UNIVERSITY OF BIRMINGHAM

Holter Electrocardiographic and Clinical Predictors of incident Paroxysmal Atrial Fibrillation in Patients with Acute Ischemic Stroke

by

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ABSTRACT:

Atrial fibrillation (AF) if left untreated, due to its silent nature, could lead to considerable morbidity and mortality due to its thromboembolic complications, especially ischemic stroke. Prolonged ECG monitoring is an increasingly advocated method to detect silent AF and other arrhythmias. The optimum duration of Holter ECG monitoring to detect underlying AF is not clear leading to a variation in practice based on differences in trial results and relevant clinical guidelines. 7-day Holter ECG appears to provide a convenient way of prolonged non-invasive monitoring for AF detection.

I looked at the 7-day Holter ECG data from an observational registry from Sandwell and West Birmingham Hospital (SWBH) with an unselected all-comer cohort of 476 patients and the interventional arm of MonDAFIS trial of 1714 patients with acute ischemic stroke to look at detection of new AF. Clinical, echocardiographic and Holter ECG parameters associated with newly detected AF where available went through association testing and logistic regression. The final model fit was tested through the ROC curve analysis.

The AF pick-up rate in SWBH cohort was 8.8%. In this cohort, the median age in the AF group was higher than the non-AF group and there was no difference in the gender. AF was more frequently seen when the 7-day Holter ECG was done to investigate palpitations and stroke. With regards to comorbidities, AF was associated with hypertension, coronary artery disease and left-sided valvular disease and for Holter ECG variables. AF patients had a longer duration of recording and higher mean heart rate, more sinus pauses and supraventricular ectopic (SVE) activity. Logistic regression analysis showed that hypertension, previous stroke, left-sided valvular disease and palpitations were independently associated with underlying

AF. In the MonDAFIS cohort, the overall AF detection was 4.6% with incremental increase per each day or recording. AF patients were older and had more underlying hypertension, diabetes, renal insufficiency increased LA size and worse LV systolic function. AF patients also had a longer duration of recording, more SVE and ventricular ectopic (VE) activity. Logistic regression analysis showed older age, frequent isolated supraventricular ectopics, SVE runs and LA dilatation as significant predictors of AF.

7-day Holter ECG monitoring has a good diagnostic yield for AF both in stroke survivors as well as an all-comer patient cohort. In general, the AF group had longer monitoring duration. There are other important similarities in the two groups in terms of clinical parameters (advancing age and hypertension in the AF group) and Holter ECG parameters (higher mean heart rates and more supraventricular ectopic activity in AF group). Combining these important clinical and Holter ECG findings can prove useful to identify patients with a high risk of underlying AF. These findings need testing through external validation and can potentially have an important real-time impact on patient care.

Dedicated to…

My Parents for teaching me the virtue of hard work, patience and belief,

My Wife for always standing by my side with utmost love and kindness,

My Children for making everything look rosy, cheerful and worthwhile.

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When I started my role as a clinical research fellow, I remember one of my senior colleagues forewarned that this time will be interesting, enjoyable, difficult and heartbreaking at the same time. Then, I did not understand this fully, but looking back, I feel that no words could have prepared me for this most amazing and occasionally painstaking journey. Like any long journey, this would be impossible without the help of some very special people.

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LIST OF ABBREVIATIONS

AF	Atrial Fibrillation
BNP	Brain Natriuretic Peptide
CABG	Coronary Artery Bypass Graft
CI	Confidence Interval
CT	Computed Tomography
CRT	Cardiac resynchronisation device
CVA	Cerebro-Vascular Accident
ECG	Electrocardiogram
EF	Ejection Fraction
ESC	European Society of cardiology
eGFR	Estimated Glomerular Filtration rate
EP	Electrophysiology
ICD	Implantable cardioverter-defibrillator
IQR	Inter-Quartile Range
LA	Left Atrium
LV	Left Ventricle
MRI	Magnetic Resonance Imaging
NIHSS	National Institute of Health Stroke Scale
NYHA	New York Heart Association
NT	N-Terminal
OR	Odds Ratio
PCI	Percutaneous Coronary Intervention
SD	Standard Deviation
TIA	Transient Ischemic Attack

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1. **Editorial on "State of Oral anticoagulation in patients with Atrial Fibrillation in Spain".**
   Jawad-Ul-Qamar, M. and P. Kirchhof, *The state of oral anticoagulant therapy in patients with atrial fibrillation in Spain.* Rev Clin Esp, 2015. **215**(2): p. 100-1.

2. "**Almanac 2015: Atrial Fibrillation research in Heart."**
   Jawad-Ul-Qamar, M. and P. Kirchhof, *Almanac 2015: atrial fibrillation research in Heart.* Heart, 2016. **102**(8): p. 573-80.

3. **Original paper:** "Detection of atrial fibrillation by prolonged ECG monitoring in an all-comer patient cohort"
   Jawad-Ul-Qamar, M., et al., *Detection of unknown atrial fibrillation by prolonged ECG monitoring in an all-comer patient cohort and association with clinical and Holter variables.* Open Heart, 2020. **7**(1).

Planned Publications:

1. **MonDAFIS main results paper (Under submission)**

2. **Holter and Clinical predictors of AF in ischemic stroke (based on MonDAFIS dataset)**

1 INTRODUCTION

1.1 Background

Atrial fibrillation (AF) is the most common cardiac arrhythmia.[1] It affects 2-3% of the population in Europe and North America.[2] In practice, AF is not always easy to detect even when it has caused further problems like stroke. In general, AF confers at least 5 times higher risk of ischemic stroke as compared to the population in sinus rhythm.[3] More so, strokes due to AF are associated with high mortality and severe disability.[4] The severity of stroke is judged through the National Institute of Health Stroke Scale (NIHSS) score.[5] Patients with underlying AF have generally more severe strokes as evidenced by the higher NIHSS scores.[6] Approximately, 5% of unselected stroke patients have newly diagnosed AF at the time of the stroke.[7] This increases significantly with further ECG monitoring as an in-patient as well as in an out-patient setting. Stratified ECG monitoring reveals as much as a quarter of patients with acute ischemic stroke having underlying AF.[8] Thus, in patients presenting with ischemic stroke or Transient Ischemic Attacks (TIA), AF is an important risk factor to recognize, delay in which can lead to recurrent events. Hence, the priority in patients with suspected AF related complication to document AF on an Electrocardiogram (ECG) so that it can be effectively treated.

If AF is diagnosed promptly, in the presence of effective modern anticoagulant therapy, strokes due to AF are essentially preventable.[9] In practice, this is not always easy and there is a considerable variation in the recommendations for duration of monitoring especially following ischemic stroke.[8,10,11] Hence, it is very important to identify and suggest a

reasonable method of ECG monitoring which is easily available, convenient for the patient and with a good diagnostic utility. In addition to this, it is also useful to predict AF before it happens so that subsequent complications from AF can be prevented. Considerable work has been done to find out the predictors of AF i.e., those with a strong association with the development of subsequent AF.[12,13] Some of these tests are associated with complex electrophysiological studies or specialised high-resolution ECGs which are beyond the scope and reach of a clinician in a standard hospital environment. However, there is no single set of ECG or clinical markers for AF with sufficient discriminatory power. It is important to find out simple ECG and clinical predictors of AF which would help a clinician identify the patients with a high-risk of underlying AF and hence recurrent stroke. Not only would this lead to the identification of a subset of patients with a high likelihood of underlying AF who can potentially be monitored for longer, but also a low-risk group in which AF can be considered unlikely and would not benefit from time-consuming and costly extensive investigations to find AF.

1.2 Why this work is important?

7-day continuous Holter ECG monitoring is widely available in many clinical settings. Its recording can be reliably analysed using commercially available dedicated software by suitably trained staff, not only to detect AF but, also to pick up other important ECG findings of clinical significance. For the shorter durations of monitoring, for example, 24-48 hours, AF due to its paroxysmal nature can be missed. The quality of the ECG recording for prolonging non-invasive monitoring beyond a week depends not only the patient compliance but and can also have cost implications.[14-16] The invasive implantable loop recorders have risks of

infection with availability being another issue.[17] 7-day Holter ECG, hence, provides a reasonable trade-off between shorter monitoring durations that could be less effective in picking up AF and very long duration of monitoring which risk patient inconvenience and infection.

The main aim of this work is to look for the detection of new AF through this method in a general all-comer population attending cardiology outpatient for 7-day Holter ECG as well as in patients with acute ischemic stroke. Moreover, the data will also be used to find an association between various clinical and other Holter ECG characteristics with underlying AF which can be which could be flagged up as risk factors or *predictors* for new AF for these patient groups. The high-risk patients identified from the study could benefit from continuous ECG monitoring through implantable loop recorder. On the other hand, patients with low-risk features for underlying AF shall prompt the treating physicians to look for other causes of ischemic stroke.

1.3 How this work was done?

This thesis uses 7-day Holter ECG dataset from two different patient populations. I set up a registry of observational registry of an all-comer patient cohort undergoing a 7-day Holter ECG in an outpatient setting for various indications, at Sandwell and West Birmingham Hospital (SWBH), NHS Trust. The first part of my work comes from that observational registry which can be considered a pilot study to find the pick-up rate of AF as well as to identify clinical and Holter ECG parameters associated with AF in a general cardiology out-patient population receiving this test.

I was also a sub-investigator in the MonDAFIS (Impact of standardised Monitoring for Detection of AF in Ischemic Stroke) trial involved with setting up an ECG core lab at the University of Birmingham, providing standardised analysis for each of the 7-day Holter ECGs in the trial. I also supervised the cardiac physiologists and ensured that the data was generated promptly and was of the highest quality as the results of the 7-Day Holter ECG determined clinical recommendations for stroke survivors. The second part of my thesis and the major data comes from the 1714 patients in the interventional arm of the MonDAFIS trial. AF detection rates through a 7-day inpatient Holter ECG will be assessed alongside baseline patient characteristics, clinical, echocardiographic and most importantly Holter ECG parameters associated with AF status in stroke survivors.

1.4 Hypothesis

This work will test the following hypothesis.

1.4.1 The hypotheses related to the SWBH dataset

In an all-comer patient cohort:

a. AF is more likely to be present in patients symptomatic with palpitations.

b. AF detection increases in the presence of underlying cardiovascular risk factors like increasing age, hypertension, diabetes, coronary artery disease, hypercholesterolemia and previous stroke or TIA.

c. Presence of excessive supraventricular ectopic (SVE) activity is associated with more AF.

1.4.2 The hypotheses related to the MonDAFIS dataset

In patients with recent ischemic stroke:

a. Higher age and concomitant cardiovascular conditions (hypertension, diabetes, heart failure, chronic kidney disease) are associated with AF.

b. Echocardiographic findings of dilated left atrium and/or left ventricular dysfunction is associated with underlying AF.

c. Higher count of isolated supraventricular ectopics in the first 24 hour period is associated with paroxysmal AF.

d. Higher counts and duration of supraventricular ectopic runs in the first 24 hours of recording is associated with underlying AF.

e. Excessive ventricular ectopic activity in the first 24 hour period is associated with paroxysmal AF.

1.5 The uniqueness of this work

This work based on SWBH dataset is unique due to various reasons. Firstly a study to look at pick up rate of AF in general cardiology patient population through 7-day Holter ECG monitoring has not been previously done. This allows us to assess the usefulness of this test to pick up AF in patients where this is an expected finding like those patients symptomatic with palpitations or with the previous stroke. It also gives an idea about the number of patients with chance detection of AF like those with chest pain or syncope. The monitoring could be requested by primary care, medical and cardiology physicians alike and it will be interesting to see if the source of referral has an impact on the AF detection.

The MonDAFIS trial is the largest of its kind to compare usual in-hospital ECG monitoring including 24 –hour Holter with an interventional group receiving 7-day standardised Holter ECG in stroke survivors. The work here uses the data from the interventional arm. This gives us an opportunity to find the in-hospital detection rate of AF in stroke survivors and also to examine patient characteristics and other relevant Holter ECG data in this group.

A combined overview of these two cohorts will also help to highlight important common clinical, as well as Holter ECG variables associated with new AF and these findings, can then be generalised in a wider patient population.

2 LITERATURE REVIEW

2.1 Definition and Types of AF

The 2016 AF guidelines from the European Society of Cardiology (ESC) defined AF as a chaotic atrial arrhythmia with no discernible p wave activity and irregular R-R interval lasting for at least 30 seconds.[18,19] It also defines paroxysmal AF as lasting for 7-days or less, persistent AF as more than 7-days and long term-persistent if it lasts for more than a year without conversion to sinus rhythm. At this point, if it is accepted by the patient and physician with rate control as the mainstay of treatment, then it is classified as permanent atrial fibrillation.[20] This classification is agreed upon by the American College of Cardiology (ACC), American Heart Association (AHA) and the European Society of Cardiology (ESC).[21] The types of AF are represented in Figure 2.1.

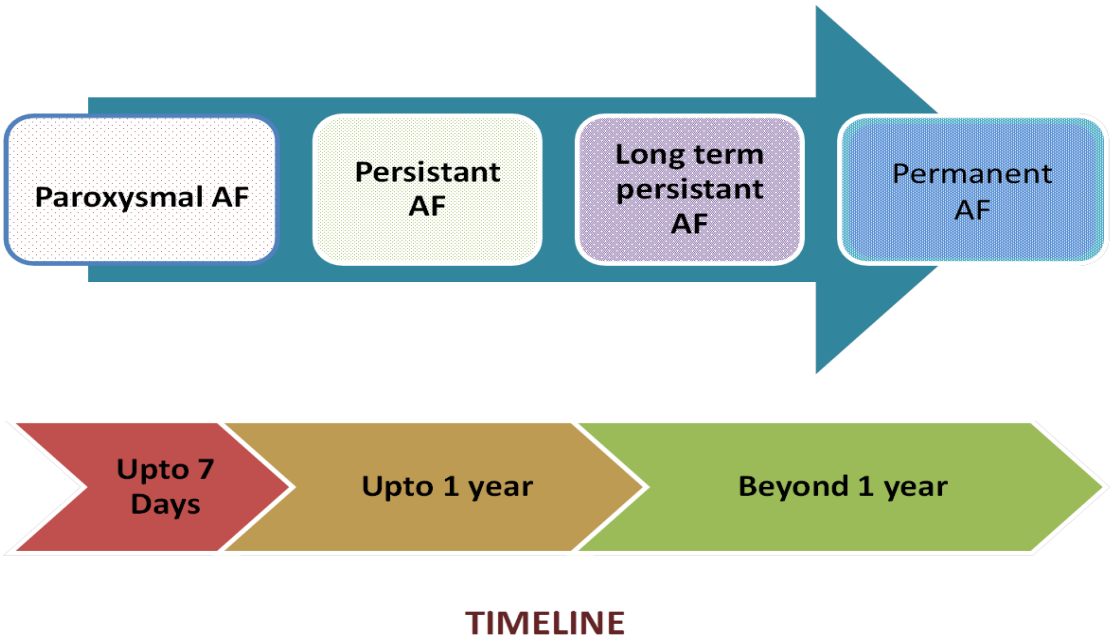


FIGURE 2.1 SCHEMATIC SHOWING TYPES OF AF ALONG THE TIMELINE THE DENSITY OF THE PATTERN IS REPRESENTATIVE OF THE TYPE OF AF.

Persistent or permanent atrial fibrillation is relatively less difficult to detect with most cases detected by 12 lead ECG, Figure 2.2. However, the paroxysmal AF, if left undetected and untreated, can be occult which causes recurrent strokes.[22] Most of these paroxysmal episodes are asymptomatic.[2] At least 25% of strokes have unknown aetiology and are called cryptogenic strokes. This figure rises to 50% for TIA.[23] There is a suspicion that a significant number of these cryptogenic strokes may be due to undetected AF, which further outlines the importance of timely detection of AF.[24] Undetected AF after ischemic stroke or TIA will not only lead to further disabling strokes due to unaddressed risk of systemic embolism, but may also lead to worsening of LV systolic function.[25,26] Initiating the treatment with an appropriate oral anticoagulant can reduce the relative risk of recurrent stroke in patients with AF by a two-third.[27] Hence, the timely diagnosis of paroxysmal AF in ischemic stroke or TIA survivors has direct therapeutic implications.

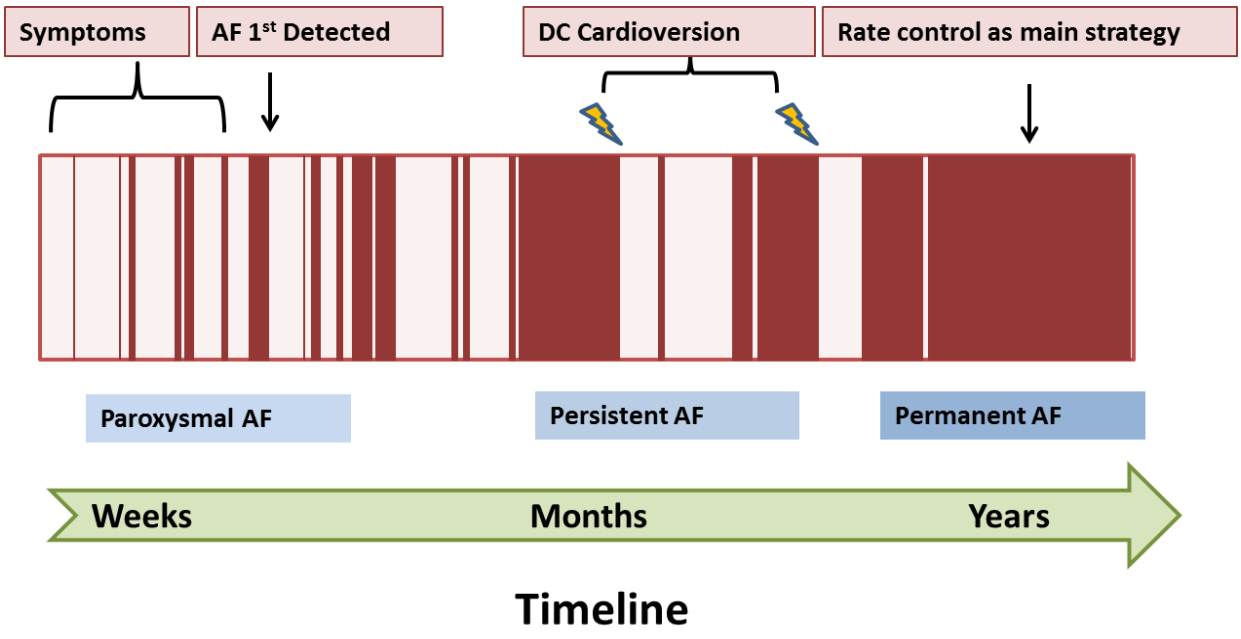


FIGURE 2.2 REPRESENTATION OF THE NATURAL HISTORY OF THE DISEASE PROCESS IN AF
Modified and adapted from Schotten U, Verheule S, Kirchhof P, Goette A. Pathophysiological mechanisms of atrial fibrillation: a translational appraisal. Physiol Rev 2011;91:265-325

2.2 Pathophysiology of AF

AF is associated with disorganised atrial electrical activity leading to loss of effective atrial contraction.[28] Age, hypertension, coronary artery disease, mitral valve disease, low-grade inflammation and genetics are important individual risk factors of AF.[29-33] Different underlying pathophysiologic mechanisms are proposed as the driving force behind atrial remodelling (left atrial dilatation and fibrosis).[34-37] This whole process involves various mechanisms described below.[36]

a. Trigger loop

The underlying key cellular mechanism is thought to be enhanced calcium ion loading. This leads to spontaneous calcium ion release, which, when coupled with autonomic imbalances and channelopathies can lead to triggered activity and automaticity which leads to atrial hyperactivity. This can initiate atrial fibrillation which due to rapid atrial rates can restart the cycle through calcium ion overload.

b. Electrical loop

Usually, ion channels protect atrial myocytes against excessive calcium ion loading. There may be an abnormal contribution of ion channels towards the action potential configuration. Atrial stretch and autonomic imbalance also contribute towards this. This leads to a decrease in effective refractory period (ERP) and leads to re-entrant circuits within the atrium that can trigger AF.

c. Structural loop

Chronic atrial stretch due to raised atrial pressures, reduced atrial contractility and increased atrial compliance activate pro-fibrotic and inflammatory pathways. This, through cellular hypertrophy and atrial fibrosis, leads to conduction slowing and heterogeneity which further enhances the re-entry circuits that maintain AF. Valvular heart disease, rheumatic heart disease, myocarditis and ageing are important factors that affect this loop.

d. Hemodynamic loop

Loss of atrial contraction leads to increased atrial volume and causes a chronic atrial stretch. On the other hand, due to rapid and irregular ventricular rate, there may be LV systolic dysfunction which through ventricular filling defect can exacerbate the stretching of the left atrial wall. Hypertension and underlying heart failure can enhance this process. This leads to the development of long term substrate for sustaining persistent or permanent atrial arrhythmia. This is shown in Figure 2.3.

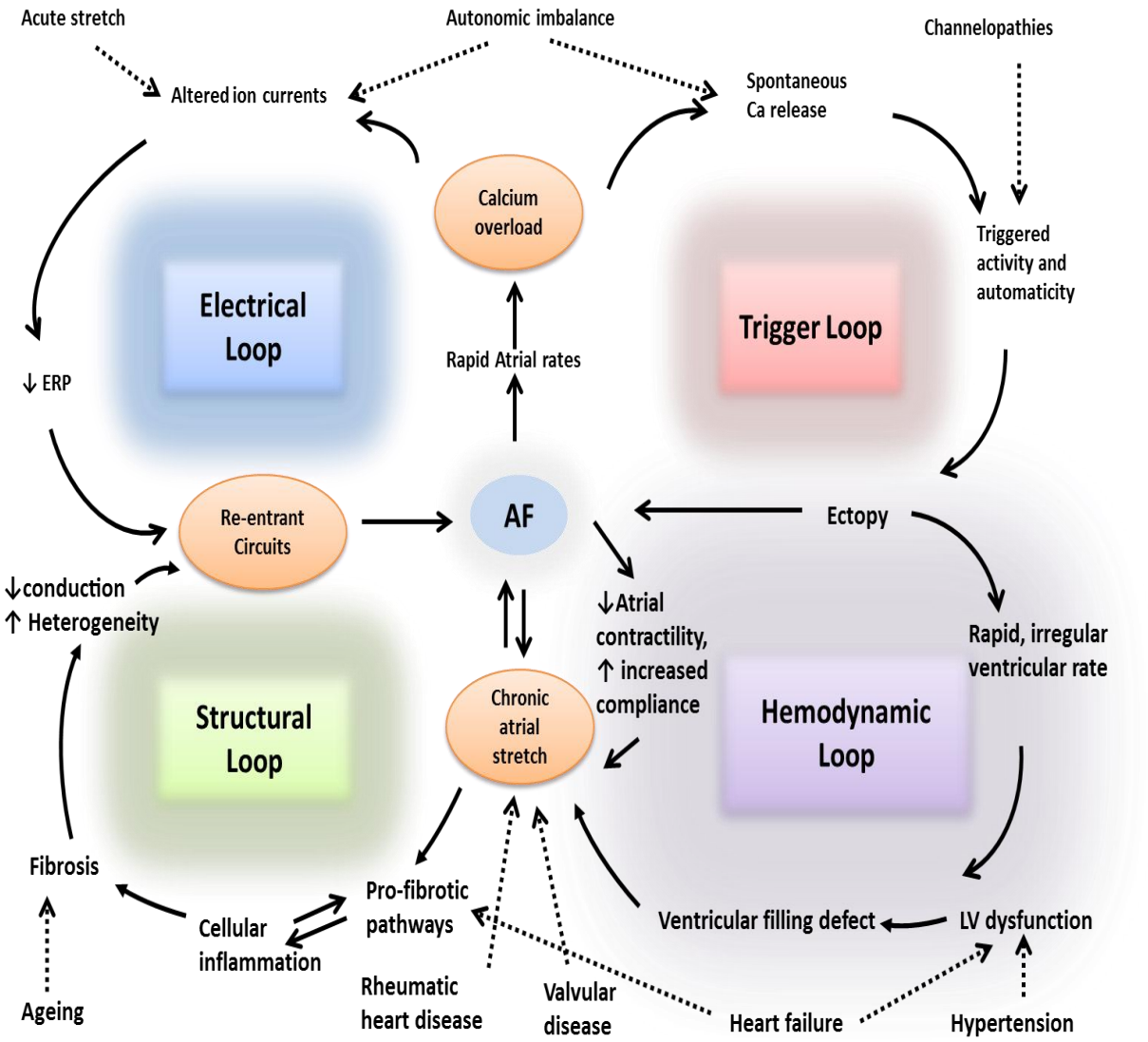


FIGURE 2.3 PATHOPHYSIOLOGY OF AF

A schematic diagram showing the interplay between various pathways that individually or in combination contribute towards AF.

