a screening tool. AF detection is high in supporting evidence and whilst inaccuracies can still present, over-reading by a competent clinician can assist in clarity over diagnosis. Whilst not universally applicable, clinical practice shows that more younger people have digital technology and therefore, whilst widening the scope for heart rhythm screening, may not be targeting the higher-risk groups. Responses from the interview-based research referred to technology know-how, as a contributory factor to utilising such mHealth devices, but age specifically, was not. Two studies based around the use of smartwatches and wearables, revealed a mean age of 35 years and 41 years with an AF yield, similarly low at 0.09% and 0.4% (Guo et al, 2019; Perez et al, 2019). The cost and availability of digital devices whilst promising for many, can potentially exacerbate disparities in healthcare along sociodemographic lines (Varma et al, 2021). Smartphone use differs by income and less affluent communities and low resource settings have less equitable access to such devices (Tsetsi & Rains, 2017; Varma et al, 2021). Findings from the patient interviews detailed patients concern over the cost of the AliveCor® device and additional hardware, with some suggesting this would not be possible for self-purchase. It has been shown that it is the lack of access to mobile devices and familiarity that precludes their use, rather than lack of engagement (Varma et al, 2021). Until there can be an overarching strategic investment with agreed platforms, this divide may continue to exist.

7.8.2 Targeted groups for atrial fibrillation screening.

The AF screening study targeted people with diabetes but with a wide-age criterion (eligible over 18 years, range 22-90 years). Results showed that AF was more prevalent

in people with diabetes, compared to the general population. AF was also more prevalent in older people, with diabetes. Previous evidence has shown correlation with increasing age and AF prevalence, with or without other risk factors. Targeting AF screening agendas therefore to people of older age, might be advisable. Older age groups, and this is often specified as over the age of 65 years, are frequently targeted in AF screening programmes due to perceived cost effectiveness and anticipated prevalence. Additionally, high-risk populations by means of their comorbid health conditions (including and beyond diabetes), have been a focus amongst screening studies (Davis et al, 2012; Desteghe et al, 2017; Khan et al, 2020; Samol et al, 2013; Svennberg et al, 2017; Turakhia et al, 2015). There is some variation in perceived high-risk groups, with many studies including a variety of coexisting disease, therefore making outcomes more difficult to interpret, unless confounders are controlled for within analyses. Hypertension, diabetes, heart failure, renal dysfunction and myocardial infarction are commonly cited within AF screening inclusion groups, often in keeping with risks within the CHA_2DS_2-VASc risk stratification scoring system (Davis et al, 2012; Hall et al, 2022; Khan et al, 2020; Samol et al, 2013; Turakhia et al, 2015). It would be useful to replicate the research from *Study 1*, with other high-risk groups as individual targeted groups where possible (accepting that many patients with chronic disease have comorbidities), to better understand their contribution to AF development.

There is an argument for targeting the younger population, but this may be more relevant across cardiovascular screening rather than AF specifically. Addressing contributory lifestyle behaviours, might reduce cardiovascular risk and complications such as smoking cessation, exercise, and weight control to reduce risk factors relating to hypertension and coronary artery disease. As such, these patient groups have also been targeted in screening programmes (Davis et al, 2012; Chan & Choy, 2017; Samol et al, 2013; Sun et al, 2014). It is the younger population also who predominate the purchase and utilisation of mobile devices and along with technological confidence, are candidates for targeting watch and wearable applications. The disadvantages here, centre around the potential exclusion of people who do not own such a device and so health related data is less representative of the wider population.

7.8.3 Screening frequency for the identification of atrial fibrillation.

Screening for and diagnosing AF has shown congruence with duration of monitoring and single timepoint ECGs as recorded in the AF screening study, which revealed a 5.3% AF prevalence in the targeted population. This compares to single timepoint screening in other AF screening studies using the AliveCor® device, where AF detection ranged from 1.8% to 36% (Chan & Choy, 2017; Desteghe et al, 2017). This variance is related to older age, screening location and study design. Community mass screening yielded lower numbers with AF with wider age inclusion (Chan & Choy, 2017). Outpatient clinics including diabetes and general medicine (Evans et al, 2017) and inpatient cardiology and geriatric wards (Desteghe et al, 2017) demonstrated higher numbers with AF, reflecting the targeted groups and research design.

As previously discussed, AF of a paroxysmal form may be missed by single timepoint ECGs and thus, enhanced by intermittent or continuous monitoring. The value of repeated screenings is evident when AF has been detected beyond the initial screening episode (Soni et al, 2016; Svennberg et al, 2015). Intermittent, repeated ECGs will be more likely to result in a higher yield of AF detection than a single ECG recording and a continuous ECG of the same duration as the intermittent schedule, an even higher yield (Fredriksson et al, 2020). The benefit of detecting more AF, means patients can be assessed for anticoagulation to reduce the risk of thromboembolism or stroke. In the STROKESTOP report, a new diagnosis of AF was made in 3% of participants, of whom 90% initiated anticoagulation (Svennberg et al, 2015).

With the advent of digital and mobile health tools, methods for AF screening have increased. The paradigm shift in consumer and patient-initiated ECG monitoring has opened greater opportunities for AF screening. The traditional HM whilst still used successfully in clinical practice, has limitations through the inconvenience of design and limited duration of wear, which can be incongruent with symptoms and therefore ineffectual. There is an abundance of ongoing research utilising digital and remote ECG monitoring and a search of The Clinical Trials database exposed forty-five trials on a recent database search, where screening for AF was the primary outcome. These

incorporated an array of screening tools, highlighting the ongoing interest and desire to search for undiagnosed AF.

7.9 Cost effectiveness of screening for atrial fibrillation.

Maximising cost effectiveness and efficiency of AF screening is managed in part by targeting the most at-risk groups and in whom anticoagulation would offer the most benefit given the high economic burden of stroke (Welton et al, 2017). Costs relate to the screening method, healthcare personnel involvement, analysis, testing requirements and the subsequent management of a positive AF diagnosis. These effects can move beyond physical impact and can have wider societal costs.

The cost per AF diagnosis according to UK NHS tariffs is £8255 (Halcox et al, 2017). This was calculated through evaluation of device costs, defective technology costs, patient training, overreading and more detailed analysis of ECGs and pathway coordination (Halcox et al, 2017). Furthermore, the cost of an AF related stroke is estimated to be significantly greater than a non-AF related stroke with an associated 25-37% increase in inpatient costs and a 50-60% cost increase when rehabilitation costs are included (Ali, Howe & Abdel-Hafiz, 2015; Winter et al, 2009).

Screening for AF using the AliveCor® device with pharmacy customers aged 65 years and over was evaluated as a cost-effective approach and was well within the fundable range on a population basis (Lowres et al, 2014). Analysis incorporated calculations of anticoagulant prescription and adherence and identified improved cost-effectiveness with DOACs compared to vitamin k antagonists (Lowres et al, 2014). Healthcare economic models have been developed to explore the long-term trajectory and costs of AF screened patients versus no systematic screening in terms of anticoagulation uptake and thromboembolic or major bleeding events (Kemp Gudmundsdottir et al, 2020; Mant et al, 2007; Svennberg et al, 2015). The clinical and economic value of systematic screening for AF was assessed using either one-time screening or intermittent screening for 14 days with a single-lead ECG device, compared to no

screening in people aged over 75 years (Oguz et al, 2020). Their model demonstrated cost effectiveness at conventional thresholds with extended screening compared with no screening (Oguz et al, 2020). Another study performed 12 lead ECGs in the general population and concluded that screening people younger than 65 years, is not cost-effective but improves with increasing age, risk factor burden and when simpler methods for detection are used (Perez et al, 2019; Schnabel et al, 2022). This echoes findings from the AF screening study, whereby AF prevalence was higher in older people, using a simple and single timepoint screening method, whilst focusing on an at-risk population. Evidence from cost effectiveness modelling has also highlighted that screening strategies are less cost effective in octogenarians and older, due to the reduced life expectancy (Lowres et al, 2014; Svennberg et al, 2015; Welton et al, 2017).

7.10 Implications.

It is estimated that about 15% of people with AF are undiagnosed and up to 75% of these, may be eligible for anticoagulation (Turakhia et al, 2018). There were an estimated 33 million people worldwide with AF in 2010 and this number is expected to double by 2050 (Morillo, Banerjee, Perel, Wood & Jouven, 2017). Screening people with diabetes for AF has several implications, from detection that could enable treatment initiation to reduce the risk of health deterioration, to costs and resource of implementing screening programmes and dilemmas relating to the ethics of screening and reliability of screening methods. The AliveCor® device has demonstrated this favourably and the implications of using this device widely in clinical practice, could assist with the subsequent detection of heart rhythm disorders as well as AF. This could then facilitate appropriate and timely treatment to reduce further risk. Incorporating the AliveCor® device into screening programmes and research may encourage more engagement with AF screening due to the ease of application, immediate visualisation of the ECG and overall effectiveness of the device at identifying AF. Having an AliveCor® device, or similarly effective alternative available in GP surgeries in the same way a blood pressure monitor is available, could offer a

feasible way of performing AF screening in eligible patients (and in this scenario, people with diabetes). Alerts could be enabled on GP computer programmes to remind the practitioner of the need to screen for AF, in the same way an alert may trigger if a medication update is needed or a contraindication to a prescription is advised. This approach could be utilised in other clinical scenarios, for example in medical clinics beyond the GP surgery. A screening device could be on the desk of practitioners involved in speciality reviews e.g., a diabetes clinic, cardiology, renal and care of the older person clinics. These screening methods are quick and easy to complete during a consultation and take no longer than a blood pressure check.