(ERP-Effective refractory period, Valvular disease-predominantly left-sided valvular disease)

Modified and adapted from Schotten U, Verheule S, Kirchhof P, Goette A. Pathophysiological mechanisms of atrial fibrillation: a translational appraisal. Physiol Rev 2011;91:265-325

2.3 Detection methods of AF

The following methods are frequently used in detecting underlying AF in a high-risk population such as stroke.

I. Non-Invasive

A. Short duration:

a. Single 12 lead ECG

b. Serial ECGs

B. Long duration (24 hours to 4 weeks):

a. Continuous hospital telemetry (Few hours to a few days)

b. Holter ECG monitoring (1-7-days)

c. Patient triggered event recorders (1-4 weeks)

d. Prolonged ambulatory ECG (Mobile cardiovascular telemetry)

II. Invasive (Several weeks to years):

a. Implantable loop recorders

b. Implanted cardiac devices (pacemakers, Implantable cardioverter defibrillators [ICD] or cardiac resynchronisation therapy [CRT] device)

The various types of ECG monitoring methods are given in Figure 2.4.

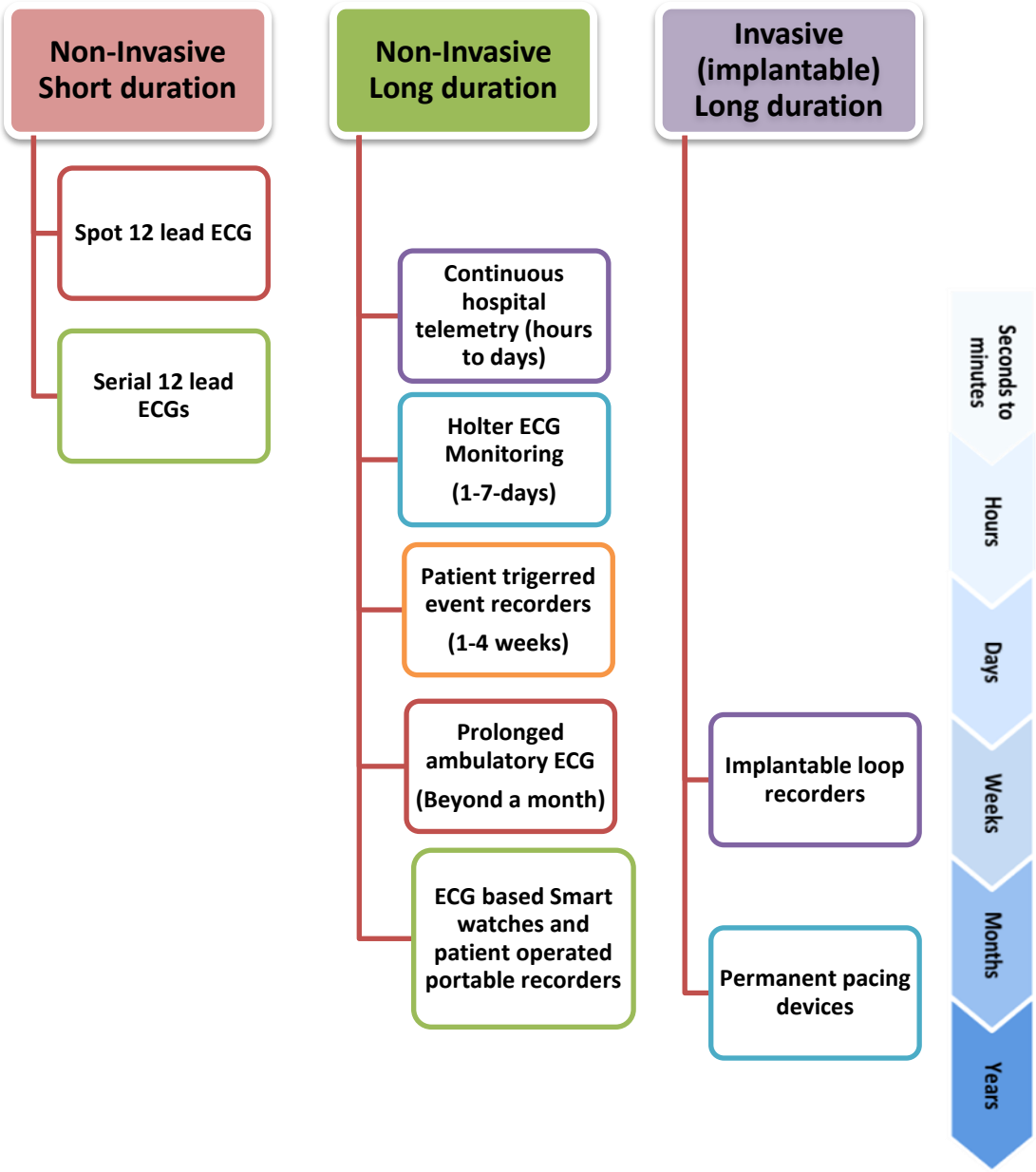


FIGURE 2.4 A GRAPHICAL REPRESENTATION OF TYPES OF ECG MONITORING METHODS THIS IS BASED ON TYPE (INVASIVE/NON-INVASIVE) AND DURATION OF MONITORING

Patients with recent ischemic stroke/TIA are routinely investigated for the presence of underlying AF with Holter ECG. The sensitivity of 24-hour Holter for detection of paroxysmal AF after ischemic stroke is variable and will miss the diagnosis of paroxysmal AF in many patients.[38] Better rates of AF detection were observed with longer duration of ECG monitoring following stroke/TIA.[24] There is increasing evidence that longer duration of ECG monitoring either with standard Holter ECG recorders (48 hours to 7-days) or further prolongation of ECG monitoring using portable or implanted loop recorders (7-days – several weeks or up to 36 months) improves the rate of detection of underlying AF.[9,17] However, there is a limit to the duration of ECG monitoring as it incurs significant costs for prolonged monitoring, especially non-invasive testing beyond a few days is associated with patient discomfort and the yield from such monitoring is subject to patient compliance. Similarly, invasive monitoring may not be preferable to all patients and is better suited for high-risk patients. Recently patient operated portable ECG recording devices and smartwatches to detect AF have generated much interest.[39-41] In general, the sensitivity of heart rate based AF and photoplethysmography is low and its accuracy depends on the diagnostic algorithm for the given device. 1 lead ECG electrode-based AF detection methods currently require a physician to confirm a recorded AF episode.[42] In the future, this will require refinement of detection algorithms to improve the diagnostic accuracy of these devices. Currently NICE does not endorse the routine use of these devices as per the 2019 review.

The fact remains that the standard of diagnostic tests used in various health care settings to detect paroxysmal AF is also based on local practice standards. It would be highly desirable to identify the patient group most suited for a longer duration of non-invasive or even invasive monitoring based on their clinical and ECG markers. Similarly, it would be useful to

identify low-risk patients with very little chances of underlying AF. In such patients, all types of ECG monitoring would have low diagnostic yield for AF detection and may be considered a burden on limited resources.

2.4 Predictors of Atrial Fibrillation

AF is a major but preventable cause of ischemic stroke and TIAs.[43-46] However, detection of AF is not always easy and in some cases requires a long duration of monitoring to detect paroxysmal AF.[47-49] Due to the elusive nature of this condition, there has been a lot of research in predicting incidental or recurrent AF in various patient groups and clinical settings.

It will be useful to understand some of the high-risk factors or "predictors" associated with incidental AF, new-onset AF or AF recurrence after successful pharmacological or electrical cardioversion and/or ablation. For description these are divided into the following main groups:

1. Clinical predictors

2. Blood biomarkers

3. Electrocardiographic predictors

4. Imaging predictors

5. Electrophysiological predictors

6. Miscellaneous

This is highlighted in figure 2.5 and shows the interplay of a combination of various factors. Due to a wide variety of risk factors of AF, the predictors of AF can be different for various patient groups based on their clinical situation, presentation and concurrent disease processes.

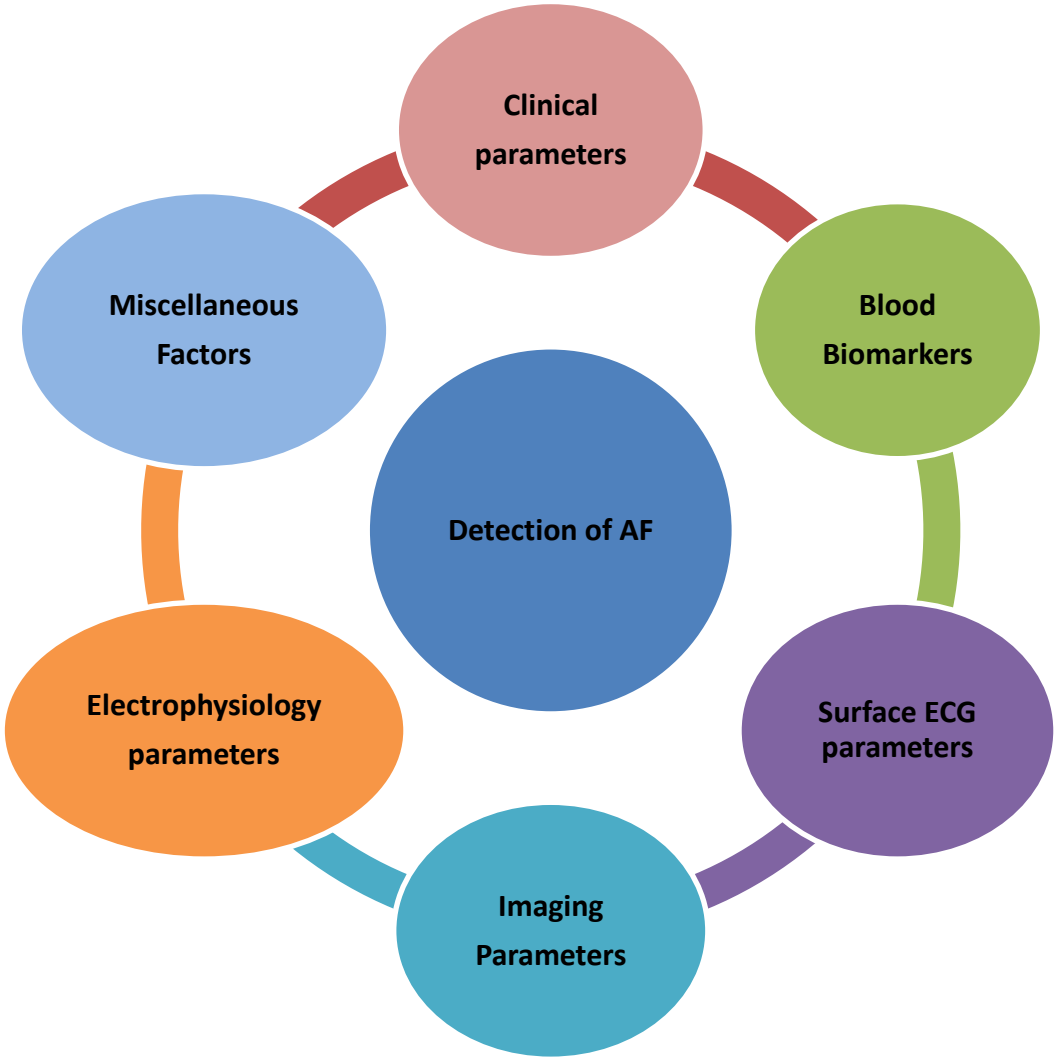


FIGURE 2.5 VARIOUS RISK FACTORS OR PREDICTORS OF ATRIAL FIBRILLATION

2.4.1 Clinical predictors

a. Age

Various studies have shown age as an independent predictor of AF. There is good evidence that advancing age increases the chances of underlying AF. The cut-off for age at which the risk of underlying AF rises from the general population is not yet established.[50-52]

b. Gender

There is conflicting evidence from various studies showing male or female gender conferring a higher risk. However, this observed variation in association from previous studies can be due to other confounding baseline factors and comorbidities in small cohorts.[51-53]

c. Hypertension

Systolic BP more than 160mm Hg has been considered as a risk factor for developing AF. This can be due to the effects of persistently raised blood pressure on LA and LV hemodynamic, with long term remodelling of LV (leading to LVH and diastolic dysfunction) and atrial enlargement. This can be also due to the effect of hypertension on the progression of coronary artery disease predisposing to ischemia and AF. [51,52] Arterial stiffness in hypertensive patients has also been found in one study to be independently linked to the development of AF in future independent of age and left atrial diameter.[54]

d. Heart failure status

Clinically significant heart failure (NYHA II-IV) is found to be linked to underlying AF. The AF prevalence is proportional to heart failure severity and this can be the cause or effect of

atrial fibrillation. One hypothesis states that raised left ventricular filling pressures, activation of the renin-angiotensin-aldosterone system leading to volume retention and function valvular pathology leads to chronic left atrial stretch leading myocardial substrate increasing chances of developing AF.[55-57] Moreover, both AF and heart failure share common underlying risk factors like hypertension, obesity and coronary artery disease among others. In some cases, AF can be presented in as much as 50% of advanced heart failure patients.[58] There is mounting evidence that development of heart failure on top of AF and vice versa leads to poor prognosis.[59] Heart failure is an important factor to look for as possible predictor of underlying AF regardless of left ventricular ejection fraction.[25,52,60,61]

The association of left ventricular ejection fraction with incident AF is less well understood. One study showed a higher incidence of AF in patients with reduced ejection fraction at 18% vs normal ejection fraction at 11%.[62] A meta-analysis showed that in patients after AF ablation, LV ejection fraction does not predict recurrence of AF.[63]

e. Stroke/Transient ischemic attack along with NIH Stroke scale[47-49,64-66]

Although the risk of underlying AF in all stroke population is around 30%, a further 20% of cryptogenic strokes can be attributed to underlying AF. History of recurrent stroke and TIA is a very useful variable. NIHSS (categorized: 0-4, 5-15), modified Rankin scale before and during recording (categorized: 0-2, 3-5) and duration of stroke-associated symptoms (≤ 1 hour, 1-24, ≥ 24 hours) will be measured against association with AF detection.

f. Diabetes

Diabetes is not only an important clinical risk factor for underlying AF but also increases the chances of recurrent AF after initial success in rhythm control therapy. This may be due to the effect on micro or macro vasculature leading to ischemic injury and development of pro-arrhythmogenic substrate in the atria.[51,52,67,68]

g. Vascular disease

Vascular disease in this context could be previous coronary artery disease, peripheral vascular disease or any other systemic vascular process secondary to atherosclerosis or vascular dysfunction. Any known previous significant coronary artery disease or peripheral vascular disease is considered an important risk factor for AF. Coronary artery disease as a risk factor is particularly important in patients with a previous history of myocardial revascularisation especially coronary artery bypass surgery.[69-71]

Patients with peripheral vascular disease are thought to have one of many pathophysiological mechanisms including arterial obstruction, vascular or skeletal muscle dysfunction, inflammation, impaired angiogenesis and microvascular occlusion.[72] Most of these are a systemic phenomenon and share some of their common risk factors like advanced age, underlying diabetes and coronary artery disease with atrial fibrillation. [73] A study done by Winkel et al showed that AF coexisted in peripheral arterial disease in around 10% of the patients and predicts a worse 2-year cardiovascular vascular outcome.[74] In 2016, a very large observational study of more than 58000 patients found that peripheral vascular disease was an independent predictor of AF with worse CV outcomes if both co-existed together.[75]

h. Raised BMI (more than 30)

Raised BMI is tipped as a risk factor for underlying AF in some studies. However, this has not been validated as an independent risk factor. Associated diastolic dysfunction may be the culprit in this setting.[69,76,77]

i. Severe renal impairment Chronic Kidney Disease (CKD) stage 4 or 5:

This is especially for patients dependant on haemodialysis. During haemodialysis, hemodynamic changes and fluctuations in serum potassium levels can predispose to atrial fibrillation.[78] In a meta-analysis of 4 observational studies, CKD was found to be associated with more recurrence of AF after AF ablation.[79]

j. Symptoms of Atrial Fibrillation:

Although symptoms of palpitation, awareness of heartbeat, dizziness have less than ideal predictive value and sensitivity of underlying AF, nevertheless, it is still an important item to record in baseline.[80-83]

k. Sleep apnoea:

Obstructive sleep apnoea (OSA) is the commonest disorder in sleep-breathing and is usually associated with obesity.[84] It shares many risk factors with cardiovascular risk factors with AF but they are complex and multi-factorial. It is also an independent predictor of stroke.[85] Sleep apnoea is not only found to be a strong predictor of new AF after coronary artery cardiac and coronary artery bypass surgery but also linked to AF recurrence after AF ablation.[86-90] It has been found that AF recurrence after AF ablation reduces after effective management of obstructive sleep apnoea.

l. Other factors:

Smoking status[91-94], alcohol consumption[95-97], level of physical activity[98-100], concomitant medications like Ivabradine[101], non-alcoholic fatty liver disease[102], opium addiction have all been linked to the development of AF or increases chances of underlying AF.

2.4.2 Electrocardiographic predictors

a. P wave axis:

P wave axis of outside the range of 0-75 degrees is found to have a slightly higher prevalence of finding incidental AF after adjusting for age, gender, ethnicity and other comorbidities.[103]

b. P wave morphology:

Abnormal P wave morphology was found to be an independent and significant predictor of developing AF (HR 1.75) and sudden cardiac death (HR 2.66) in patients included in Multi-centre Automated Defibrillator Implantation Trial II (MADIT-II).[104]

c. P wave duration:

A large Copenhagen study using computerised analysis of ECGs from primary care population, identified very short (<89ms), long (120-129ms) very long (>130ms) as risk identifiers for AF and risk of cardiovascular death, as compared to normal p wave duration (100-105ms).[105] In an observational study, P wave duration and Standard Deviation (SD) of a beat-to-beat Euclidean interval between the p waves were suggestive of identifying underlying paroxysmal AF. Longer P wave durations and more varied morphologies were predictive of paroxysmal AF. Similarly, abnormal P wave duration is also predictive of

recurrence of AF after catheter ablation.[106] P wave duration of more than or equal to 140ms was found to be an important predictor of AF recurrence post-AF ablation when compared with p wave duration of less than 140ms, (63% vs 38%, $p<0.05$).[107]

d. PR interval:

The role of PR interval as a predictor of the risk of underlying AF is controversial and is probably based on sub-components of PR interval.[108] An observational study done by Chun et al indicates that prolonged PR interval in the presence of frequent premature atrial ectopics (>100/day) is a predictor of AF occurrence.[109]

e. Advanced Intra Atrial block

This is also found to have increased association with AF recurrence after AF ablation.[110]It has been seen that patients undergoing cavo-tricuspid isthmus ablation for typical atrial flutter are associated with the development of AF. It is shown that advanced intra-atrial block is a key predictor for high-risk for new-onset AF even after successful ablation of typical atrial flutter through cavo-tricuspid ablation.[111]

Similarly on surface ECGs advanced intra-atrial block (with P wave duration of >120ms and biphasic morphology in inferior leads) is also shown to predict AF in patients with severe LV systolic dysfunction and cardiac resynchronization therapy.[112] It would be interesting to see if this parameter is applicable to even those with normal LV systolic function without any resynchronization therapy.

f. Premature Atrial contraction (PAC)

Atrial ectopics were first shown to be associated with AF in 1998 by Haïssaguerre et al.[113] Premature atrial contraction (PAC) or atrial ectopics (AE) or supraventricular ectopics (SVE) are shown in various studies to be a useful predictor of AF[114-117]. Another study shows that adding atrial premature contractions to Framingham AF model improved the 10 year AF risk discrimination (c-statistic improved from 0.65 to 0.72 p<0.001)[118]

Koshhausner et al in 2014 suggested that an increased number of atrial premature contractions in patients is strongly linked with AF, however, the number of patients in his study were less.[119] In 2015, Gladstone published his data of 30-day event recorder for more than 200 patients which again highlighted a very strong dose-dependent association of atrial ectopics with underlying AF.[120] Since atrial ectopics are very easily detected and reported in most ECG monitoring devices in clinical practice, this makes atrial ectopics a very attractive, as well as feasible to study variable in AF prediction model.

g. Heart rate variability (HRV):

Heart rate variability (HRV) is a function of the cardiac response to autonomic regulation.[121,122] In one prospective study, taking the Cohort from the OPERA study, heart rate variability using various spectral and time-domain indices was measured at baseline. After a mean follow up of 16.5 +/- 3.5 years, it was found that impaired heart rate variability measured by Low frequency (LF) spectral component (HR 2.81, p0.006) was significant predictors of developing symptomatic atrial fibrillation, along with age and systolic blood pressure.[123]

2.4.3 Blood Biomarkers

2.4.3.1 For incidental AF

a. NT pro-BNP (N-Terminal pro Brain natriuretic peptide)

Raised NT pro-BNP is shown to be an independent predictor of incidental AF. It was found in one study that raised levels of NT pro-BNP was associated with a higher risk of detecting new AF in two different cohorts and when added to AF prediction score CHARGE-AF, it offers a modest increase in c-statistic from 0.62 to 0.68.[124] Another study in a large cohort of multi-ethnic population confirmed the strong association of NT pro-BNP with underlying AF across different ethnicities.[125] Elevated BNP levels are also found to have an association with prevalent atrial fibrillation in patients admitted with acute ischemic stroke.[126] It has been shown to predict imminent episodes of AF which can be very useful in a clinical setting. [127]

A large meta-analysis has shown that for a patient undergoing thoracic surgery, high pre-operative levels of NT pro-BNP significantly increase the risk of detecting new atrial fibrillation post-surgery (OR 3.13).[128] Another group found a similar association of higher levels of this biomarker with new-onset AF after cardiac surgery.[129]