The AF screening study demonstrated a higher prevalence of AF in people with diabetes than the general population. AF prevalence was higher in participants who were older, so adopting an approach whereby the higher risk groups are screened, particularly in combination with older age, might reduce the number needed to screen and direct resources appropriately. This would be more likely to achieve a higher yield of AF detection and subsequently, target and treat those at higher risks of complications and who may, for example, benefit from anticoagulation to reduce stroke risk. The implications of screening younger people, besides detecting lower numbers, could result in unnecessary tests, but also induce anxiety over a new diagnosis with potentially, little consequence. However, screening younger people may be advantageous by facilitating advice regarding modifiable behaviours to reduce health risks.

It is in part, the younger generation, and their use of digital technology, that attracts the increasing availability of digital health applications, although the use of mobile phones and the internet is evident across ages with older age not necessarily being a barrier. The advent of mHealth and versatile ECG monitoring devices offers new perspectives to the consumer and health professional and implications within findings from the systematic review and interview study within this research, show that there is engagement and acceptance over the use of these devices across age groups. Familiarity with digital devices was not a barrier, education for use was minimal and adaptability to low resource settings, demonstrates the utility of remote ECG monitoring devices, such as the AliveCor® device. Tailoring ECG monitoring to the

individual is important though, to ensure the tool is appropriate and justified for that individual and the reason for monitoring. The implications of over monitoring can lead to anxiety and obsessive practices. There are wider implications also, around the implementation of mHealth, promoting equitable access within the socioeconomic divide and streamlining governance principles and policy relating to the integration and collaboration of digital tools within healthcare, that must be supported by a sound evidence base.

Among these considerations, should be the clinical cost implications. With 2020 as the focus, AF was predicted to directly cost the NHS between £1.4 billion to £2.5 billion, depending on prevalence (Burdett & Lip, 2022). Costs appear mostly from primary admissions, representing 0.9% to 4.27% of total NHS expenditure (Burdett & Lip, 2022). Over the next two decades, this is expected to increase by 1.35% to 4.27% (Burdett & Lip, 2022). Controlling symptoms of AF is also important as this contributes to reduced hospitalisation and improved QoL. Data from the QoL study shows how the two disease groups in combination, negatively impact QoL. The implications of compromise to QoL, from any of the components, can be devastating to the individual be this through physical incapacity, inability to work, reduction in social activities or disengagement with family. Integrating QoL assessment with these patient groups, particularly as this research shows, when combined, has implications that could lead to more focused treatments or support. The wider implications could lead to consideration of QoL assessment in comorbid patient groups on a routine basis, and not just at disease onset or initial consultation, but as on ongoing and repeated measure.

Implications for moving forward centre around the need for ongoing research into AF screening and particularly, the optimal methods and approaches to increase participation and comprehension around screening importance, AF, and AF management. The implications around implementing AF screening in people with diabetes is wide reaching, in relation to the practicalities beyond the initial screening episode obtained via a screening device in primary care, for example. Screening opportunistically, as recommended by cardiovascular societies and consensus guidance (Hindricks et al, 2021; Mairesse et al, 2017), would make this more

affordable than structuring a systematic screening programme. There would be less resource needed in terms of organisation, making patient contact and promotion, although arguably, a systematic approach could target the required population more appropriately. The onward management of patients identified with AF would need focus and this would be ideally placed with the patients' GP, although in Jersey, this comes with a fee, so could impact attendance for both screening and subsequent management. Appointment availability is another potential obstacle, as is the populations who attend and those who typically do not attend for primary care review. Nevertheless, this would still seem to be the most appropriate location for onward assessment with the GP central to coordination and assessment of patients' management. This is where initial treatment could and should be arranged, including assessment for anticoagulation and rate control to optimise related symptoms, in line with the ABC Better Care Pathway (Lip, 2017). Then, if additional speciality support is needed, the patient can be referred to an AF clinic or cardiology department, in accordance with services available in that locality.