Interestingly, a relatively large study of 562 patients derived from the OPERA trial was published in the same year as the meta-analysis mentioned above. The study concluded that pre and post-surgical levels of NT Pro BNP and high sensitivity troponins are not predictive of risk of postoperative AF.[130] Another study also found a slight but statistically non-significant association with risk of AF after cardiac surgery. This makes NT-pro BNP an exciting but controversial predictor of incidental AF, especially in patients undergoing cardiac surgery.

b. Fibroblast growth factor 23 (FGF23)

FGF 23 levels usually rise with renal dysfunction but recently it has been linked with cardiovascular disease, due to left ventricular hypertrophy, incident coronary artery disease and heart failure.[131,132]

A link between AF and FGF 23 has been described by Sieler et al in 2011 that showed a correlation between AF and Left ventricular systolic dysfunction in the absence of renal dysfunction.[133] Another multi-ethnic registry has also shown evidence of its association with new AF.[134] In a recent study, by Chua and Purmah et al, this was further shown alongside BNP to be one of only two among more than 90 biomarkers to be strongly associated with prevalent AF.[135]

c. Atrial natriuretic peptide (ANP):

In a population-based study in elderly men, it was found that higher levels of baseline ANP had up to 3.3 times higher risk of developing AF after 16 years follow up.[136]

d. Troponin-I:

A study in ischemic stroke and TIA survivors found a predictive role in delayed diagnosis of underlying paroxysmal AF during long term ECG monitoring. 30% of those with raised Troponin-I had AF diagnosed through ECG monitoring vs 6.1% of those without raised Troponin-I.[137]

e. Type III Procollagen-N-peptide:

A large retrospective observational sub-study of around 3000 participants, aged 65 and older, based on the sample from Cardiovascular Heart Study (CHS), identified a non-linear relation between levels of type III Procollagen N terminal peptide and risk on incidental AF. The maximum association was found at median levels of the biomarker.[138]

Elevated levels of type III procollagen-N-peptide which is a marker of atrial inflammation and fibrosis is found to be significantly associated with recurrence of AF after successful DC cardioversion (odds ratio 2.61, $p<0.008$).[139]

f. Cystatin C:

Cystatin C is considered as a biomarker of cardiac extracellular remodelling and fibrosis[140,141]
In a study involving approximately 500 hypertensive patients without CKD (eGFR.60ml/min/1.73m^2) it was found that higher levels of Cystatin C are associated with a significantly higher risk of incidental AF (OR 4.123)

Cardiovascular health study also showed that renal impairment measured by Cystatin C levels is associated with a higher prevalence of AF.[142]

2.4.3.2 For AF recurrence after Electrical/chemical cardioversion or Ablation:

a. Serum Metalloproteinases-9

The level of this enzyme was higher in patients with AF recurrence after AF ablation after adjusting for co-variates.[143]

b. Cardiotrophin-1

It was found in one small hypothesis-generating study that serum cardiotrophin-1 (CT-1) levels were raised in AF patients as compared to age and gender-matched healthy controls. Furthermore, a higher value of CT-1 levels at baseline was associated with increased frequency of AF relapses 6 months after DC cardioversion.

c. Serum Connective tissue growth factor (CTGF):

This can be considered an indirect marker of atrial structural remodelling. A study measured the changes in CTGF at baseline and 2 months post-ablation. Higher levels of baseline CTGF, along with raised left atrial diameter in patients with non-paroxysmal AF undergoing ablation were predictive of AF recurrence.[144]

d. Type III Procollagen-N-peptide:

Elevated levels of type III procollagen-N-peptide which is a marker of atrial inflammation and fibrosis is found to be significantly associated with recurrence of AF after successful DC cardioversion (odds ratio 2.61, $p<0.008$).[139]

e. High sensitivity C-Reactive protein

Progression of inflammation detected through C-reactive protein as a function of atrial remodelling is predictive of recurrence of AF after DC cardioversion or AF ablation through pulmonary vein isolation. Studies have shown that higher levels of high sensitivity CRP pre-procedure, as significantly predictive of AF recurrence for both paroxysmal and persistent types.[145,146]

f. Interleukins:

Interleukin 6, 8 and 10 were found to be significantly elevated in AF population in various studies signifying the importance of inflammatory markers in predicting the risk of underlying AF[147,148].

2.4.3.3 New-onset AF Post MI and Post-operative:

a. Neutrophil/Lymphocyte ratio(NLR)

Neutrophil/lymphocyte ration in the STEMI population predicts non-reflow, New-onset AF, and major in-hospital adverse effects.[149] Similar associations between NLR and risk of developing AF is confirmed in a meta-analysis which also shows that the risk of AF recurrence after cardioversion or AF ablation also increases with raised NLR.[150] Another study has shown an association between high NLR and risk of AF recurrence after successful chemical cardioversion by Amiodarone.[151]

b. Serum resistin Levels:

Resistin is a hormone secreted by adipocytes.[152] A small hypothesis-generating study, identified a potential blood biomarker for predicting AF in patients after coronary artery bypass surgery. Although the pre-operative resistin levels were higher in the AF group, due to the small number of patients (n=40) it was not statistically significant.[153]

2.4.4 Imaging predictors

2.4.4.1 Incidental AF

a. Left ventricular systolic dysfunction measured by global longitudinal strain (GLS)

In one community-based cohort study, it was found that impaired left ventricular systolic function measured by GLS (>-14.7%) is associated with increased risk of developing AF (HR 3.2, p<0.007) Along with abnormal left atrial volume index, the combined Hazard ratio is 12.1 (p<00.1)[154]

b. Doppler derived LV negative dp/dt

One study, in patients with normal ejection fraction but moderate to severe degenerative mitral regurgitation, has shown that Doppler derived LV – dp/dt and E/E' were significant predictors of new-onset AF or stroke.[155]

c. Left atrial function assessed by Speckle tracking echocardiography

The left atrial function is considered a marker of LA remodelling. Speckle tracking is a novel technique through which a longitudinal strain curve can be generated for the left atrium.[156] A study has shown that speckle tracking echocardiography is the strongest predictor of progression of AF from paroxysmal to persistent.[157] Abnormal left atrial emptying function assessed through speckle tracking echocardiography is found to be independently predictive of the development of AF after a follow up of 28 months with a sensitivity and specificity of 88% and 81% respectively.[158]

2.4.4.2 For AF recurrence after cardioversion or ablation:

a. Functional mitral regurgitation (MR)

Functional MR is found to have an association with higher recurrence rates of AF after 22.9 +/- 6 months after successful AF ablation. This was associated with the presence of Low Voltage Zones (LVZ) on LA mapping after ablation, in 64.9% of patient with functional mitral regurgitation vs 22.1% in patients without FMR (p-value<0.001)[159]

b. Epicardial adipose tissue thickness (EAT)

Epicardial adipose tissue thickness, especially in the peri-atrial area, measured by multi-detector CT has a modest association with late AF recurrence post-AF ablation.[160]

c. Left Atrial Emptying Fraction (LAEF) by Multi-slice CT

In one study, with the use of Multi-slice CT, Left atrial emptying fraction (LAEF) was shown to have an association of AF recurrence after AF ablation.[161]

d. Left atrial volumetry

Left atrial volume of less than 106 mL assessed by Multi-detector CT is a significant predictor of maintained SR especially in Pulmonary vein ablation for paroxysmal AF.[162] Other studies have found similar results using echocardiographic measurements.[163,164]

e. High Residual Fibrosis (Substrate modification):

A cardiac MRI study using late gadolinium enhancement (LGE) on patients undergoing AF ablation has shown that baseline and high residual fibrosis were associated with significant recurrence of AF post ablation with HR of 2.2 (p<0.01)[165]

f. L wave to assess severe diastolic dysfunction:

L wave measures mid-diastolic trans-mitral flow. Echocardiographic measurement of the L wave to assess for diastolic dysfunction has been found as a novel predictor of AF recurrence in a small study.[166]

2.4.4.3 New-onset AF Post MI and Post-operative:

a. Left Atrial Strain:

Several studies to assess for left atrial deformation of strain, especially in elderly patients, show that LA strain impairment, measured through speckle tracking echocardiography may be a useful predictor for the development of AF postoperatively.[167,168] Another study has also shown similar findings for AF recurrence after AF ablation.[169]

b. Decrease in left atrial appendage emptying velocity

Left atrial appendage, a small pyramidal structure situated at the lateral surface of the LA, between the pulmonary artery and LV. Reduction in LAA emptying velocity, both in early and late diastole is dependent on advancing age.[170] Although there has been some conflicting evidence, it is also found to be an independent variable in the development of postoperative AF after CABG.[171] Another study has shown this to be one of three factors alongside the duration of AF and LA size to predict success after DC cardioversion.[172]

c. Total Pulmonary vein diameter

Total pulmonary vein diameter is also found in one study to be a significant predictor of developing AF after on-pump CABG. [173]

2.4.5 Electrophysiological predictors

a. High entropy values in RA

High entropy values in the right atrium at the time of ablation in one study predicted higher recurrence rates of AF after successful AF ablation through pulmonary vein isolation.[174]

b. Acute pulmonary vein reconnection:

A small prospective observational study showed that acute pulmonary vein reconnection soon after pulmonary vein radiofrequency ablation was an independent predictor of AF recurrence. The pulmonary vein reconnection was identified by a 30-minute wait after the initial ablation and given adenosine and isoproterenol infusion. Any identified connections were subsequently treated in the same procedure. However, those with acute pulmonary vein connection had 50% AF recurrence at 1 year as compared to 11% without pulmonary vein connection (HR-6.36, p<009).[175]

Another study, using a cryo-balloon technique, identified balloon warming time as the strongest predictor of late pulmonary vein reconnection and hence AF recurrence.[176]

c. Longer duration of the procedure for radiofrequency ablation:

In an observational study in a case series those with early AF recurrence by 3 months from the index procedures had longer ablation and procedural times.[177] It is unclear whether the procedure times and longer ablation durations were seen because AF was difficult to ablate in the first instance.

d. Elevated left atrial pressure at trans-septal puncture:

In a study left atrial pressure was measured at trans-septal puncture in all patients with paroxysmal or persistent AF undergoing first pulmonary vein isolation procedure. Mean LA pressures were found to be higher in patients with AF recurrence and with each 1 mm Hg rise in LA pressure, the risk of AF recurrence increased by 11 % at 2 years follow up.[178]

2.4.6 Other/Miscellaneous

a. Genetic predictor-KCNIP1 Copy number Variation (CNV) mutation

This gene encodes a family of Voltage-gated Potassium channel interacting protein. Its mutation may induce susceptibility to develop atrial fibrillation which was seen in a study in Taiwanese population.[179]

b. Common gene variants, e.g. on chromosome 4q25, close to the PITX2 gene

2 sequence variants (rs2200733 and rs10033464) on chromosome 4q25 have shown significant association with underlying AF in a study done in 2007 and was later also confirmed in a meta-analysis.[180,181] A novel finding of PITXC2 mutation has generated a lot of interest as responsible for idiopathic AF. This is a loss of function mutation and confers enhanced susceptibility to AF. [182]

c. Apnoea-Hypnoea Index (AHI) in sleep studies

This is found to be an independent predictor of recurrence of AF after pulmonary vein isolation (PVI) ablation for paroxysmal AF. It has not shown a significant relationship to recurrence post-ablation for persistent AF.[183]

d. Peri-oesophageal Vagal plexus injuries:

Interestingly, peri-oesophageal vagal plexus injuries (PNI), which are considered as a side effect of AF ablation leading to decreased gastric tone and symptomatic gastric hypomotility has been found to have a protective effect against recurrence of AF after successful AF ablation. Patients with PNI had more AF free days after ablation than those without PNI.[184]

Another study has linked gastroesophageal reflux disease (GERD) with more recurrence of AF post AF ablation. After multiple regression analysis, the odds ratio is found to be 8.5 (p=0.011)

2.5 Important AF prediction scores

There have been various efforts to come up with AF predictive scores to identify incidental AF risk in large general or selected populations. These predictive scores are particularly useful as they take into account useful clinical and demographic variables which are readily available for most patients. Some of the notable AF prediction scores are described in this section.

2.5.1 HATCH Score

In 2010 De Vos and colleagues proposed a clinical score to predict progression of AF from paroxysmal to persistent/permanent AF derived from the Euro Heart survey.[185] This led to the HATCH scoring system that included heart failure, Age>75, previous transient ischemic attack (TIA) or stroke, chronic obstructive pulmonary disease, and hypertension as the independent predictors of AF progression. Heart failure and previous history of TIA or stroke were given 2 points and the rest were given 1 point each. A score of >5 was considered predictive of progression of AF from paroxysmal to more sustained forms.

This score was further validated by Suinari et al in Asian population using the Taiwan National Health Insurance Research Database in more than 670 thousand patient records.[186] This adjusted for gender and other comorbidities showed good correlation in predicting new-onset AF. Another study found that a relatively low cut-off (>1) for HATCH score for predicting postoperative AF in patients undergoing coronary artery bypass graft surgery.[187]

2.5.2 HAVOC score

HAVOC score was based on the Stanford Translational Research Integrated Database Environment (STRIDE) looking at patients with stroke and transient ischemic attack.[188] This combined age, obesity, coronary artery disease, peripheral vascular disease, congestive heart failure, hypertension and valvular disease. These variables were used to classify AF risk into 3 subgroups with good discrimination and area under the curve of 0.77. They proposed this would helo identify stroke survivors requiring a longer duration of monitoring to look for AF.

This work was externally validated by Ntaios et al.[189] They found a modest AF risk discrimination at low HAVOC scores and area under the curve of 0.68.

2.5.3 $CHADS_2$ and CHA_2DS_2VASc scores:

There have also been efforts to validate scores such as $CHADS_2$ and CHA_2DS_2VASC to predict new-onset AF which are otherwise widely used to calculate stroke risk in AF.[190,191] A very large registry of more than a million patients in Israel looked to validate these scores to predict new AF and found an increase of hazards ratio of 1.57 for each unit increase in score.[192]

2.5.4 ATLAS score

ATLAS score was developed to predict recurrence of AF following AF ablation through pulmonary vein isolation in a registry base on around 2 thousand patients.[193] The identified variables included age >60 years (1 point), female sex (4 points), non-paroxysmal AF (2 points), current smoking (7 points) and indexed LA volume (1 point/10 mL/m2 increase).

2.5.5 APPLE score

The APPLE score was developed by Kornej et al in 2015 to predict recurrence of AF in patients post AF ablation.[194] This took into account and gave 1 point each for age >65 years, persistent AF, impaired eGFR (<60 ml/min/1.73 m^2), LA diameter ≥43 mm, EF < 50 %. They showed that this score performed better than $CHADS_2$ and CHA_2DS_2VASc.

2.5.6 CHARGE-AF score

CHARGE-AF uses individual data from 3 large cohorts in the United States in more than 18556 patient records from Atherosclerosis Risk in Communities (ARIC) study, the Cardiovascular Health Study (CHS), and the Framingham Heart Study (FHS) to develop the 5-year risk of developing new AF using various predictive variables.[195] This was externally validated in 7672 participants from the Age, Gene and Environment susceptibility-Reykjavik study (AGES) and the Rotterdam Study (RS). The predictive model was based on age, ethnicity, height, weight, blood pressure, smoking status, being on antihypertensive medications, diabetes, and history of myocardial infarction and heart failure. This gave a good c-statistic of 0.76 in the derivative model and a modest c-statistic on 0.66 in the validation cohort. Further work was done to add biomarkers such as B-type natriuretic peptide and high sensitivity CRP to this model which showed that the addition of B-type natriuretic peptide but not CRP substantially increased the risk prediction of the model.[196]

2.5.7 Risk scores from other population-based cohort studies

Other scores are derived from Framingham study, FHS (10-year risk)[197], Atherosclerosis in Risk in communities, ARIC (10-year risk)[198], Women Health Study, WHS (10-year risk)[199] and

Cohorts for Heart and Aging Research in Genomic Epidemiology atrial fibrillation. The methods of the derivation of these scores, their detailed description and validation are beyond the scope of this chapter.

2.6 Relevant AF predictors based on large registries and validation cohorts

A summary of the most relevant AF scores based on large registries and observational cohorts is given in table 2.1. The table explains the various categories of variables for example, clinical, electrocardiographic, blood biomarkers and cardiac imaging. The ease of collection of these variables is colour coded into categorised such as green for risk factors identified from patient demographics, clinical notes and history, amber for routine in-hospital investigations like 12 lead or Holter ECG, echocardiogram etc and red for tests requiring special techniques or assays.

These items are further categorised into the various levels of evidence which are modified and adapted from Oxford Centre for Evidence-based Medicine – Levels of evidence (March 2009)[200]. The evidence levels are usually difficult to describe for epidemiological risk factors which are frequently assessed by large population-based observational studies. These types of studies are considered a reference standard for such an analysis. Based on this, for this description, a Level 1 evidence is derived from multiple large population-based and validated observational studies and/or meta-analysis. Level 2 is derived from prospective observational studies. Level 3 which is the lowest level of evidence is based on Case-control study, Case report/case series, or derived from the consensus of expert opinion. A systematic review to identify risk factor for incidental AF and also the progression of AF has not currently been done. A protocol for one such review, however, has been published by

Dretzke et al in 2019.[201] Most of the evidence currently available comes from population-based observational cohorts and large registries. Some risk factors are identified as part of secondary analysis in a randomised controlled trial. An example of this is the association of atrial ectopic burden with new AF in stroke survivors undergoing ECG Holter ECG monitoring.[120] These type of analyses are not designed to look for these risk factors but these variables were analysed retrospectively which places them at a lower level than the prospective observational studies.[202]

Finally, there are a few exciting variables which are identified from basic science work in the laboratories and small case series. Although these if properly studied and validated may be of great importance in predicting AF, but currently, cannot be routinely recommended for risk factor analysis of AF as they are not proven from large epidemiological studies.

Table 2.1 Predictors of AF			
Variable	Ease of collection*	Evidence level**	Use in risk score***
Clinical variables			
Age[190,191,193,195,197-199,203]	Demographic record	2	CHARGE-AF, CHA_2DS_2VASC, HATCH, ATLAS, APPLE, FHS, ARIC, WHS
Gender[190,191,193,197]	Demographic record	2	CHA_2DS_2VASC, ATLAS, FHS
Hypertension[186,187,190,191,195,197-199,203]	Clinical records	2	CHARGE-AF, CHA_2DS_2VASC, HATCH, FHS, ARIC, WHS
Vascular disease[190,191,198]	Clinical history/records	2	CHA_2DS_2VASC, ARIC
TIA/Stroke[186,187]	Clinical history/records	2	HATCH
Heart-Failure status[190,191,197-199,203]	Clinical history/records	2	CHARGE-AF, CHA_2DS_2VASC, HATCH, FHS, WHS
Diabetes[190,191,195,198,203]	Clinical history/records	2	CHARGE-AF, CHA_2DS_2VASC, ARIC
Raised BMI[197,199]	Clinical records	2	FHS, WHS
Smoking[193,195,198,199]	Clinical history	2	CHARGE-AF, ATLAS, ARIC, WHS
COPD[186,187]	Clinical history/records	2	HATCH
Alcohol consumption[199]	Clinical history	2	WHS
Electrocardiographic variables			
PR interval[195,197]	12 lead/Holter ECG	2	FHS, CHARGE-AF
Atrial ectopic burden[120]	Holter ECG	3	-
LVH on ECG[195,198]	12 lead ECG	2	ARIC, CHARGE-AF
Heart rate variability[123]	Holter ECG	2	-
Blood biomarkers			
NT-pro BNP/BNP[198,204,205]	Routine hospital lab	2	ARIC, CHARGE-AF
Troponin-I[137]	Routine hospital lab	3	-
FGF-23[134,135]	Specialised assay	3	-
Imaging variables			
LA size[193,194,205,206]	Routine echocardiography	2	ATLAS, APPLE
LV function[154,194]	Routine echocardiography	2	APPLE
Valvular pathology[197]	Routine echocardiography	2	FHS

***Ease of collection:** Green – History/clinical record, Orange - Routine hospital test, Red –Special study

****Level of evidence for risk factors assessment (derived from Oxford Centre for Evidence-based Medicine – Levels of Evidence (March 2009)[200]:** 1- Systematic review/meta-analysis, 2-Derived from multiple large population-based observational studies 3- Case-control study, Case report/case series, expert consensus.

*****Risk scores: APPLE**[194] - **A**ge, **P**ersistent AF, im**P**aired eGFR, **L**A diameter ≥43 mm, **E**F <50%, **HAVOC**[188] - Hypertension, Age, Valvular disease, obesity, coronary artery disease/CCF. **HATCH**[186] – Hypertension, Age, TIA, COPD, HF. **FHS**[197]-Framingham Heart Study, ARIC[198,204]- Atherosclerosis Risk in Communities, **WHS**[199]- Women Health Study, **CHARGE-AF** [195,196]- Cohorts for Heart and Aging Research in Genomic Epidemiology atrial fibrillation (revalidated in MESA), **MESA**[203] – Multiethnic study of atherosclerosis.

2.7 The relevance of the literature review to my research

In this chapter, a commentary of various clinical, ECG and echocardiographic predictors was provided are important in identifying relevant predictors for AF. As previously mentioned, the main aim of my work is to look for the detection of new AF through 7-day Holter ECG in two different cohorts. Firstly, an all-comer patient population attending cardiology outpatient and secondly, in patients with acute ischemic stroke. All relevant and readily available risk factors within the scope of this research will be analysed to assess for their association with AF. In summary, this will include risk factors identified from patient demographics, cardiovascular risk profile, Holter ECG and transthoracic echocardiogram. All of these variables are easily available to a clinician as part of their routine practice which increases the feasibility and relevance of this work. Due to fundamental differences in the patient populations and methodologies for the two cohorts, it is not always possible to match all variables across both groups which remains an important limitation. However, an effort will be made, where possible, to identify common high-risk variables for AF that stand out from both populations.

3 MATERIALS AND METHODS FOR SWBH DATASET

This part of the thesis shall examine a database of patients who have undergone 7-day Holter (event recorder) analysis from Sandwell and West Birmingham Hospitals (SWBH) NHS Trust.

It is pertinent to mention that this work has been published as a paper in the *OpenHeart* journal in May 2020. It was also presented as an abstract at European Heart Rhythm Congress (EHRA), 2017 in Vienna and British Cardiovascular Society (BCS), 2017 in Manchester.

3.1 Objectives related to SWBH Dataset

1. To report the diagnostic yield of 7-day Holter ECG monitoring in an all-comer population requested through primary care or hospital physicians.
2. To analyse clinical and Holter ECG parameters associated with new AF in a consecutive patient sample presenting for various indications for 7-day Holter ECG monitoring.

3.2 Introduction to SWBH dataset

3.2.1 General outline

SWB Hospital has a catchment population of more than 2 million residents. With regards to cardiology services, it is not only a major primary PCI and emergency cardiology but also caters for a significant proportion of outpatient cardiology services for the community. These patients could be referred for various cardiology diagnostic tests including 7-day Holter ECG monitoring to look for various arrhythmic conditions. These 7-day Holter monitors could be requested for a myriad of symptoms which include chest pain, dizziness,

palpitations, syncope, previous stroke or TIA. This service is available to cardiology or medical physicians from the hospital and there is also an open-access provision to the primary care physicians. This project was initially started as an audit to report the rate of AF in an all-comer cohort, presenting to a tertiary care hospital with various indications from various sources. This later took shape to form a registry of patients and various clinical and echo variables were also recorded.