7.11 Recommendations.

AF screening is advocated by national and international guidelines and global campaigns (Hindricks et al, 2021; NICE, 2021; Freedman et al, 2017). The prescribed way of doing this is yet to be determined, in terms of method and approach. What is accepted, is the increased risk of AF in the older population and findings from this research would support the recommendation to screen people who are over 65 years of age. This recommendation comes from prevalence data from the AF screening study, supporting evidence around cost implications of detecting AF and stroke prevention and the overall acceptance from patients, that screening for AF is beneficial. In addition to screening people over 65 years of age, at-risk populations should be considered in screening targets. Whilst this research focuses on diabetes, the accumulation effect of comorbid disease would lend any chronic condition to be a catalyst for screening initiation. Practically, this might involve a heart rhythm check by

means of pulse taking, and use of an ECG recording device where available. This can be completed quickly, within one minute, and recorded during a consultation or check up with either the GP or practice nurse. This was the preferred approach from patient feedback and therefore, could optimise engagement. AF checks could be performed at routine appointments when the patient may be renewing their prescriptions or having surveillance screening as part of their diabetes management. This would then not require additional appointments or personnel and could be incorporated into existing care. This could also be performed by an allied healthcare professional as many of the ECG recording devices are designed for use by the lay person. Where there is an increased risk of stroke, it would be advantageous to provide an ECG monitoring device for patients to utilise on a regular basis, for repeated screenings for a designated period. Resource constraints make this challenging and collaboration with policy makers and governance structures would be important for support and influence over availability. This could extend beyond primary care and alerts could similarly be placed on patients computerised medical records which would reach across the trajectory of their care locations such as in secondary and tertiary care.

The AF screening study focuses directly on diabetes as the target population, rather than mixed, comorbid high-risk groups. Since starting this research, one further paper has been published whereby diabetes and renal function has been explored in relation to AF risk. Their findings support the need for AF screening in people with diabetes, by indicating a 35% higher risk of AF in people with diabetes, compared to age and sex matched controls from the general population (Ahmadi et al, 2020). This therefore reflects with some confidence, a recommendation that AF screening in the diabetic population necessitates further consideration. However, before significant changes to policy and practice can be made, further research relating to individual high-risk groups as predictors for AF would be advantageous by means of large experimental outcome studies to strengthen the evidence base. It is acknowledged that often concomitant chronic disease exists in the presence of AF and diabetes and would therefore need to be accounted for within analyses to ensure accurate findings.

Outcome recommendations from this research would also include ongoing utilisation of the AliveCor® device within screening programmes and clinical practice. This is a validated, effective, feasible and accepted device for AF detection. It might also be beneficial to repeat the screening study with slight protocol alterations, for larger groups and with other high-risk populations, incorporating longer duration ECG monitoring. This could be through intermittent ECG recordings whereby participants are provided with the AliveCor® device and instructed to record their ECG on a regular, repeated basis. Alternatively, providing a wearable or patch type ECG recording device that continually records for a longer duration, would in accordance with previous evidence, detect more AF where paroxysmal AF may be missed.

This research also leads to the recommendation of mandatory and repeated QoL assessment. The detrimental effect of AF and diabetes on QoL, exacerbated when in combination, highlights the importance through utilisation of QoL assessment tools. Where time allows, employing a disease specific along with a generic tool would be advantageous, to ensure all-encompassing aspects of QoL are understood. However, this is not always practical and therefore using an AF or diabetes specific tool when one condition exists, would be recommended to target the areas known to cause specific compromise.

Chapter 8.

Conclusion.

The focus of this research was to explore whether people with diabetes should be screened for AF. There is yet to be a universally agreed procedure for AF screening. Recommendations generally focus on opportunistic screening of people over 65 years of age or a more targeted approach with people deemed high-risk. This risk category, however, lacks clarity.

The rationale for screening is based on the supposition that there are many people with undiagnosed AF, many with a stroke risk that justifies anticoagulation. The primary aim of screening is to reduce the risk of disease through early detection, enabling treatment initiation where appropriate. AF screening meets many of the Wilson & Jungner (1968) criteria for a successful screening programme. Many people with AF have no symptoms and their diagnosis may go undetected without screening. Risks associated with AF can be catastrophic with stroke risk increased further in the presence of AF and comorbid disease, such as diabetes.