3.2.2 Purpose of the study

The main purpose of this work was to serve as a pilot study for my thesis to identify useful clinical and ECG variables that could be used for the main analysis of the MonDAFIS dataset.

This will also provide very useful information about the association of various patient characteristics, symptoms and comorbidities with AF in a group which is truly reflective of the patient population that attends cardiology outpatient services for 7-day Holter ECG for a wide selection of symptoms.

3.2.3 Role in the study

I was the lead investigator and was involved in data collection and validation of AF on the Holter ECGs and further analysis. Other cardiology physicians, YP and MN, helped in the validation of ECG findings and data collection. PK had oversight of the whole project and coordinated data collection efforts and checked the integrity of the database. WC helped with the statistical analysis and data presentation.

3.3 Workflow for the SWBH data

3.3.1 Sample size and Data collection

The data was collected by 3 researchers, JQ, YP and MN from 1st April 2014 to 31st April 2017. A total of 584 records were collected.

Clinical data was taken by going through clinical (hospital and primary care) records. Holter ECG data was previously analysed by trained hospital physiologists. The findings were taken from the standardised report. The presence of AF was confirmed on review of the ECG data from the Holter recording. The definition for AF (described later) was based on the duration of at least 30 seconds.

3.3.2 Inclusion criteria

All patients presenting for 7-day continuous Holter ECG monitoring above the age of 18 years presenting within the timeline described above were included.

There were no pre-set criteria for the 7-day Holter requests but such test requests were left on the discretion of the clinical judgement of the physicians. Some of these patients may have had prior investigations like 24 or 48-hour Holter ECG before undergoing 7-day Holter ECG. Having prior a prior shorter duration of ECG monitoring for similar symptoms was not an exclusion criterion. The data for the patients having such prior tests is not available and this is mentioned as a limitation of the study.

The test was performed for the indications of palpitations, dizziness, syncope, chest pain and ischemic stroke or TIA. There was no restriction for the holter monitoring being performed within a certain time frame after the index event.

3.3.3 Exclusion criteria

76 patients were excluded based on the following criteria to ensure adequate data quality and a standardised patient cohort:

- Age <18 years
- <110 hours recording (<66% of intended duration of recording)
- >10% of the total being an artefact.

This led to 508 patient records. 32 patients had known AF and were excluded from further analysis. Here a final cohort of 476 patients is presented. This is shown in Figure 3.1.

3.3.4 Intra/Interobservariability

Due to the retrospective, observational nature of this study intra-observer variability could not be assessed as the Holter recordings were already analysed by the qualified hospital cardiac physiologist. A random sample of 50 Holter ECGs was re-analysed by JQ, YP and MN to assess for quality of ECG data especially for presence or absence of AF looking at the ECG data available for review. Moreover, for all cases with pre-reported AF, the reviewers reviewed the ECG to confirm it. There was no discrepancy in AF diagnosis between the three observers (JQ, YP and MN).

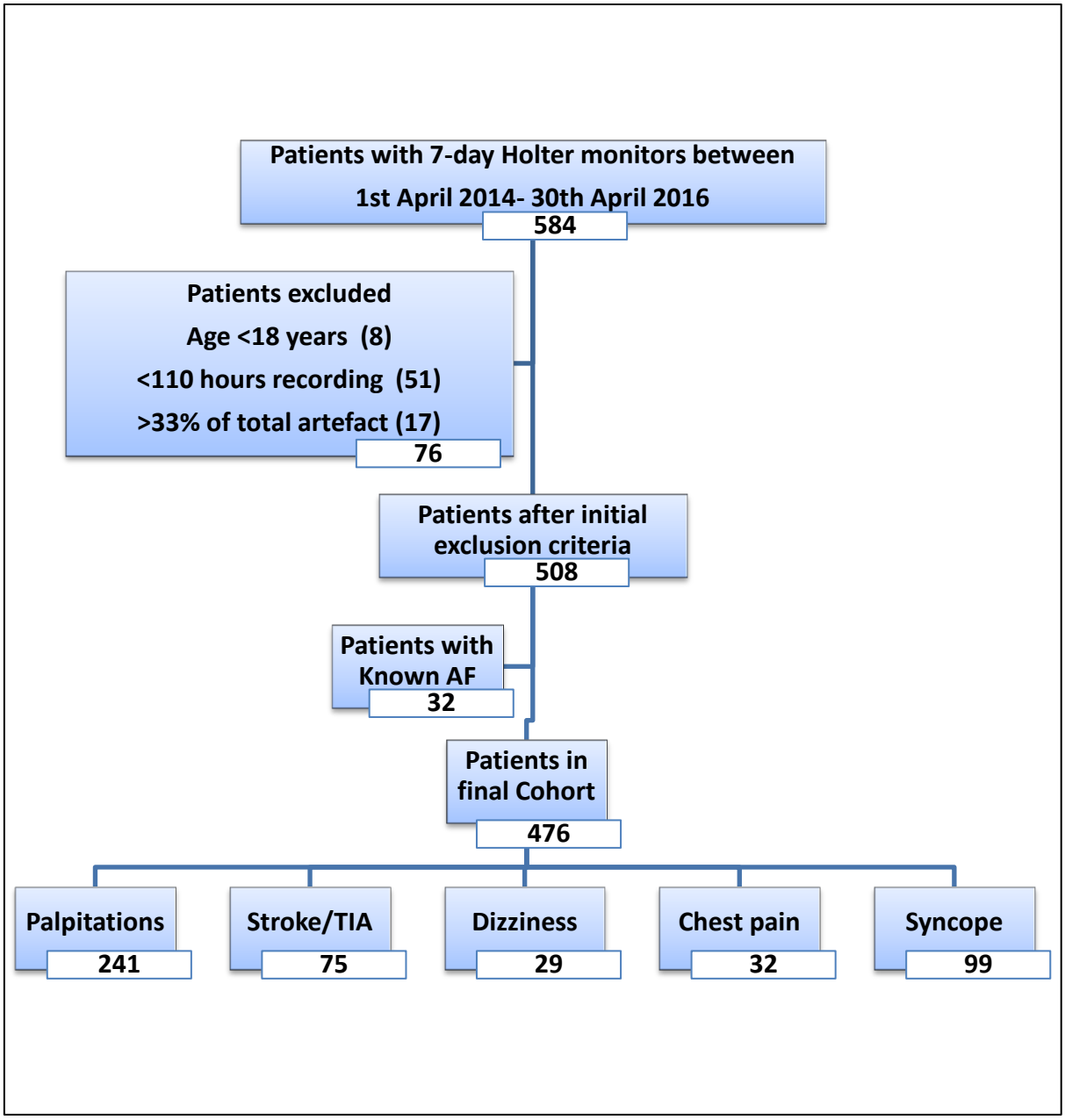


FIGURE 3.1 CONSORT CHART FOR PATIENT NUMBERS AND EXCLUSION CRITERIA

3.4 Definitions

To maintain consistency in reporting the findings, the definitions of Holter ECG parameters are adapted from the detection threshold of these findings through the Pathfinder version used for ECG analysis.

Atrial ectopics: Supraventricular ectopic activity with different morphology of p wave or absent p wave and 80% (+/-5%) of prevailing NN interval.

Premature ventricular ectopics: Ventricular ectopic activity with wide QRS complex with no preceding p wave activity and 90% (+/-3%) of prevailing NN interval.

Supraventricular runs: 3 or more consecutive atrial (supraventricular beats).

All comorbidities were taken as previously documented through records from primary care or specialist clinics. The valvular disease was taken as moderate to severe left-sided (mitral or aortic) valvular disease, stenosis or regurgitation, confirmed on prior echocardiography.

3.5 Hypotheses

In an all-comer patient cohort:

a. AF is more likely to be present in patients symptomatic with palpitations.

b. AF detection increases in the presence of underlying cardiovascular risk factors like increasing age, hypertension, diabetes, coronary artery disease, hypercholesterolemia and previous stroke or TIA.

c. Presence of excessive supraventricular ectopic (SVE) activity is associated with more AF.

3.6 Statistical analysis

3.6.1 Descriptive statistics

For normally distributed variables I shall present mean and standard deviation; otherwise, median value and quartiles will be presented. The descriptive statistics shall be described in tabular form or graphs (pie chart, histogram and bar charts) or both. Normality will be tested by inspection of the distribution curves and Kolmonorov-Smirnov test. A value of <0.05 on Kolmonorov-Smirnov test indicates the non-normal distribution of data.

3.6.2 Univariate association testing (including Odds ratio, CI)

Univariate associations between ECG parameters and finding of AF are evaluated by the independent student T-test or Man-Whitney U test for continuous variables dependant on whether the data is normally distributed or Chi-square (x^2)test as appropriate. Receiver operating characteristics (ROC) curve analysis shall be performed for various Holter parameters to find the optimum cut off for sensitivity and 1-specificity using Youden's index. These cut-offs are then used as dichotomous variables in the univariate logistic regression analysis. This will give the odds ratio (OR) that will be reported alongside 95% confidence intervals (CI) and p-value. The p-values <0.05 will be considered statistically significant.

3.6.3 Multiple logistic regression, adjusted variables and bootstrapping

Multiple logistic regression analyses will also be performed to evaluate the covariate-adjusted association of the variable(s) of interest with the detection of new incidental AF. These variables will be chosen based on their clinical relevance and importance in previous research work. A formal multiple testing correction will not be done. These variables going

into the multivariate model will be limited to 1 variable/10 AF-outcomes. The derived model will be adjusted for age, sex and duration of the recording. The model will internally be validated using bootstrapping to produce an optimism-adjusted model. Multivariate association of the variables with AF will be reported through OR, 95% CI and p-value. The model fit will be tested observing the Nagelkerke $r^{2.}$ A value closer to 1 will indicate better model fit.

The bootstrapped model's performance will be assessed by quantifying the C-statistic (equivalent to the area under the ROC curve) reported alongside 95% CI and p values. All the statistical calculation will be done in SPSS (IBM) software v.24.0.0.0 (64-bit edition).

3.7 Research Governance

The project was registered with the clinical effectiveness department at Sandwell and West Birmingham Hospitals NHS trust (QIP Approval Number SG323) following the guidelines of the Good Clinical Practice (GCP), following GCP training. This work was initially registered as a quality improvement project looking at the retrospective registry data, hence formal ethical approval was not needed. This project conformed to strict clinical data governance standards with no patient identifiable information stored on any 3rd party computers or devices as per guidelines from the General Medical Council and Information Commissioner's office.

4 MATERIALS AND METHODS FOR MONDAFIS DATASET

4.1 Objectives related to MonDAFIS dataset

The analysis of MonDAFIS dataset for this thesis and further publications is relevant and important for reasons described below.

a. Baseline clinical characteristics, comorbidities and echo data in stroke patients

The dataset will provide useful insights into clinical characteristics, comorbidities, basic echocardiographic parameters for patients with acute ischemic stroke.

b. Defining baseline Holter ECG findings for a large cohort with acute stroke

The Holter ECG parameters for up to 7-days in a large cohort of patients presenting with acute ischemic stroke has not been previously defined. It would be important to define what constitutes as "*baseline"* or "*normal"* for this group of patients.

c. The relevance of duration of ECG monitoring on AF detection

AF detection per 24-hour increase in the duration of ECG monitoring to describe detection rates at 24 and 72 hours up to a maximum of 7-days will be seen.

d. Description of important association of AF with clinical or Holter ECG findings

Any significant association of new-onset AF with the clinical, echocardiographic, and Holter ECG parameters shall be described.

d. Suggest important predictors of incident AF

A regression analysis shall be performed to look for any clinical, echocardiographic or ECG variables which alone or in combination may serve as predictors of AF.

4.2 Introduction to MonDAFIS Trial

The main component of my research data comes from the baseline dataset from the MonDAFIS trial.

This is explained in detail under the following headings

4.2.1 General Outline of MonDAFIS Trial

4.2.2 Purpose of the trial

4.2.3 The rationale of the trail.

4.2.4 Role in the MonDAFIS trial

4.2.5 Analysis workflow

4.2.1 General Outline of MonDAFIS Trial

This will be a major part of the dissertation. It shall make use of the baseline clinical, echocardiographic, brain imaging as well as 7-day Holter ECG data collected for the intervention arm of the randomised multicentre MonDAFIS Trial (**MonDAFIS**-Impact of Standardized **Mon**itoring for **D**etection of **A**trial **F**ibrillation in **I**schemic **S**troke).

4.2.2 The purpose of the trial

The methodology of the MonDAFIS trial including purpose of the trial, funding, sample size and recruitment details, inclusion and exclusion criteria and analysis data points are previously described in detail in the design paper.[207] In summary, this is an investigator-initiated prospective randomized multi-centre study to uncover the true burden of paroxysmal AF in a representative population of acute stroke patients without known AF.

4.2.3 The rationale of the trial

Stroke secondary to AF, in general shows poor prognosis and high risk of recurrent stroke. Undetected paroxysmal (silent) AF in this population is a major diagnostic challenge. Prolonged ECG monitoring and systematic analysis improves AF detection. This trial compares a longer duration of ECG recording in post-stroke patients compared to standard 24-hour Holter which forms part of the usual in-hospital diagnostic protocols for AF detection. The primary endpoint of the trial is the number of patients on oral anticoagulation for AF at 1-year follow-up with further detail of secondary end-points already published in the trial design paper.[207]

4.2.4 Role in the Trial

I worked as a Sub-Investigator general cardiologist in the trial with the responsibility to perform standardised analysis of ECGs for detection of AF at the core lab which was set up at the University of Birmingham, under supervision of Prof Paulus Kirchhof (Director of the Core lab). I led a team of 5 physiologists and review all the ECG findings from all the Holter recordings from the intervention arm. All investigators and physiologists received formal training from the Spacelabs (provider for ECG recording device and analysis software) to perform reliably and consistently reproducible analysis of Holter ECGs. I have personally analysed or reviewed all 7-day Holter ECG recordings performed in the intervention arm of the MonDAFIS trial.

4.2.5 The analysis workflow

The details of the work-flow at the study site (in Germany), in the Core Lab (UK) and finally in trial coordinating centre at the Charité (Germany) are described here (Figure 4.1).

a. Workflow processes at Study Site and Charité(Germany)

39 specialist and certified German stroke centres took part in the MonDAFIS trial. These centres were distributed among "regional", "non-university based" and "university-based" centres in 40%:30%:30% ratio. These centres enrolled acute patients with suspected stroke and TIA. The diagnosis of stroke was based on clinical symptoms and brain imaging. All the patients received Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) of the brain and in some case both, as soon as possible after admission.

According to the study protocol, the patients get recruited in the MonDAFIS trial through informed signed consent within 24 hours of admission. They are randomised either to the standard of care (including a 24 hour Holter ECG) or the intervention arm providing standardised Holter ECG monitoring up to 7-days. The patient data is pseudo-anonymised and assigned a study ID number. The inclusion and exclusion criteria are given below.[207]

Inclusion criteria

- Informed and written consent
- Age ≥ 18 years
- Acute ischemic stroke or TIA with the persistent neurological deficit with or without a matched lesion of the MRI brain.
- Admission to a stroke unit within 72 hours of the onset of stroke-related symptoms

- Enrolment in MonDAFIS and start of ECG recording (as per randomisation) within 24 hours of admission
- Sufficient knowledge of the German language
- Consent to participate in the follow-up

Exclusion criteria

- Previously known AF
- AF previously seen on the 12-lead ECG following hospital admission
- AF seen during ECG monitoring on the stroke unit before the patient is enrolled
- Life expectancy < 1-year pre-stroke
- Life expectancy <1 month post-stroke
- Participation in a concomitant interventional study
- Women who are pregnant or breast-feeding.
- Presence of an implanted device with the provision of ECG recording.

The trained study personnel (a nurse or a doctor) for the MonDAFIS trial connect the Holter ECG recorder (Spacelabs healthcare, modular digital Holter recorder, with Lifecard CF) with the patient. This recorded a 2 or three-channel ECG up with up to 7-day of continuous ECG with 12-bit resolution. The device also recorded a voice file which is used for patient ID in English and German. The recordings are uploaded from the study site by the research nurse on the REDCap 6.15.15 - © 2017 Vanderbilt University. This database was monitored and handled by the Charité in Berlin. The study nurses or doctors do a visit every day and look after the electrode to identify any disconnected electrodes.

The ECG is recorded in 4 files.

b. Cnav.dat 8 Kb

c. Config.dat 1 Kb

d. ECG.dat 93 Mb

e. Patient.wav 64 Kb

Each of these file types is essential to the analysis as any missing component led to the loss of ECG dataset. These files are uploaded on the secure REDCAP server at the end of the recording by the study physician/nurse.

b. Workflow processes at the core lab (University of Birmingham, UK)

The investigator at core lab downloads the files from the REDCAP system on to a 90 MB Spacelabs CF card (Figure 4.1, Figure 4.2). Data is then retrieved on a Dual 21-inch screen dedicated Workstation running Sentinel database V9.0.2.4491 and stored on a secure local server. This system is set up by the IT department of the University of Birmingham in association with Spacelabs healthcare. This transmitted ECG is linked with an audio file confirming the patient ID in English and German. The ECG is analysed through Pathfinder SL Software Version 1.7.1.2718 (Copyrights Spacelabs Healthcare). The ECG reports are analysed by trained physiologists and findings are verified and rechecked by the sub-investigator general cardiologist (myself). All the team involved in ECG analysis have received adequate training for the software and analysis through Spacelab healthcare (provider for ECG recording device and specialised analysis software and hardware). The Sentinel and pathfinder system screenshots are shown in Figure 4.3.

All the analysed data is stored on the local database. The formal Personal Digital Format (PDF) report and analysed (.ISHNE) and original (*.sntl*) ECG data files are resent through the REDCAP system to the trial centre.

c. Workflow processes at the Charité – Universitätsmedizin Berlin, Germany

The Holter summary report is created in English alongside German translation as per standardised templates for various possible Holter findings. The German version was then released to the recruiting trial centre and the treating physicians which informed them of initiating any oral anticoagulant therapy or action relevant steps based on the ECG findings. The exported ISHNE data files were processed through a dedicated Sentinel workstation at the Charité, Berlin to generate a spreadsheet incorporating the database of recorded ECG findings. The further validation efforts to verify the ECG data points is described in the next subsection

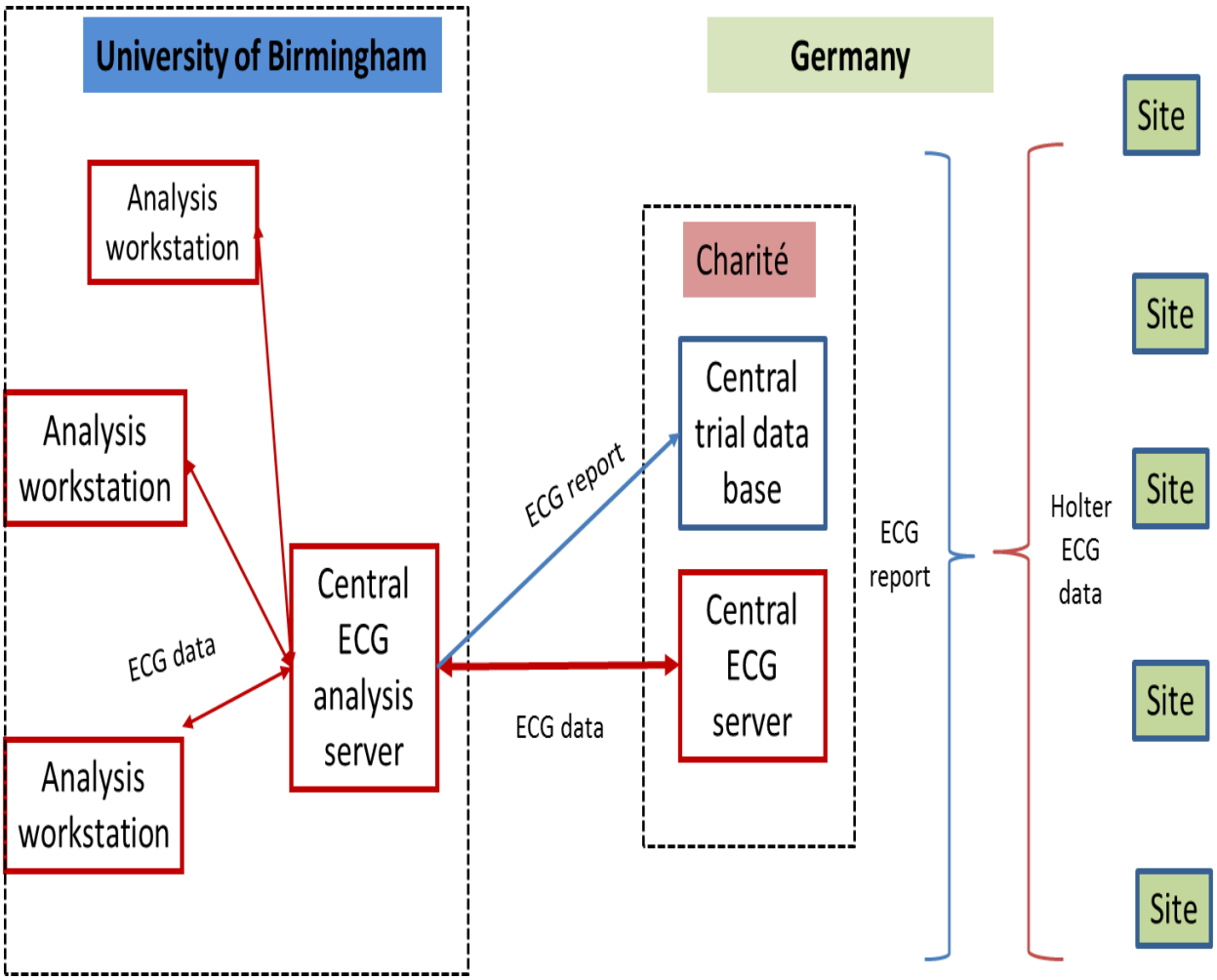
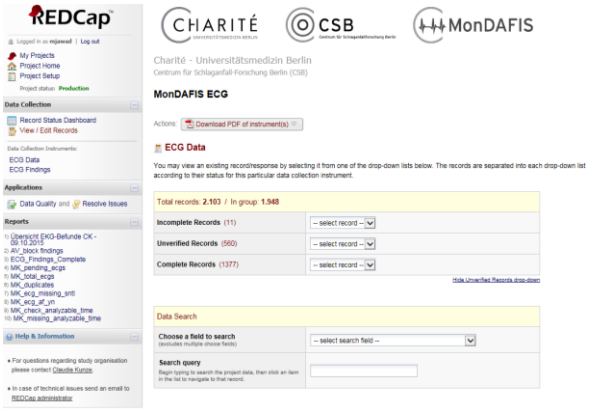
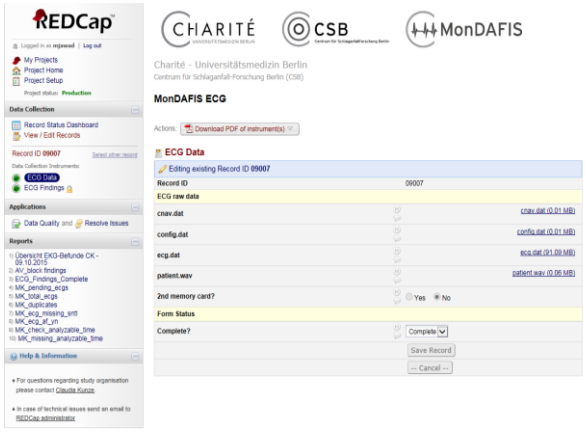


FIGURE 4.1 MONDAFIS HOLTER ECG DATA WORKFLOW



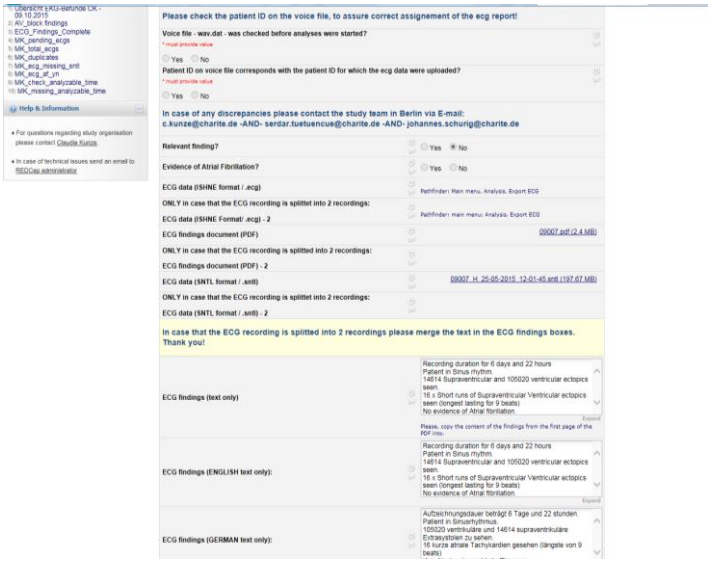
Screen 1: Main Home Screen

Option to look for the full list of trial patients for search based on study ID



Screen 2: Patient data

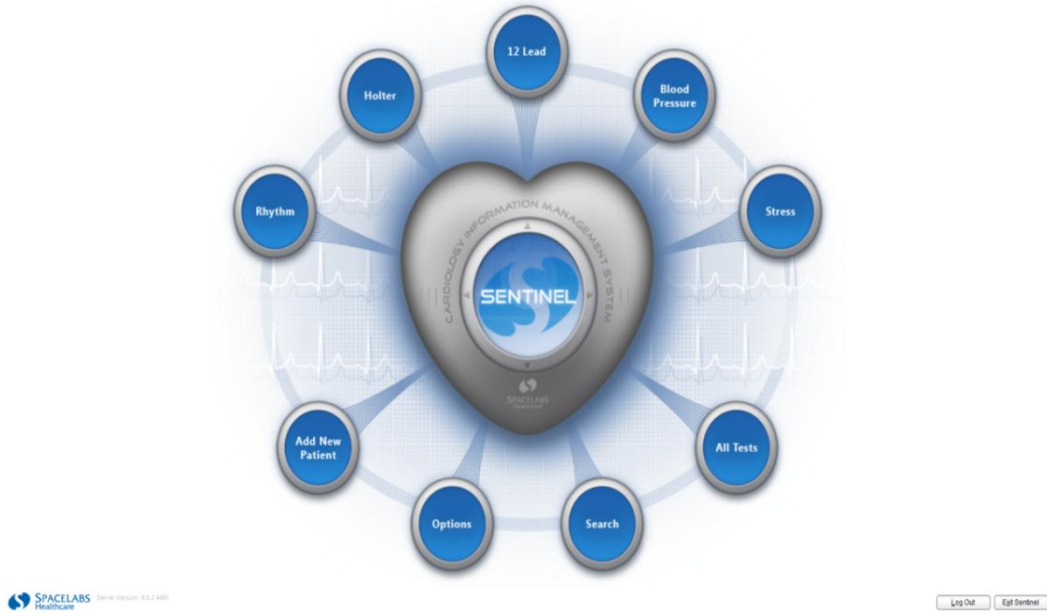
The data screen contains the complete dataset which includes the main ecg.dat, cnav.dat, config.dat and patient.wav file



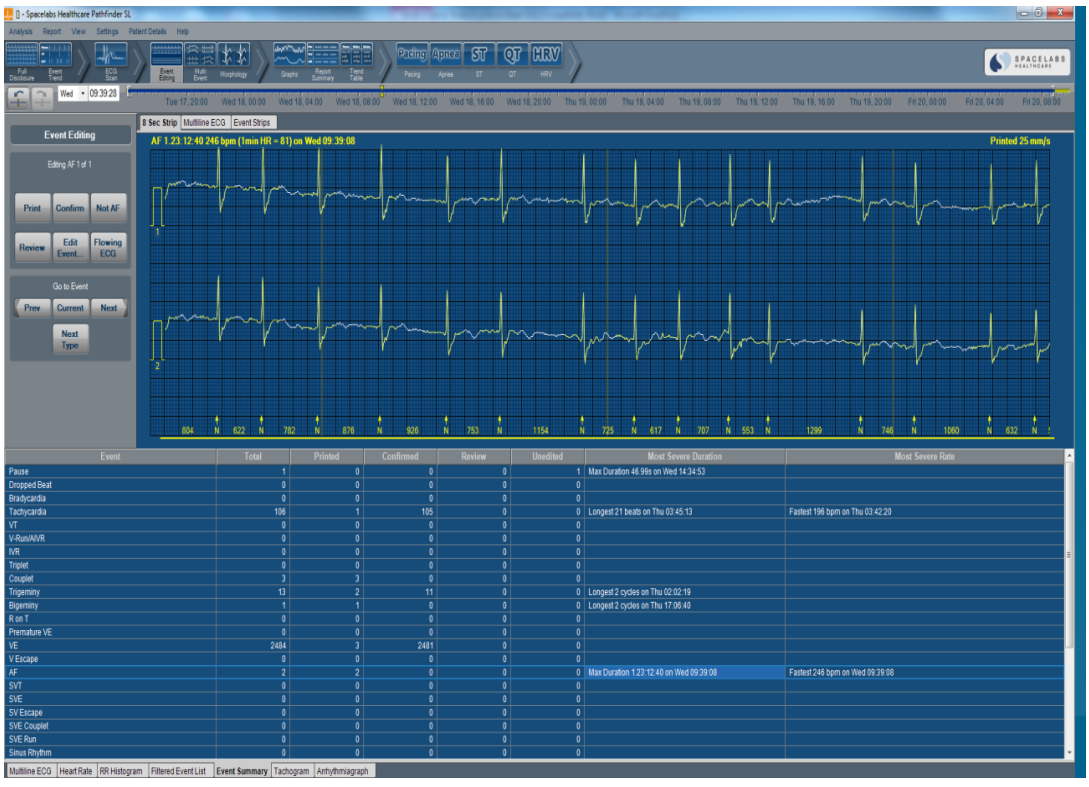
Screen 3: Results entry

This uses checkboxes to rule in (or out) AF. It also uses a safety net to ask the user to recheck the voice file to ensure the voice matches the patient ID. The report is uploaded as a PDF file as well as a summary is written in free text.

FIGURE 4.2 WORKFLOW ON REDCAP SYSTEM



A. **Sentinel Database**



B. **Pathfinder Analysis software**

FIGURE 4.3 SENTINEL DATABASE AND PATHFINDER

4.3 Quality control and data validation

The purpose of the validation process is to ensure a correct, traceable, complete, and analysable database of all relevant variables recorded by the Holter ECG that are relevant to the study. The complete dataset for MonDAFIS was continuously validated through quality control measures that involved rechecking that the Holter ECG report matches the summary descriptions and all the counts within the report are valid without any contradictions.

Those ECG data with 2 recordings were merged into a single file and their accuracy rechecked against the source (Sentinel dataset). A final validation check was done once the ECG data was converted from the Sentinel data file to the SPSS spreadsheets to ensure the accuracy of data. The whole process of data validation is described below:

4.3.1 Possible sources of error:

a. Quality of ECG analysis including Intra and inter-observer variability

It is important to check that the ECG analysis that was performed was of the highest standard and there were no major discrepancies in the findings. Most importantly the episodes and durations of AF as well as important study secondary endpoints needed to be verified independently.

b. Presence of multiple *.sntl* files for each ECG dataset:

A *.sntl* was the final file generated after the analysis of the Holter recording. Thus was generated through the Sentinel server at the Core lab. In many cases, more than one *.sntl*-file was generated and stored within the Core lab in Birmingham. These *.sntl* files were transferred to the central database in Berlin and stored within the eCRF (REDCap™ ECG-project). The latest available *.sntl* file for each patient was used to generate a single *.xml* file.

It was important to ensure that each *.xml* file is derived from the correct corresponding *.sntl* file and matches the final report of the ECG findings as per the analysis.

c. Automatic generation of *.xml* files:

An error could occur during generation of *.xml* file. These files were created by the Pathfinder SL Software. The Software complies with the requirements of the Medical Device Directive (93/42/EEC – 2007/47/EC) and the Directive on Restriction of Hazardous Substances in Electrical and Electronic Equipment (2011/65/EU).

d. Restructuring of the *.xml* file into an analysable SPSS-file:

This is a potential source of discrepancy in the final data and was addressed to be reviewed by the validation process detailed below.

4.3.2 Steps to rectify sources of error

a. Defining primary and secondary ECG endpoints:

It was very important to define relevant items for validation which are primary and/or secondary endpoints of the study. These include atrial fibrillation and flutter, supraventricular ectopics (SVE), and supraventricular ectopics runs (SVE runs). The SVEs and SVE runs were defined based on the set criteria as described above, taking into account the analysis algorithm of Pathfinder SL Software.

b. Steps to minimize Intra and inter-observer variability

Standardised training and SOPs

Before the setting up the core lab, four experienced and qualified cardiac physiologists were recruited in core lab analysis team. All of them were already trained and working on a similar version of Sentinel Pathfinder (version 1.7.1.2718). All members of the team including the

trial physician (myself) and the principal investigator (PK) underwent further training from the Spacelabs™ representative and standard operating procedures (SOPs) were made to ensure that the analysis is performed in a standardised way.

Setting up similar analysis thresholds on the workstations

All the work stations had a similar threshold set to automatically pick up events like atrial ectopics and ventricular ectopics etc. These thresholds were kept constant throughout the trial analysis. All events including AF episodes wee manually checked before finalising.

Final review of all recordings by one reviewer

All the analysed recordings before uploading to the trial database underwent final quality control check by one reviewer (myself) for all the recordings. This ensured that ECG analysis from all the physiologists was up to the same standard.

Internal validation of the results (checking for intra-observer variability)

The trial statisticians proposed a method for validating the quality of the generated dataset. This involved random identification of 10% patient records based on the recorded patient identification (Pat ID) numbers. Verification of the patient ID and validation of a qualifying number of analysed items was performed at the ECG Core lab. This purpose of this validation was to establish that the information deposited in the analysis database matches the information coded in the original analyses as well as to look for intraobserver variability. The matching was based on patient ID numbers (pseudonymised). A new eCRF-form in the REDCap™ ECG-project was created for documenting the results of the validation and classification procedure. The validation process involved the comparison of the *SPSS* file with the ECG raw data case by case to check the validity of primary and secondary ECG endpoints. This also involved checking the number and duration of episodes of atrial fibrillation and

supraventricular ectopic runs and supraventricular ectopics in total and for each 24-hour period.

The difference for atrial and/or supraventricular ectopics between the actual ECG analysis and the *SPSS* file was set as less than 10%. Similarly, for the required number of validation cases, less than 10% of studies should fail the validation process.

This found no difference between the pre-reported outcomes and the validation results.

External validation of results (checking for Inter-observer variability)

External validation was carried out by the trial steering committee to check a randomly selected sample of the cohort for the presence of AF and found all the pre-reported results were compatible with the validation findings.

c. Correct labelling of *.sntl* files

All *.sntl* files were correctly labelled to ensure reproducibility of the dataset. It was important to check that each *.sntl* file, and in case of more than one *.sntl* file for the one Pat ID, the correct file has been used to transcribe the ECG findings.

4.4 Patient recruitment and sample size

The planned duration of entire MonDAFIS study including the follow-up protocol is for 5 years. A total of 3470 patients were recruited in the total study with 1738, randomised to the prolonged ECG monitoring arm. The first patient was recruited in December 2014 and the last patient was recruited in December 2017. The inclusion and exclusion criteria are described earlier.

The total sample size calculation for randomization in the MonDAFIS trial (including the control and intervention arm) is calculated to be 3470 and is previously described in the design paper.[207]

The analyses performed here are confined to the intervention arm of the MonDAFIS trial.

The consort chart for the sample is given in Figure 4.4

The Holter analyses were split into 2 durations.

1. Holter ECG parameters in the 1st 24 hours (Hours 1-24)

2. Holter ECG parameters for all 7-days

Holter ECG variables during the first 24 hours were assessed in relation to AF for association testing and further logistic regression for ECG variables.

The data from complete 7-day Holter ECG for the total duration of recording and heart rate parameters were included as these were available for total recording only.

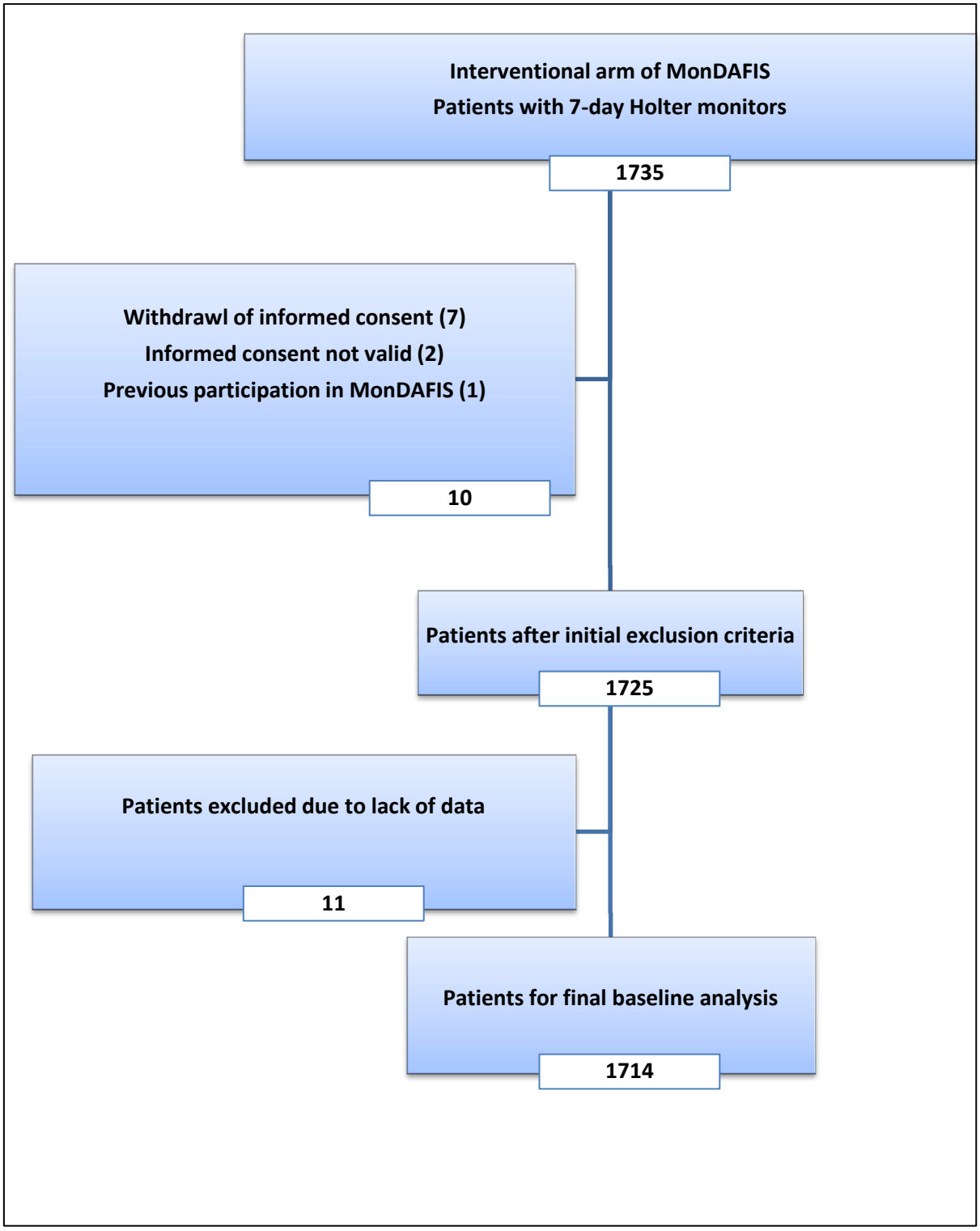


FIGURE 4.4 PATIENT RECRUITMENT AND ECG ANALYSIS IN MONDAFIS TRIAL

4.5 Baseline Data

The comparison between different variables from across the groups shall include

- Patient characteristics
- Duration and severity of the stroke and associated symptoms
- Comorbidities
- Imaging parameters (Echocardiography and Neurovascular imaging)
- Holter ECG variables

4.5.1 Patient Characteristics

Predefined baseline patient characteristics will be used to describe the patient population as then potentially be used to predict paroxysmal AF. This shall include age and gender as a whole and then described for AF and non-AF group separately including their height, weight and body mass index (BMI). Alcohol and Nicotine intake is also recorded. Alcohol intake is marked as frequent for >14 units of alcohol in females and >21 units in male. Lesser consumption than the threshold described above is marked as occasional. Nicotine intake could be in oral form (chewing tobacco), snuff or cigarette smoking. I shall describe either an ongoing history or past use of Nicotine and compare with those who never had any nicotine intake.

4.5.2 Stroke duration, severity and associated symptoms

The duration of stroke symptoms shall be described based on whether they presented before or after 24 hours since the onset of symptoms. The stroke severity will be assessed using the National Institute of Health Stroke Scale (NIHSS) which utilises various neurological

features including conscious level, speech, upper and lower limb motor functions, coordination, sensation, vision and visual fields. The scale uses a range between 0-42 points. Patients on recruitment were screened for any co-existing associated significant symptoms of palpitations, dizziness or pre-syncope (sensation of near loss of consciousness). The symptoms were described as frequent the recurrence was daily to at least once per week, and occasional if they were less than once per week. The maximum and minimum duration of symptoms was not collected as part of the dataset.

4.5.3 Comorbidities

This is described as follows:

a. Hypertension

Hypertension was defined as a previously established diagnosis with or without medication. This is further defined as untreated systolic BP of >160mm Hg.

b. Diabetes

Diabetes was defined as a previously established diagnosis with or without medications or a fasting glucose of ≥7.1mmol/L, 2-hour postprandial ≥11.1mmol/L or HBA1C ≥48mmol/mol.

c. Heart failure status

Any patients diagnosed by a physician as having heart failure syndrome clinically, radiologically and/or with echocardiographic findings, regardless of their left ventricular ejection fraction (LVEF). This could include, but would not be limited to symptoms of

shortness of breath on exertion or at rest, orthopnoea, peripheral nocturnal dyspnoea and swelling of the ankles or above.

Heart failure is quantified as per New York heart associated (NYHA) classification given below. Significant heart failure will be defined as patients in NYHA category II-IV.

Class I - No obvious symptoms with any evidence of limitation in ordinary physical activity. For example, constitutes shortness of breath when walking uphill or climbing stairs.

Class II - Mild symptoms (mild shortness of breath) along with slight limitation during ordinary physical activity.

Class III - Marked limitation inactivity due to symptoms, even during minimal activity but comfortable at rest. For example, a patient getting breathless on walking for short distances of about 20-100 yards.

Class IV - Severe limitation of physical activity and the patient would experience symptoms even while at rest. These patients are mostly bed-bound.

While all patients in the data set will have an acute stroke or TIA, there are still some markers of vascular disease severity that can be assessed.

d. Previous history of Transient ischemic attack and ischemic stroke

A transient ischemic attack was defined as a neurological deficit which resolved in less than 24 hours confirmed by a physician using brain imaging and clinical features.

Stroke was defined as a neurological deficit consistent with either persistent disability or symptoms resolution after 24 hours, confirmed by a physician using brain imaging and clinical features.

e. Coronary artery disease

Coronary artery disease was defined as a history of known myocardial infarction with troponin rise (treated with revascularisation or medical management), elective coronary artery bypass surgery (CABG) or percutaneous intervention (PCI) or coronary angiography with >50% epicardial vessel stenosis.

f. Peripheral vascular disease

Symptoms of claudication on exertion or previous history of limb ischemia, peripheral arterial angioplasty, bypass and/or amputation with confirmed radiographic/angiographic of findings compatible with the clinical syndrome.

g. *Intracranial bleed*

The previous history of spontaneous or traumatic established bleed/hematoma confirmed on radiological diagnosis, within the brain parenchyma and outside the parenchyma which includes epidural, subdural or subarachnoid bleed

h. Renal Impairment

A previously established estimated glomerular filtration rate of less than 60 ml/min or diagnosed after admission.

4.5.4 Echocardiographic parameters

The patients shall have transthoracic, trans-oesophageal or both forms of cardiac imaging during admission. This shall look for:

a. Left atrial dimension
b. Left Atrial thrombus
c. Left ventricular function
d. Left ventricular thrombus
e. Evidence of patent foramen ovale and aneurysmal interatrial septum

The observed echocardiographic variables were recorded as per the local echo guidelines. However, a minimum echo dataset included the variables mentioned above. The details of the equipment used for the echocardiography not available.

4.5.5 ECG Variables

The variables are described as follows:

Atrial fibrillation and Flutter:

Atrial fibrillation was defined as an atrial arrhythmia with loss of p wave activity and irregular R-R interval lasting for at least 30 seconds.[11] Atrial flutter was defined as sustained atrial arrhythmia lasting for at least 30 seconds with typical flutter waves in the baseline with either regular or irregular R-R interval. Both were reported as AF outcome for this study.

Supraventricular ectopics (SVE):

Defined as a narrow QRS complex similar in morphology to sinus beat with different or absent p wave and <80% of the prevailing RR interval.

Supraventricular couplets:

A combination of two consecutive SVEs would be classed as SV couplet.

Supraventricular runs (SVE runs):

This was classed as regular or irregular runs of 3 or more consecutive SVEs lasting for less than 30 seconds.

Ventricular ectopics (VE):

This is defined as a premature or delayed ectopic activity with wide QRS complex with no preceding p wave activity and in case of premature ectopics a delay of 90% (+/-3%) of prevailing NN interval.

Ventricular Couplet and Triplet:

A combination of two or three consecutive VEs would be classed as a ventricular couplet or triplets, respectively.

The ECG variables of interest are given in **Table 4.1**.

TABLE 4.1 ECG VARIABLES RELEVANT TO THE MONDAFIS ANALYSIS	
Markers in ECG (Proposed predictors of AF)	Variables measured, Count (%)
Isolated SVE in first 24 hours	N^{24} (%)
SVE runs (<30 seconds) in first 24	N^{24} (%) Duration (seconds)
SVE couplets in the first 24 hours	N^{24} (%)
VE in first 24 hours of ECG	N^{24} (%)
Couplets in first 24 hours of ECG	N^{24} (%)
Triplets in first 24 hours of ECG	N^{24} (%)
Ventricular runs in first 24 hours of ECG	N^{24} (%) Duration (seconds)
HR more than 100	% of the total
Maximal Heart rate	Rate/min

4.6 Hypothesis

a. Higher age and concomitant cardiovascular conditions (hypertension, diabetes, heart failure, chronic kidney disease) are associated with AF in stroke survivors.

b. Echocardiographic findings of dilated left atrium or left ventricular dysfunction is associated with underlying AF

c. A high count of isolated supraventricular ectopics in the first 24 hour period is associated with paroxysmal AF.

d. Higher counts and duration of supraventricular ectopic runs in the first 24 hours of recording is associated with underlying AF.

e. Excessive ventricular ectopic activity in the first 24 hour period is associated with paroxysmal AF.