The research within this thesis attempts to address the complexities around AF screening through utilisation of independent yet relatable research studies. The systematic review presents a critical analysis of the AliveCor® device and demonstrates this to be a feasible and acceptable tool with high validity for AF detection. Metrics exploring the integration, utility, scientific components, and resource were rated favourably. The AliveCor® device is used often in AF screening studies and clinical practice. The availability and growing supply of enhanced digital monitoring tools, promotes choice to the consumer along with augmented screening opportunities. Balance of costs, resource, suitability, and wider policy related issues, requires careful consideration. Demonstration of the clinical practicality and efficiency of mHealth has the potential to revolutionise how people interact and integrate with health services worldwide.

The AF screening study (*Study 1, Chapter 4*) adds valuable data to existing evidence around screening targeted groups and is the first study, to the author's knowledge,

whereby diabetes has been the direct focus. The growing prevalence of AF and diabetes requires attention with both increasing mortality and morbidity. Prevalence of AF in people with diabetes was higher in this research, than the general population. Increasing age was the strongest predictor for AF in this study, supporting findings from previous screening research. Screening approaches and screening orientated research design varies, resulting in fragmented outcomes. Whole population screening can be costly depending on the programme, whilst others less expensive, such as pulse palpation to check for an irregularity whenever people attend for a pre-existing medical appointment. Adding an ECG rhythm recording incurs an initial cost through the device purchase, but if a handheld tool such as the AliveCor® device is available in all GP surgeries, this could increase the sensitivity and specificity beyond a pulse check and assist with screening accuracy. Targeted screening whereby older age or specific disease groups are systematically screened, optimises detection, provides a clearer focus, and leads to stroke risk evaluation. At risk groups are yet to be formally defined (besides age), but adopting risks identified in the CHA_2DS_2-VASc stroke and thromboembolic risk stratification scoring system offers a justifiable approach. Diabetes among other risks, falls into this group.

The impact of these long-term conditions on QoL is emphasised in the survey-acquired data in *Study 2 (Chapter 5)*, which showed QoL in people with both AF and diabetes, was worse in six of the eight domains. AF management can be contradictory in terms of treatment pathways and symptom presentation but assessing QoL can provide a reliable solution to the guidance of individualised care. Obtaining QoL data from the general AF population, rather than specifically in clinical trials of intervention, is important when understanding the impact these conditions have to daily lives.

Patient feedback is fundamental when research is patient orientated and gaining views from lived experience, brings an important contribution to the acquisition of quantitative orientated data. *Study 3,* (*Chapter 6*), highlighted the need for well-articulated health information to improve patients' understanding. Participants also felt screening for AF was worthwhile and verbalised their acceptance of the AliveCor® device as an ECG screening and monitoring tool.

These research studies in combination, therefore, link from firstly identifying undiagnosed AF through screening, having explored in detail, the scientific and feasibility metrics of a portable ECG recording device. This device is then employed within the AF screening study, with a target population. Patients' views of this tool and AF screening were later sought in the interview-based research. Patients' involvement and feedback is fundamental for healthcare planning, delivery, and optimised outcomes. This patient-centred-care incorporates patients' beliefs and experiences and correlates with self-assessment of their health. QoL evaluation is thus associated within this important approach within healthcare.

Combining quantitative and qualitative orientated research into a mixed methods approach, creates a cohesive bridge between two research traditions, connecting separate yet dialectically related approaches. MMR extends the breadth and range of inquiry and moves away from the historical quantitative, positivist domination. The conventional research methodologies have limitations and do not always cater for the increasingly complex research aims. MMR therefore takes advantage of the inherent gains of positivism to produce empirical evidence of truth and reality through promotion of counts and statistics, whilst combining with scholars of constructivists who advocate building of social construction of meaning, from lived experience. This demonstrates a pragmatic approach by incorporating the most appropriate methods to address the research phenomena by constructing, confirming, and theorising at the same time, leading to more credible findings to strengthen research conclusions.

This research adds significance to the discussion around AF screening - who, how and when to screen. Recommendations for future research, to further inform this complex area of practice, should centre on large-scale research, powered by endpoints such as cost effectiveness and stroke rates. This can help address evidence gaps to determine the best way to invest healthcare resources in AF management. Focusing on high-risk groups should also be considered whilst controlling for confounders, to ensure findings are directly relatable to each risk factor. To direct resources appropriately, detecting AF in groups whereby the subsequent risks and benefits are greater, would be more cost effective by minimising the burden to populations where subsequent risks are inconsequential. Screening programmes are social as much as they are

medical interventions and therefore benefit from scrutiny, informed by social and psychological theories. Screening is surrounded by debates and controversies and having an analytical purchase on these complexities should assist in reaching more effective and beneficial agendas. Factoring digital health solutions into this approach is important and should be embraced, to reach communities more widely and promote the opportunities these bring.

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