4.7 Statistical analysis

4.7.1 Descriptive Statistics

a. Categorical variables will be described in percentage values.

b. For continuous variables will be presented as follows:

   i. For normally distributed variables, mean and SD will be presented.

   ii. For skewed data median and inter-quartile range will be presented.

c. Descriptive statistics shall be described in tabular form or graphs (histogram, bar charts, box plots) or both.

4.7.2 Tests of Normality

Normality will be tested by inspection of the distribution curve and Kolmonorov-Smirnov test. A value of <0.05 on Kolmonorov-Smirnov test indicates the skewed distribution of data.

4.7.3 Univariate Analyses

This shall identify whether there is an association between a predictor variable and presence or absence of AF (response/outcome). All the variables will go through univariate analyses and Odds ratio testing alongside confidence interval testing. Only those significant (P <0.05) at this stage will proceed to the multivariate analyses and logistic regression.

a. For categorical variables, a Chi-Square test or Fisher-exact test based on sample size for the variable will be performed.

b. For continuous variables, a T-test or Mann-Whitney test based on whether the data is normally distributed or not will be performed, respectively. Two-tailed tests of significance will be reported, and *P-value*s <0.05 will be considered statistically significant.

ROC analysis shall be performed for various Holter parameters to find the optimum cut off for sensitivity and 1-specificity using Youden's index. These cut-offs are then used as dichotomous variables in the univariate logistic regression analysis.

4.7.4 Multivariate Analyses and Logistic regression

The Statistically significant variables identified through univariate analyses will go into the multivariate analyses and a predictive model based on binary logistic regression using the Enter method. Binary logistic regression is chosen due to the categorical nature of the outcome (AF present or absent). These variables will be chosen based on their clinical relevance and importance in previous research work. Multiple hypothesis testing was not accounted for. These variables going into the multivariate model will be limited to 1 variable/10 AF-outcomes. A p-value of 0.05 will be taken as significant. The model will internally be validated using bootstrapping to produce an optimism-adjusted model. Multivariate association of the variables with AF will be reported through OR, 95% CI and p-value. The model fit will be tested observing the Nagelkerke $r^{2.}$ A value closer to 1 will indicate better model fit.

The model's performance will be assessed by quantifying the C-statistic (equivalent to the area under the ROC curve) reported alongside 95% CI and p values. All the statistical calculation will be done in SPSS (IBM) software v.24.0.0.0 (64-bit edition).

4.8 Confidentiality and Research governance

The confidentiality in this trial has been monitored by the clinical trials quality assurance manager from the University of Birmingham and the methods used to ensure patient confidentiality and data protection are found to be satisfactory.

The main sponsor of the MonDAFIS trial was the Charité - Universitätsmedizin Berlin (Clinicaltrials.gov NCT02204267). Its was primarily approved by the Ethics Committee of the Charité - Universitätsmedizin Berlin, Germany (EA2/033/14). Furthermore, the participating centres procured approval from their respective ethics committees. The study protocol was per the principles of Good Clinical Practice and the Declaration of Helsinki. All study patients have to give informed consent.

The trial conduct at the core lab was in full compliance with the principals of Good Clinical Practice (GCP) in the UK. I completed the GCP online as well as full training to understand the principals of clinical research governance. All the investigators at core lab further went through confidentiality and research governance training modules offered by the University of Birmingham to be compliant with the standards of practice expected of me.

It is important to mention that until the baseline trial results are published the contents of this manuscript are strictly confidential. The University of Birmingham has agreed to hold the manuscript in restricted access until 31st December 2021.

5 RESULTS FOR SWBH 7-DAY HOLTER DATASET

This shall be explained under the following headings:

5.1. Descriptive statistics of baseline dataset

5.2 Association and dependency tests with AF

5.3 Logistic regression analysis and tests of model fit

5.1 Descriptive statistics of the baseline dataset

This is explained as:

5.1.1 Patient characteristics and comorbidities

5.1.2 Indications and referral pathway for Holter

5.1.3 Holter ECG parameters

Various descriptive statistics were recorded. These include age, gender, reasons or indications for test and source of referral.

5.1.1 Patient characteristics and comorbidities

a. Age and gender

Mean [SD] age of the patients was 54.61 [15.96] years. The 50-59 years age group had the highest number of patients, n (%), 107 (22.48%). Moreover, 297 (62.39%) patients were at age 50 or above, given in Figure 5.1 Age categories per decile. 266 (55.66%) of the total patients were female.

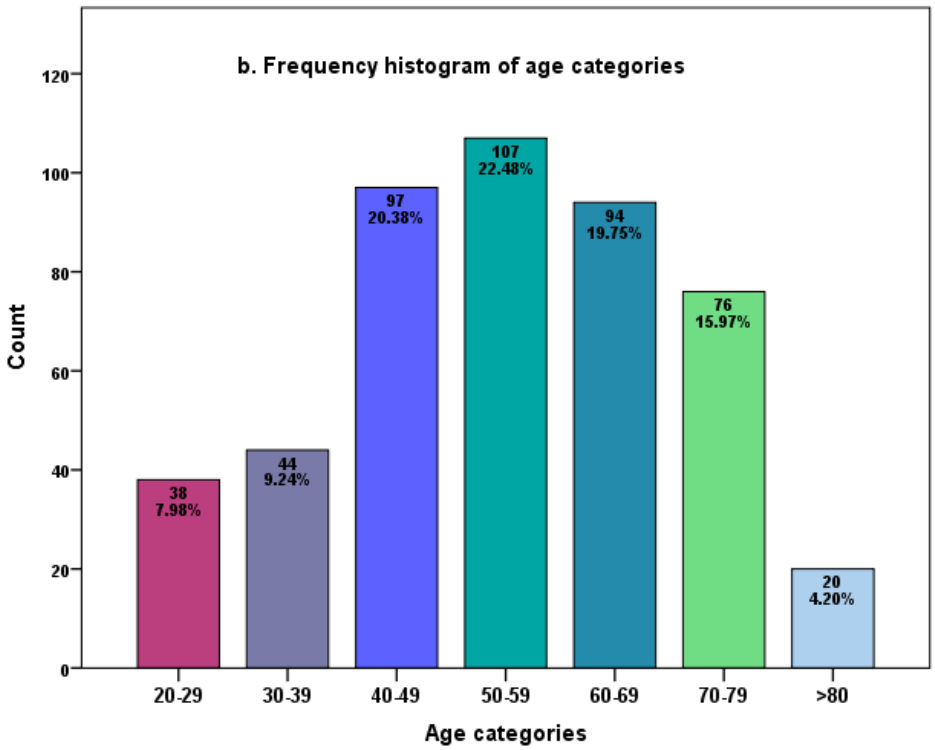


FIGURE 5.1 AGE CATEGORIES PER DECILE

b. Comorbidities

The number (%) of various comorbidities like hypertension, diabetes, coronary artery disease, hypercholesterolemia, history of previous stroke or TIA, and moderate to severe left-sided valvular disease is given in the table below.

TABLE 5.1 BASELINE PATIENT CHARACTERISTICS (N=476)	
Variable	**Total**
Age, years, mean (SD)	56.4 (17.0)
Age categories, n(%)	
20-29 years	38 (7.9%)
30-39 years	44 (9.2%)
40-49 years	97 (20.3%)
50-59 years	107 (22.4%)
60-69 years	94 (19.7%)
70-79 years	76 (15.9%)
≥80 years	20 (4.2%)
Female, n (%)	266 (56%)
Hypertension, n (%)	173(36.3%)
Diabetes, n (%)	78 (16.3%)
Coronary artery disease, n (%)	102 (21.4%)
Hypercholesterolemia, n (%)	177 (37.1%)
History of stroke or TIA, n (%)	111 (23.3%)
Valvular disease, n (%)	72 (15.1%)

5.1.2 Indications for monitoring and referral pathway

Most of the test requests came from cardiology and general medicine, n (%), at 210 (45.8%) and 210 (44.1%) respectively.

Palpitations were by far the most common indication, n (%), at 251 (50.6%), followed by syncope 99 (20.8%) and then stroke or TIA at 75 (15.8%). These trends are summarised below.

TABLE 5.2 INDICATION FOR HOLTER TEST AND REFERRAL PATHWAY (N=476)		
	Variable	**n (%)**
Referral pathway	Cardiology	218 (45.8)
	Medicine	210 (44.1)
	GP	44 (9.2)
	Other specialities	4 (0.8)
	Total	476 (100.0)
Indications	Palpitations	241 (50.6)
	Syncope	99 (20.8)
	Dizziness	29 (6.1)
	Chest pain	32 (6.7)
	Stroke/TIA	75 (15.8)
	Total	476 (100.0)

5.1.3 Holter ECG parameters

This is described as:

a. Duration of total recording

b. Heart rate parameters

c. Supraventricular ectopic parameters

d. Ventricular ectopic parameters

e. Detection of AF

f. Other associated findings

a. Duration of recording

The duration of the recording had a skewed distribution pattern. The median [IQR] of the total duration of recording in hours was 127.50 [116.00-152.00].

b. Heart rate parameters

The median [IQR] of maximum, minimum and mean heart rate in beats per minute (bpm) is 142.00 [124.00-152.00], 49.00 [44.00-55.00], 78.00 [70.00-88.00] respectively and followed a non-normal distribution.

c. Supraventricular ectopic parameters

The count (%) for isolated supraventricular ectopics (SVE), SVE couplets, SVE runs and longest SVE runs is 430 (90.33%), 143 (30.04%) and 70 (14.70%), respectively. The median [IQR] for the number of isolated SVE, SVE couplet and SVE runs was 536 [186-1321], 48 [28-198] and 6 [3-18] respectively. The median [IQR] of longest SVE run was 8 [6-11] beats. The optimal cut-off for isolated SVE was calculated as ≥ 50 SVE/day through the ROC curve against sensitivity and 1-specificity as described before in methods. This showed that 156 patients had ≥ 50 SVE/day.

d. Ventricular ectopic (VE) parameters

The median count [IQR] for isolated ventricular ectopics and couplets was 371 [74-773] and 14 [2-53] respectively.

e. Detection of AF

Out of 476 patients, n(%), 42 (8.8%) had new AF detected. 39/42 (92.9%) patients with AF had paroxysmal and the rest had persistent AF.

f. Other associated findings

Other medically relevant findings were sinus pauses, ≥ 10/ day or ≥50/entire recording (77/476, 16.1%) 2nd degree AV block (10/476, 2.1%), 3rd degree AV block (2/476, 0.4%) and non-sustained VT (12/476, 2.5%). These were all detected in patients who underwent monitoring for dizziness. Artefact burden in the final cohort was 3.3% (SD 3.5). Only 2 (0.4%) patients had permanent pacemakers.

5.2 Association and dependency testing

5.2.1 Clinical parameters associated with AF:

a. Age and gender

The median [IQR] age in the AF and non-AF groups were 71.0 [59.00-78.00] and 52.00 [44.00-65.00] years respectively, $p<0.0001$. Number n (% of total) of female patients with or without AF was not significantly different at 22(4.62%) and 20 (4.20%), $p= 0.632$.

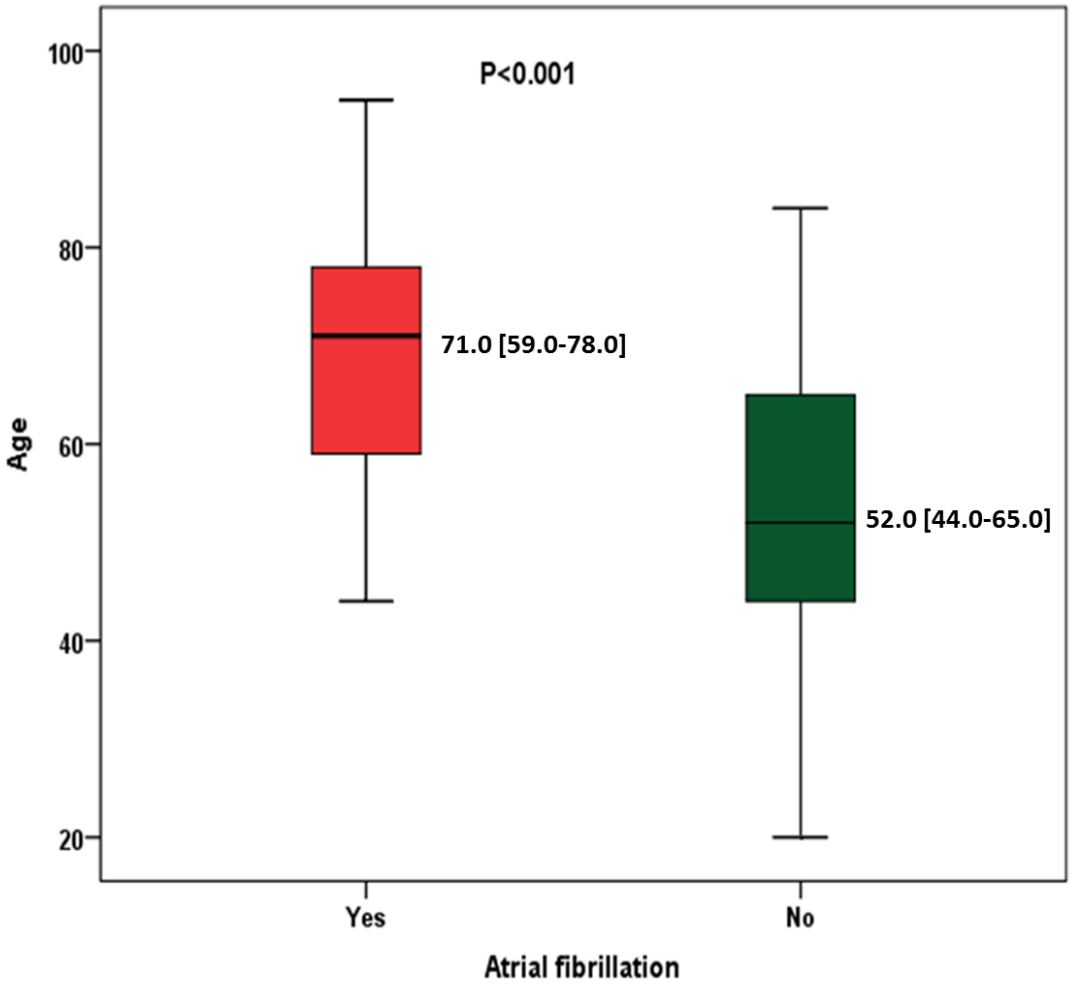


FIGURE 5.2 ASSOCIATION OF AGE WITH AF DETECTION
Median, Interquartile range and Range

b. Association of AF detection with the indication of test and mode of referral

For various symptoms, n (% within each group of indication), patients with palpitations had the highest detection rate for AF 30 (12.44%), followed by previous CVA 7 (9.33%) and dizziness 2 (6.89%) with chest pain and syncope having low detection rates at 1 (3.1%) and 2 (2.0%) respectively (P = 0.026), given below.

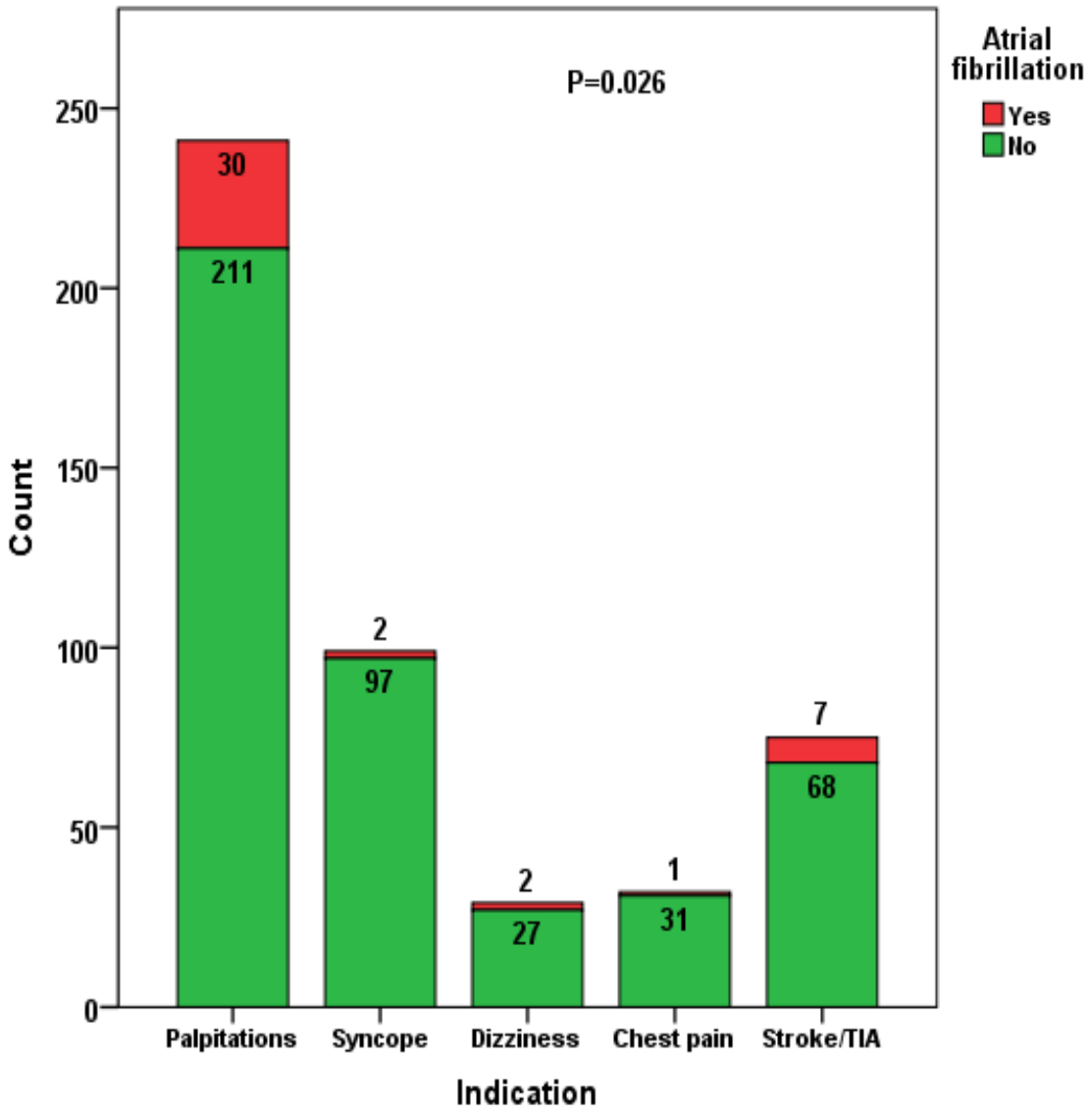


FIGURE 5.3 DETECTION OF ATRIAL FIBRILLATION WITH TEST INDICATION

There was no significant difference between the referral pathway and AF detection with, n (% within the group) for cardiology, medicine, GP being 19 (8.71), 19 (9.47), 4 (9.90), respectively, p=0.939, given below.

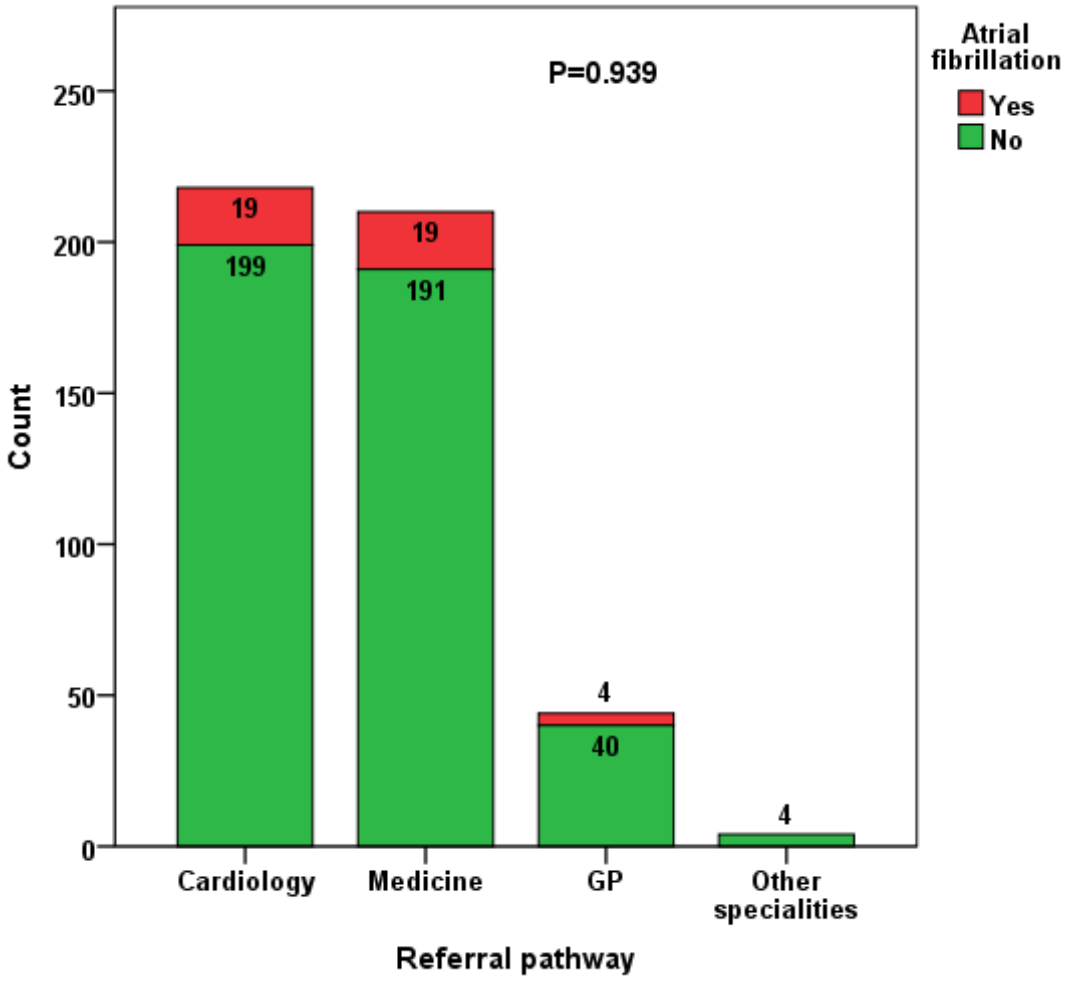


FIGURE 5.4 DETECTION OF AF PER REFERRAL PATHWAY

c. Duration of recording

In the cohort, the median [IQR] for the duration of recording in the AF group was 153.4 [133.7-166.0] hours and that in the non-AF group was 124.0 [115.0-127.5] hours. There was a significant difference between the two groups with p = 0.001.

d. Comorbidities

There was a significant difference between AF and non-AF group for Hypertension, n(%), 32 (76.1%) and 141 (32.4%), p<0.001, coronary artery disease 16 (40.4%) and 85 (19.5%), p=0.002, history of stroke or TIA 23 (54.7%) and 88 (20.2%), p<0.001 and valvular heart

disease 18 (42.8%), 54 (12.4%), p<0.001. Table 5.3 gives the association of AF with baseline characteristics and comorbidities.

TABLE 5.3 AF ASSOCIATION WITH BASELINE CHARACTERISTICS AND COMORBIDITIES

Variable	Total	AF	AF Not	P-value
Age, years, mean (SD)	56.4 (17.0)	69.81 (12.2)	53.1 (16.7)	**<0.001**
Female, n (%)	266 (56)	22 (52)	244 (56)	0.632
Hypertension, n (%)	173(36.3)	32 (76.1)	141 (32.4)	**<0.001***
Diabetes, n (%)	78 (16.3)	11 (26.2)	67 (18)	0.072
Coronary artery disease, n (%)	102 (21.4)	17 (40.4)	85 (19.5)	**0.002***
Hypercholesterolemia, n (%)	177 (37.1)	17 (40.4)	160 (36.8)	0.644
History of stroke or TIA, n (%)	111 (23.3)	23 (54.7)	88 (20.2)	**<0.001***
Valvular disease, n (%)	72 (15.1)	18 (42.8)	54 (12.4)	**<0.001***

5.2.2 Holter parameters

There was a significant difference between AF and non-AF group for the duration of recording, maximum heart rate, ≥10 sinus pauses/day, ≥ 50 SVE/day, presence of SVE runs and duration of SVE run. The table below shows the difference between AF and non-AF group for various Holter parameters.

TABLE 5.4 AF ASSOCIATION WITH HOLTER ECG PARAMETERS

Variable	Total	AF	No AF	P-value
Recording, hrs, median (IQR)	127.5 (116-152)	153.4 (133.7-166.0)	124.0 (115.0-127.5)	**0.001***
Mean Heart rate, bpm, mean (SD)	79.9 (13.3)	104.7 (13.0)	77.5 (11.2)	**0.001***
Max heart rate, bpm, mean (SD)	139.1 (18.2)	144.9 (12.4)	138.5 (18.6)	**0.004***
Min heart rate, bpm, mean (SD)	49.2 (8.3)	50.4 (10.5)	49.0 (8.1)	0.417
≥ 10 Sinus pauses/day (%)	77 (16.1)	26 (61.9)	51 (11.7)	**<0.001***
≥ 50 SVE/day (%)	156 (32.7)	36 (85.7)	120 (27.6)	**<0.001***
≥70 VE/day (%)	443 (93)	42 (100)	401 (92.3)	0.064
SVE runs, (%)	70 (14.7)	26 (61.9)	44 (10.1)	<**0.001***
Longest SVE run, mean (SD)	8.7 (4.0)	10.9 (2.8)	8.1 (4.0)	**<0.001***

5.3 Binary Logistic Regression Analysis

I performed binary logistic regression for various clinical variables like age, Hypertension, coronary artery disease, history of CVA, valvular disease and Holter variables like isolated duration of recording, mean and maximum heart rate, isolated SVE, SVE runs and sinus pauses. This is shown below.

TABLE 5.5 UNIVARIATE LOGISTIC REGRESSION ANALYSIS

Variables	OR	95% Confidence intervals		P-value
		Lower limit	Upper limit	
Age (per year increase)	1.08	1.06	1.11	**<0.001**
Hypertension	6.65	3.17	13.90	**<0.001**
Diabetes	1.94	0.93	4.07	0.077
Coronary artery disease	2.79	1.44	5.40	**0.002**
Hypercholesterolemia	1.16	0.61	2.22	0.644
Valvular disease	5.27	2.68	10.35	**<0.001**
Previous CVA/TIA	4.76	2.48	9.12	**<0.001**
Palpitations	3.44	1.65	7.18	**0.001**
Recording duration (per hour increase)	1.05	1.03	1.07	**<0.001**
≥10 Sinus pauses/day	12.2	6.13	24.27	**<0.001**
≥50 SVE/day	15.7	6.45	38.21	**<0.001**
Presence of SVE Runs	14.4	7.17	28.90	**<0.001**

OR: Odds ratio, VE: Supraventricular ectopic, SVE: supraventricular ectopic, VE: Ventricular ectopic, TIA: Transient ischemic attack, CAD: Coronary artery disease, SAE: significant atrial Ectopic activity.

5.4 Multivariate Logistic regression

Multivariate logistic regression was performed for Hypertension, previous CVA, valvular disease and palpitations through the Enter method. The results are described below in Table 5.6 and Figure 5.5.

TABLE 5.6 MULTIVARIATE LOGISTIC REGRESSION ANALYSIS				
Variables (Bootstrapped)	**OR**	**95% Confidence intervals**		**P-value**
		Lower limit	**Upper limit**	
Hypertension	2.54	1.08	8.61	**0.034**
Previous CVA	4.14	1.81	13.01	**0.001**
Valvular disease	5.07	2.48	18.70	**<0.001**
Palpitations	2.86	1.33	10.44	**0.015**

OR: Odds ratio, CVA: Cerebrovascular accident

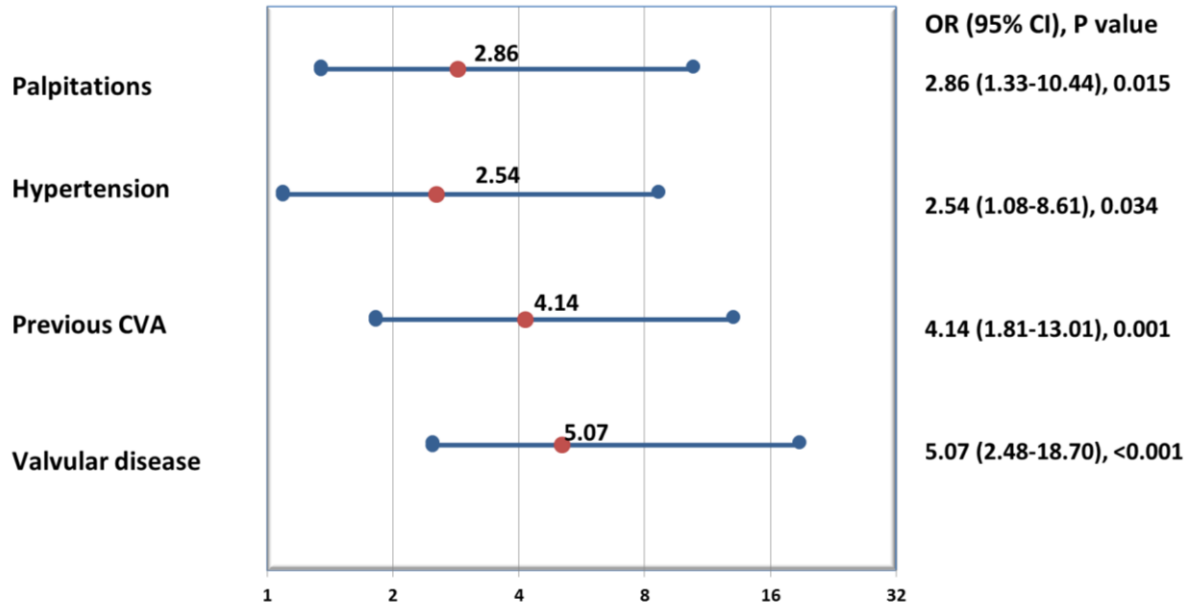


FIGURE 5.5 FORREST PLOT FOR CLINICAL VARIABLES ASSOCIATED WITH UNKNOWN AF

5.5 Model performance

The area under the curve (C statistic) for the multivariate model was 0.91 (95% CI 0.87-0.95) with individual C-statistics for each variable mentioned in Figure 5.6 and Table 5.7.

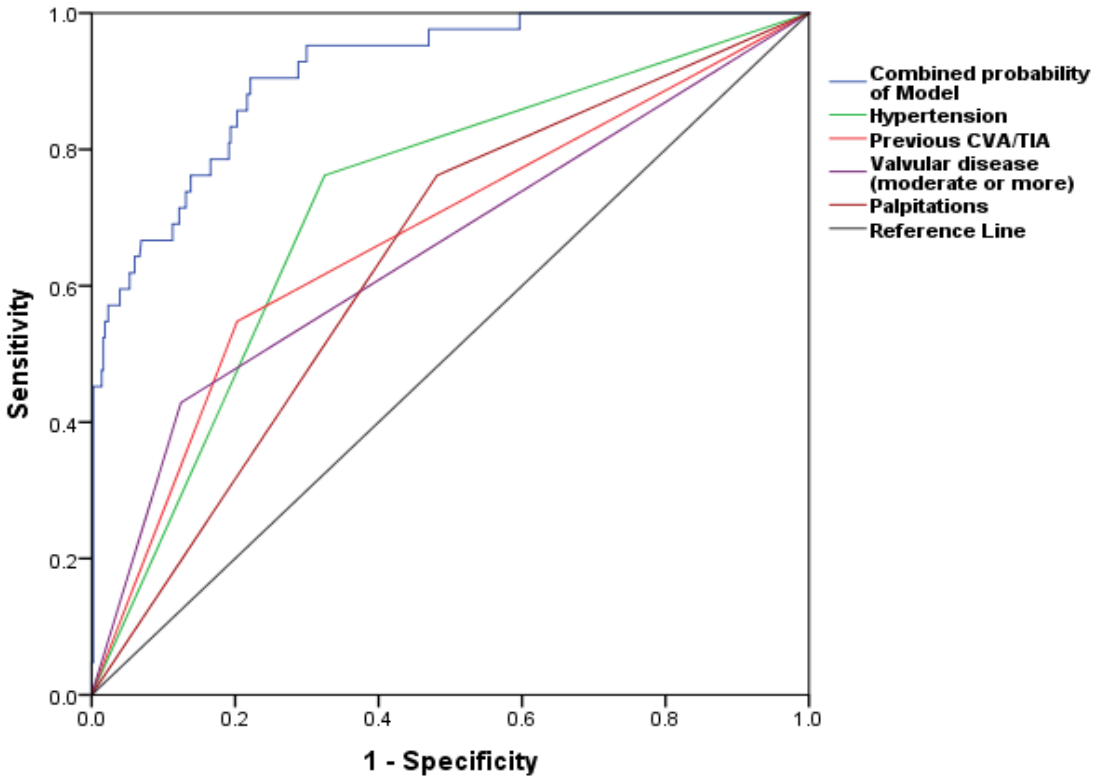


FIGURE 5.6 AUC PLOT SHOWING PREDICTIVE POWER OF THE COMBINED MODEL

TABLE 5.7 AUC FOR INDIVIDUAL VARIABLES AND COMBINED MODEL

Variable(s)	Area	95% CI Interval		Significance
		Lower	Upper	
Combined model	0.912	0.870	0.954	**<0.001**
Hypertension	0.719	0.639	0.798	**<0.001**
Previous CVA	0.672	0.580	0.765	**<0.001**
Valvular disease	0.652	0.555	0.749	**<0.001**
Palpitations	0.640	0.558	0.723	**0.003**

6 RESULTS FOR MONDAFIS DATASET

This chapter will describe the results related to the MonDAFIS dataset. As mentioned in the previous chapter, these results, until the publication of formal trial outcomes are strictly confidential and only for the review of the supervisors and examiners.

The definitions of various variables in the results have previously been explained in methods.

The results are explained under the following sub-chapters.

6.1 Baseline patient data

6.2 Holter ECG data

6.3 Association and dependency of AF with baseline patient and ECG dataset

6.4 Multivariate analysis, logistic regression and ROC analysis

6.1 Baseline patient data

The findings the baseline dataset are described in a subchapter due to the relevance, importance and its effect on the rest of the analysis.

This is explained as:

6.1.1 Patient characteristics

6.1.2 Stroke duration and severity and other associated symptoms.

6.1.3 Comorbidities

6.1.4 Relevant imaging investigations (Echocardiogram and Neurovascular imaging)

6.1.1 Patient characteristics

This includes all relevant data related to,

a. Age and gender
b. Height, weight and body mass index
c. Alcohol and Nicotine consumption

a. Age and gender

For the MonDAFIS cohort the median [IQR] of age, in years, was 67 [57-76]. Although on inspection of the age histogram this appears to be a bell-shaped distribution curve, however, a test of normality confirmed a non-normal distribution of the age for the complete dataset. 1018 (59.39%) of the patients were male.

b. Height, weight and BMI:

The mean [SD] are given for height 1.71m [0.09], weight 81.09 kg [17.06] and BMI 27.87 kg/m^2 [4.87]. These were normally distributed across the cohort.

c. Alcohol and Nicotine consumption

Definition of categories alcohol and nicotine intake has previously been described in methods. The number (%) of patients in each of the categories for alcohol and nicotine intake is given below.

TABLE 6.1 ALCOHOL AND NICOTINE INTAKE (N=1714)	
Alcohol consumption	**n (%)**
No	709 (41.4)
Occasional	748 (43.6)
Frequent	250 (14.6)
Nicotine consumption	**n (%)**
No nicotine history	852 (49.7)
Previous or current nicotine use	848 (49.5)

6.1.2 Details of index event

a. Duration and severity of stroke related symptoms

1198 (69.9%) of the patients had symptoms lasting for more than 24 hours before they presented to the stroke centre, followed by 435 (25.4%) of patients presenting between 1-24 hours. Only 75 (4.4%) patients presented within an hour of onset of symptoms.

The stroke severity was judged using the National Institute of Health Stroke Scale (NIHSS) and its median [IQR] was 2 [1-4]

b. Associated symptoms

The presence of palpitations, dizziness or pre-syncope was assessed. The reported symptoms could be more than one in a single patient.

The most commonly associated symptom was dizziness in a total of 490 (28.8%) occasions with palpitations in 285 (16.7%) and syncope or pre-syncope in 96 (5.6%) times. This is given below.

TABLE 6.2 FREQUENCIES OF OTHER ASSOCIATED SYMPTOMS

Symptoms	Frequent symptoms, n (%)	Occasional symptoms, n (%)	Total with Symptoms, n (%)	No symptoms, n (%)
Palpitations	50 (2.9)	239 (13.9)	289 (16.8)	1420 (82.8)
Dizziness	123 (7.2)	370(21.6)	493 (28.7)	1216 (70.9)
Presyncope	11 (0.6)	85 (5.0)	96 (5.6)	1613 (94.1)

6.1.3 Comorbidities

Various established pre-existing diagnosis (before the index event) or post-admission new diagnosis of hypertension, diabetes, coronary artery disease, heart failure syndrome, transient ischemic attack (TIA), stroke, intracranial bleed, peripheral arterial disease and renal impairment were assessed. The definitions of these are given in the methods section.

Although all patients in the study had an index event of TIA or ischemic stroke leading to current admission, the stroke and TIA mentioned in the comorbidities below are the diagnoses established before the current presentation. These findings are given in Table 6.3.

TABLE 6.3 COMORBIDITIES, DIAGNOSED BEFORE OR AFTER THE INDEX PRESENTATION, N=1714	
Comorbidities	**Total n (%)**
Arterial hypertension	1314 (76.7)
Diabetes	449 (26.2)
Heart failure	50 (2.9)
Ischemic stroke/TIA	331 (19.3)
Intracranial bleeding	26 (1.5)
Coronary artery disease	199 (11.6)
Peripheral arterial disease	68 (3.9)
Chronic renal insufficiency (eGFR<60)	132 (7.7)

Those with established or new heart failure were then categorised into their respective New York Heart Association (NYHA) classification. These are given below.

TABLE 6.4 NYHA CATEGORY FOR PATIENTS WITH ESTABLISHED HEART FAILURE, N=50	
NYHA Class	**Frequency, n (%)**
Class I	20 (1.2)
Class II	13 (0.8)
Class III	12 (0.7)
Class IV	3 (0.2)
Unknown	2 (0.1)

6.1.4 Echocardiographic findings

1371 (79.9%) out of 1714 patients in the interventional arm had echocardiography with 601 (35.1%) patient having transthoracic echo only, 251 (14.6%) with transoesophageal only and both (transthoracic and transoesophageal) in 519 (30.3%) patients. 323 (18.8%) of patients did not have any echocardiography.

The following data was collected during echo analysis:

a. Left Atrial diameter
b. Left atrial thrombus
c. Left ventricular systolic function
d. Left ventricular thrombus
e. Left ventricular regional wall motion abnormality
f. Patent foramen ovale
g. The aneurysmal appearance of the inter-atrial septum

a. **Left atrial diameter**

This was measured as the distance between the interatrial septum to the posterior wall of the left atrium. This data was available for 1249 patients and results are given in Figure 6.1.

b. **Left Atrial thrombus**

This variable was available for 1262 patients and LA thrombus visible in 10 (0.79%).

c. **Left ventricular systolic function**

This information was available for 1272 patients and is summarised in Figure 6.2.

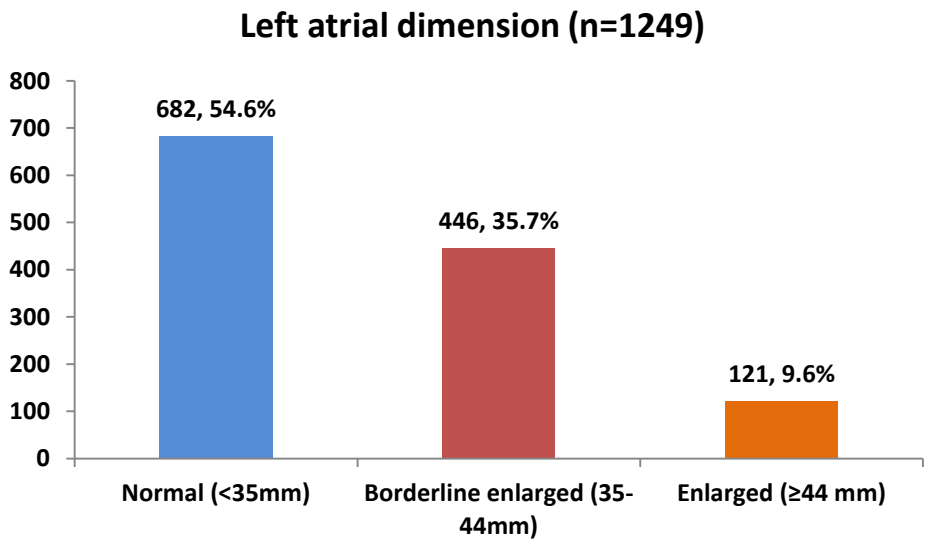


FIGURE 6.1 PROPORTION OF PATIENTS PER LA SIZE

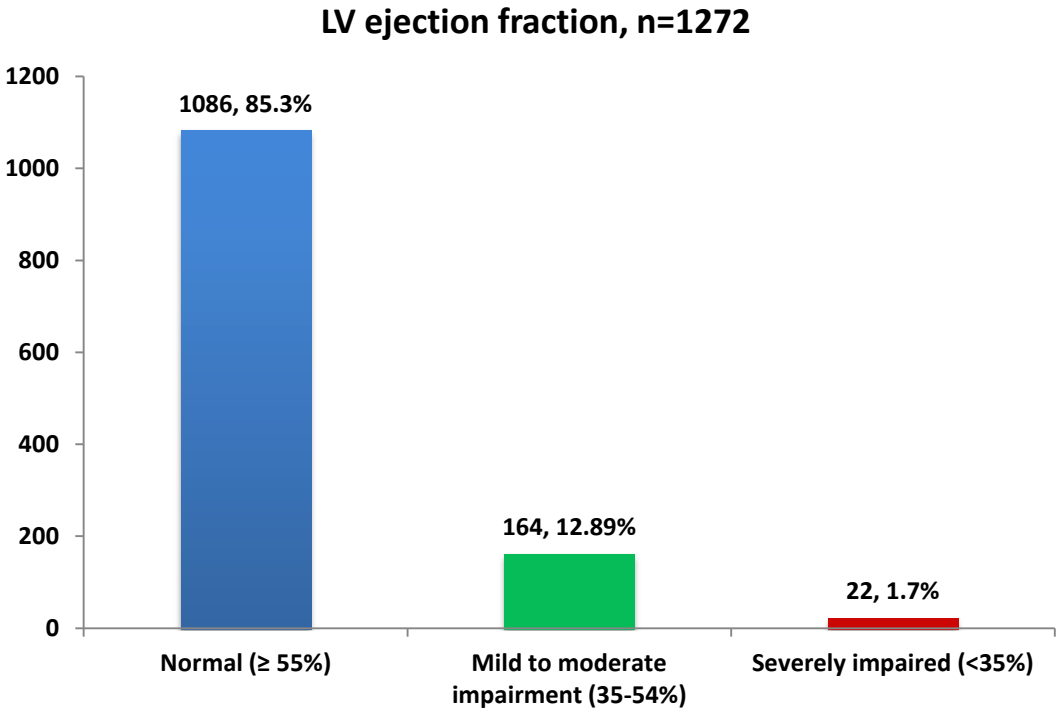


FIGURE 6.2 PROPORTION OF PATIENTS PER LV SYSTOLIC FUNCTION

d. **Left ventricular thrombus**

This data was available for 1341 patients. Left ventricular thrombus was reliably excluded in 1337 (99.69%) of patients with only 4 (0.29%) having confirmed LV thrombus.

e. **Left ventricular regional wall motion abnormality**

Regional wall motion abnormality data was available for 1335 patients, was seen in 77 (5.76%).

f. **Patent foramen ovale**

For 1184 patients for whom the data was available, the foramen ovale was confirmed to be patent in 221 (18.66%) patients.

g. **The aneurysmal appearance of the inter-atrial septum.**

An aneurysmal appearance of the inter-atrial septum is more likely to be seen in patients with a significant shunt between the atria. This was only seen in 64/1192 (5.36%) of patients.

6.2 Holter ECG baseline data

Holter ECG data was available for 1694 patients. It is desirable to know, among other things, the baseline 7-day Holter ECG characteristics for a large cohort of patients presenting immediately after an acute ischemic stroke. These Holter ECG findings, generalised in a large cohort, can provide a good baseline which can be considered *usual* or *normal* for such group of stroke patients. Moreover, it is also of academic interest as this description over such a large cohort of stroke patients has not been done before.

The following will be described

6.2.1 Duration of recording and ECG analysis

6.2.2 Heart rate parameters

6.2.3 Detection of AF

6.2.4 Atrial ectopic activity

6.2.5 Ventricular ectopic activity

6.2.6 Other parameters (pauses, artefacts)

6.2.1 Duration of recording and duration of analysis

The median [IQR] of the total duration of recording was 120.59 [73.31 – 166.14] hours. The median [IQR] of the duration of analysed recording was 96.97 [IQR 63.76 – 147.77] hours, which followed a left-skewed distribution.

623 (36.7%) of patients completed the whole 7-day of intended duration of the recording. While only 28 (1.6%) of patients had total Holter ECG monitoring done for less than 24

hours. 1050 (61.7%) of patients had the monitoring done between 24-144 hours. This is given in Figure 6.3.

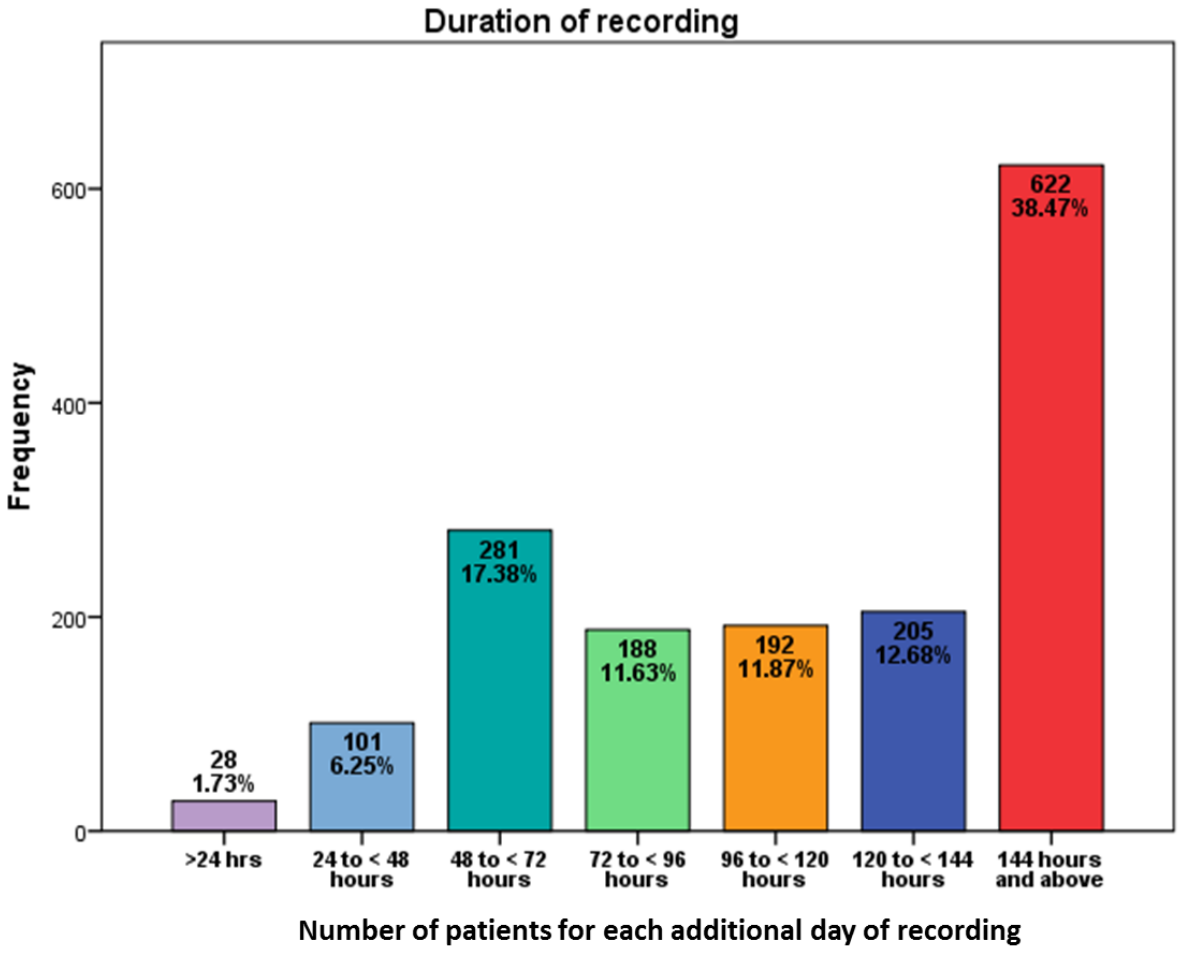


FIGURE 6.3 CASES WITH THEIR RESPECTIVE RECORDING DURATION IN DAYS

The total analysed recording was less than the duration of recording due to one of the following:

a. Accidental lead detachment

b. Interruption in recording for various tests, for example, MRI

c. Poor signal ECG trace/low voltage ECG due to lead positioning

d. Significant artefact burden

e. Improper Holter calibration/ equipment malfunction

6.2.2 Heart rate parameters

The median [IQR] for minimum heart rate and maximum heart rate was 51.0 [47.0-56.2] and 112.0 [100.0-125.0], respectively.

a. Tachycardia

252 (14.81%) of patients had episodes of tachycardia recorded in the first 24 hours and 487 (28.63%) in total duration of the recording. The mean number [SD] of individual tachycardia episodes for the first 24 hours and total recording were 15.54 [198.23] and 54.57 [440.71] respectively.

b. Bradycardia

341 (20.04%) patients had bradycardia recorded in the first 24 hours and 547 (32.15%) in total duration of the recording. The Mean [SD] of bradycardia episodes for the first 24 hours and total recording were 29.53 [129.11] and 129.36 [557.42], respectively.

6.2.3 Detection of AF

a. Overall AF detection

The total detection rate of AF was 78/1714 (4.5%). The median [IQR] for the AF episodes for complete recording was 3 [1-11]. The median [IQR] of the longest AF episode was 155.71 [6.56-703.97] mins.

b. AF detection per total recording duration

The detection of AF was assessed for each group of completed ECG recordings within every 24 hours up to 7-days. Of 28 patients who had a total duration of recording of 24 hours or less recording only 1 patient had their first and only AF episode detected (AF detection rate 3.5%). A further 4(3.92%) AF cases were detected in 101 recordings of up to 48 hours duration, and 14 (4.96%) cases in 281 recordings of up to 72 hours duration. 208 recordings of from 72 hours up to 96 hours revealed an additional 7 cases (AF detection rate 3.79%) and 212 recordings of up to 120 hours picked up an extra 4 cases (AF detection 1.88%). The highest AF detection was seen in patients having a recording of up to 144 hours with 13 (5.34%) patients out of a total of 243 and those completing >144 hours of monitoring 35(5.61%) out of 623 patients.

This is given in Table 6.5 and Figure 6.4.

TABLE 6.5 AF DETECTION RATE BASED ON THE DURATION OF MONITORING (N=1694)

Recording duration	AF Detected		Total	AF detection (%)
	Yes	No		
≤24 Hours	1	27	28	**3.57%**
>24 to ≤48 hours	4	97	101	**3.96%**
>48 to ≤72 hours	14	267	281	**4.98%**
>72 to ≤96 hours	7	201	208	**3.33%**
>96 to ≤120 hours	4	207	211	**1.89%**
>120 to ≤144 hours	13	230	243	**5.34%**
>144 hours	35	587	622	**5.62%**
Total	78	1616	1694	**4.60%**

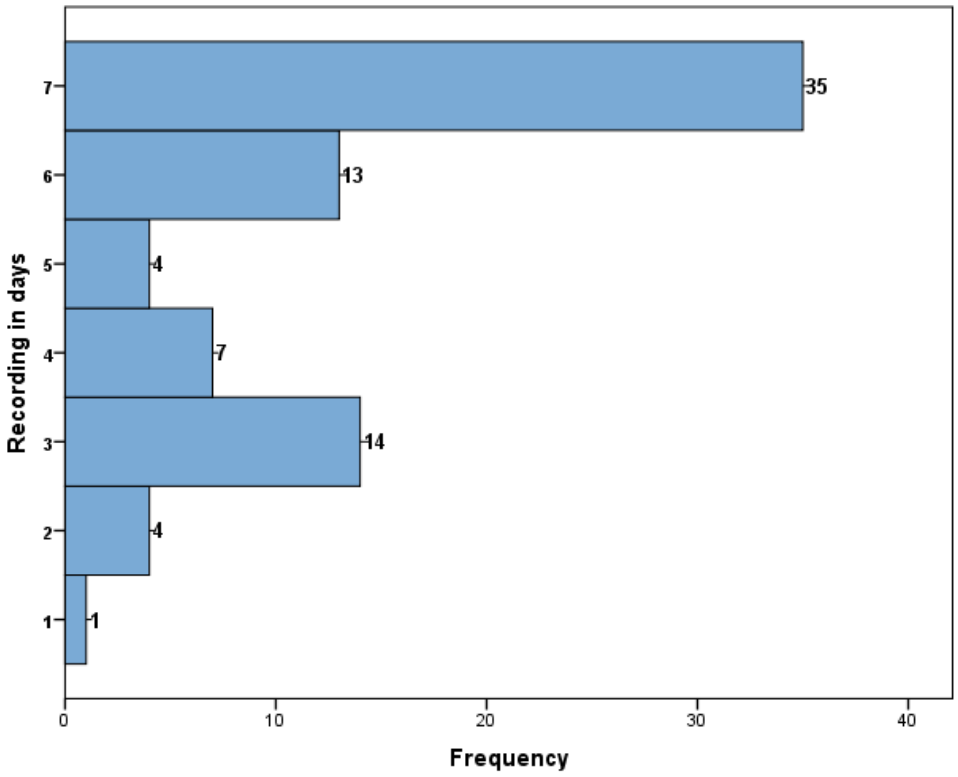


FIGURE 6.4 FIRST AF DETECTION FOR RECORDING DURATION IN DAYS

38 (2.2%) of patients had their first episode of AF detected within the first 24 hours of recording. A further 13 patients uring the 2nd 24 hour period increased the total detected AF to 51 (2.9%). For 3rd day further 8 cases were detected with a total of 59(3.4%) and on 4th day 15 new cases were found taking the total to 74 (4.3%). Only 2 more cases were found for 5th and 6th day of recording and no new cases were found for the 7th day.

TABLE 6.6 NEW AF DETECTION FOR EACH INCREMENTAL DAY (FOR COMPLETED RECORDINGS ONLY) (N=1694)			
Recording	**New AF detected N (%)**	**Cumulative AF**	**Cumulative AF detection(%)**
≤24 Hours	38 (48.71)	38 (48.71)	38 (2.24)
>24 to ≤48	13 (16.66)	51 (65.38)	51 (3.01)
>48 to ≤72	8 (10.25)	59 (75.64)	59 (3.48)
>72 to ≤96	15 (19.23)	74 (94.87)	74 (4.36)
>96 to ≤120	2 (2.56)	76 (97.43)	76 (4.48)
>120 to ≤144	2 (2.56)	78 (100)	78 (4.60)
>144 hours	0 (0)	78 (100)	78 (4.60)
Total	78 (100)	78 (100)	78 (4.60)

c. AF Burden

This is described as:

- Individual counts, daily trends and sum count of all AF episodes
- Average and longest durations of AF for each day

- **Individual counts, daily trends and sum count of all AF episodes**

A total of 27 (34.2%) of patients with detected AF had only 1 episode of AF for the entire duration of the recording. A further 24 (30.4%) patients had between 2-5 episodes. 7 (8.9%) had between 6-10 episodes. 9 (11.4%) had between 11-20 episodes, 8 (10.1%) had between 21-50 episodes. Only 5 (5.4%) patients had more than 50 episodes of AF, given in Table 6.6.

TABLE 6.6 NUMBER OF AF EPISODES PER TOTAL NUMBER OF CASES WITH AF (N=1694)	
Number of AF episodes	**Number of cases (%)**
1	26 (33.3)
2-5	24 (30.8)
6-10	7 (9.0)
11-20	9 (11.5)
21-50	8 (10.3)
51-100	1 (1.3)
101-200	1 (1.3)
>200	2 (2.6)
Total	78 (100)

- **Average and longest durations AF episodes for each day**

Median duration [IQR] of the longest AF episode in AF patients was 156.83 [10.25-702.45]. AF burden was further reported as the average duration of all AF episodes for each of the days of recording which is given in Table 6.7.

TABLE 6.7 MEAN DURATION OF AF EPISODES FOR EACH DAY AND TOTAL RECORDING	
Duration of recording	**The average duration of AF episodes (mins) Mean (SD)**
≤24 Hours	260.88 (1202.11)
>24 to ≤48 hours	99.17 (403.57)
>48 to ≤72 hours	57.37 (218.81)
>72 to ≤96 hours	195.20 (853.87)
>96 to ≤120 hours	8.03 (39.56)
>120 to ≤144 hours	1.15 (5.61)
>144 hours	2.32 (14.53)
Total recording	89.16 (219.83)

6.2.4 Atrial Ectopic activity

This is described separately for the first 24 hours and the total duration of the recording. This is further described as the following types.

a. Isolated supraventricular ectopics (SVE)

b. SVE couplets

c. SVE runs

a. Isolated Supraventricular ectopics (SVE)

A total of 1659 (97.93%) of cases had isolated SVEs during first 24 hours of recording and 1677 (98.99%) of cases had isolated SVEs during the total recording. The median and interquartile range of isolated atrial ectopics were 50 (IQR 14-253) for the first 24 hours and 211 (IQR 59-1248) for the whole duration of the recording.

Overall the proportion of SVE beats to the beat count for first 24 hours and or total recording was, mean (SD), 0.593 (SD 1.81) and 0.64 (SD 1.96) respectively. ROC curve was used to define the optimal cut-off for SVE ectopics which stands at ≥ 66 SVE ectopics. 742 (43.80%) patients had ≥ 66 SVE ectopics for the first 24 hours of recording.

b. Supraventricular ectopic (SVE) couplets

SVE couplets were recorded for 1155 (68.18%) patients during the first 24 hours and 1449 (85.53%) patients during the total recording. Median and interquartile range of SVE couplet is 2 (IQR 0-8) for the first 24 hours and 8 (IQR 2-34.5) for the whole duration of the recording. The optimum cut-off for AF detection using ROC curve was ≥ 3 SVE couplets. 750 (44.27%) of patients had ≥ 3 SVE couplets during first 24 hours of recording.

c. Supraventricular (SVE) runs

SVE run counts

931 (54.95%) of patients had SVE runs in the first 24 hours while 1278 (75.44%) of all cases had SVE runs. The median and interquartile range of number SVE runs during the first 24 hours of recording and the total duration of recording are 1 (IQR 0-3) and 3 (IQR 1-13) respectively. The optimum cut-off for SVE run was ≥ 25/day. This was seen in 84 (4.95%) patients for the first 24 hours of recording.

Longest SVE run duration

The median and interquartile range for the number of supraventricular ectopic runs (SVE runs) during first 24 hours of recording and the total duration of the recording is 1.02 (IQR 0.00-2.50 and 2.23 (IQR 0.75-4.49) respectively. The optimum cut-off was found to be ≥ 2.5 seconds which was seen in 423(24.97%) patients in the first 24 hours.

6.2.5 Ventricular ectopic activity

This is described for the first 24 hours and the total duration of the recording. It is explained under the following variables

a. Isolated ventricular ectopics
b. Ventricular couplets and triplets and short runs
c. Ventricular tachycardia
d. Bigeminy and trigeminy

a. Isolated ventricular ectopics (VE)

They were present in 1498 (88.42%) patients records for the first 24 hours and 1632 (96.34%) for the total duration of the recording.

Overall, the mean (SD) of the proportion of VE beats to the beat count for 24 hours and the total duration of recording was 0.44 (SD 1.28) and 0.44 (SD 1.33) respectively. The optimal cut-off for isolated VE was ≥ 36 and was seen in 712 (42.03%) patients in the first 24 hours.

b. Ventricular Couplets, triplets and short runs.

The frequency (%) and of ventricular couplets, triplets and short ventricular runs for first 24 hours was 476 (27.98%), 155 (11.06%) and 97 (5.70%) and for the complete recording was the frequency was 794 (46.67%), 346 (20.34%) and 256 (15.04%) respectively.

The longest ventricular run (sec) was seen in a total of 97 (5.70%) cases seen in the first 24 hours and 256 (15.04%) for the total duration of the recording.

c. Ventricular tachycardia (VT)

The frequency of ventricular tachycardia (VT) for the first 24 hours was 28 (1.64%) and for the complete recording was 86 (5.05%).

d. Bigeminy and trigeminy

The frequency of bigeminy and trigeminy for first 24 hours was 236 (13.87%) and 243 (14.28%), while, for the complete recording was 403 (23.69%) and 398 (23.39%) respectively.

6.2.6 Miscellaneous

Pauses

Pauses were seen in 35 (2.05%) patients in the first 24 hours and 82 (4.82%) in the total recording. Mean (SD) of pauses for the first 24 hours and total recording were 0.71 (17.48) and 2.04 (35.29) respectively.

Artefacts

Artefacts were seen regardless of duration in all patients for the first 24 hours and the total duration of the recording. Median [IQR] artefact duration for the first 24 hours was 13.82 [2.33-66.70] mins and *28.99 [11.65-96.54] min for total recording.*

6.3 Association and dependency of AF

This subsection shall discuss whether there is an association between a baseline clinical or Holter ECG variable with AF.

6.3.1 Association with baseline data

The comparison between the AF and non-AF group, based on detection through the Holter ECG monitoring, for their baseline and clinical characteristics, is given in Table 6.8

a. Baseline characteristics

There is a significant difference between AF and non-AF group with respect to the age. The median age [IQR] for AF group and the non-AF group is 76.00 [69.00-79.00] and 66.50 (57.00-76.00), p <0.001 respectively. There was no difference between the two groups based on gender, height, weight or BMI.

b. Alcohol and Nicotine Consumption

There was no difference between the AF and non-AF groups for Alcohol and Nicotine consumption as described below.

c. Association with comorbidities

There was a significant difference between AF and non-AF group for hypertension, diabetes, and renal insufficiency. No difference could be seen for coronary artery disease, peripheral vascular disease, previous ischemic stroke or TIA, heart failure or intracranial bleed.

TABLE 6.8 PATIENT CHARACTERISTICS AND COMORBIDITIES WITH AF					
Variable		**Total (n=1714)**	**AF Detected (n=78)**	**AF Not detected (n=1636)**	**P-value**
Clinical Parameters					
Age, years, median (IQR)		67 (57.0-76.0)	76 (69.0-79.0)	66 (57.0-76.0)	**<0.001***
Male, n (%)		1018 (58.9)	43 (55.1)	975 (59.5)	0.425
Height, m, median (IQR)		1.7 (1.6-1.8)	1.7 (1.6-1.8)	1.7 (1.6-1.8)	0.244
Weight, kg, median (IQR)		80.0 (70.0-91.0)	78.5 (68.0-90.5)	80.0 (70.0-91.0)	0.537
BMI, kg/m^2, median (IQR)		26.9 (24.2-30.0)	27.2 (24.5-29.7)	26.7 (24.2-33.6)	0.720
History of alcohol intake, n(%)	*Occassional*	745 (43.9)	34 (43.0)	711 (43.9)	0.818
	Regular	249 (14.7)	10 (12.7)	239 (14.8)	
	No intake	704 (41.5)	35 (44.3)	669 (41.3)	
History of Nicotine intake, n(%)	*Current/Ex*	844 (49.7)	34 (43.0)	810 (50.0)	0.337
	Non smoker	845 (49.8)	44 (55.7)	801 (49.5)	
Hypertension, n (%)		1314 (76.7)	69 (88.4)	1245 (76.1)	**0.012***
Diabetes, n (%)		449 (26.1)	28 (35.8)	421 (25.7)	**0.046***
Coronary artery disease, n (%)		199 (11.6)	14 (17.9)	185 (11.3)	0.074
PVD, n (%)		68 (4.0)	4 (5.1)	64 (3.8)	0.591
Heart failure, n(%)		50 (2.9)	3 (3.8)	47 (2.9)	0.618
History of stroke or TIA, n (%)		331 (19.3)	18 (23.1)	313 (19.1)	0.389
History of Intracranial bleed, n(%)		26 (1.5)	2 (2.5)	24 (1.5)	0.439
Renal insufficiency, n (%)		132 (7.7)	16 (20.5)	116 (7.1)	**<0.001***

6.3.2 Association with stroke severity, duration and related symptoms

a. Duration of stroke symptoms

There was no significant difference between in AF and non-AF group with regards to the duration of stroke-related symptoms.

TABLE 6.9 ASSOCIATION OF AF WITH THE DURATION OF STROKE SYMPTOMS				
Duration of stroke symptoms	**Total, n(%)**	**AF, n(%)**	**No AF, n(%)**	**P-value**
<1 Hr	74 (4.4)	3 (4.1)	71 (4.4)	0.412
1-24 hours	432 (25.4)	14 (17.7)	418 (25.8)	
More than 24 hours	1191 (70.1%)	62 (78.5)	1129 (69.7)	
Unknown	1 (0.1)			

b. Stroke severity (NIHSS)

NIHSS stroke scale recorded at the time of recruitment in the trial, showed no significant difference between AF and non-AF group, with a mean (SD) of 3.61 (3.57) and 3.06 (3.00), respectively with p=0.186.

c. Associated symptoms

These symptoms include palpitations, dizziness and syncope/presyncope. There was no difference for symptoms between AF and non-AF group, given in Table 6.10

TABLE 6.10 ASSOCIATION OF AF WITH OTHER ASSOCIATED SYMPTOMS, N=1709				
Symptoms	**AF, n (%)**	**No AF, n (%)**	**Total, n (%)**	**P-value**
Palpitations	18 (22.78)	271 (16.48)	289 (16.77)	0.137
Dizziness	29 (36.70)	464 (28.45)	493 (28.84)	0.096
Syncope/ Presyncope	5 (6.32)	91 (5.61)	96 (5.65)	0.660

6.3.3 Relationship of AF with echocardiographic parameters

An association of AF with various echocardiographic parameters was checked. These parameters are given below.

a. Left Atrial diameter
b. Left atrial and ventricular thrombus
c. Left ventricular systolic function
d. Left ventricular regional wall motion abnormality
e. Patent foramen ovale and aneurysmal appearance of the interatrial septum.

a. AF and left atrial diameter

There was a significant difference between AF and non-AF groups for their left atrial size. In total, the data was available for 1249 patients, out of which for AF and non-AF group, the mild dilatation of LA was seen in 27 (44.2) and 419 (37.4) and severely dilated LA was seen in 10 (14.1) and 111 (9.9), p=0.018, respectively.

b. AF and left atrial and ventricular thrombus

There was no significant difference for LA and LV thrombus between AF and non-AF group. Interestingly, LA thrombus was only seen in 10 cases and all of these were non-AF. This effect, however, was no statistically significant.

c. Left ventricular (LV) systolic function

There was a significant difference between AF and non-AF groups for the left ventricular systolic function. The data was available for 1272 patients, out of which for AF and non-AF group, the mild to moderate LV systolic dysfunction was seen in 17 (27.8) and 147 (12.1) and severely impaired LV systolic function was seen in 2 (3.2) and 20 (1.6), p=0.001, respectively.

d. Left ventricular regional wall motion abnormality (RWMA)

There was no significant difference for LV regional wall motion abnormality between AF and non-AF groups.

e. Patent foramen ovale and aneurysmal interatrial septum

There was no significant difference for both patent foramen ovale and aneurysmal interatrial septum between AF and non-AF groups. This is given in Table 6.11.

TABLE 6.11 ASSOCIATION OF AF WITH ECHO PARAMETERS					
Echocardiographic parameters		**AF, n (%)**	**No AF, n (%)**	**Total, n (%)**	**P-value**
LA diameter	*Normal (<35mm)*	24/61 (39.3)	658/1118 (58.8)	682/1249 (54.6)	**0.018**
	Mildly dilated (35-44 mm)	27/61 (44.2)	419/1118 (37.4)	446/1249 (35.7)	
	Severely dilated (>45 mm)	10/61 (14.1)	111/1118 (9.9)	121/1249 (9.6)	
LA thrombus		0/56	10/1206 (0.8%)	10/1262 (0.8%)	0.497
LV systolic function	*Normal (EF ≥ 55%)*	42/61(68.8)	1044/1211 (86.2)	1086 (85.3)	**0.001**
	Mild-moderately impaired (EF 31-54%)	17/61 (27.8)	147/1211 (12.1)	164 (12.8)	
	Severely impaired (EF ≤30%	2/61 (3.2)	20/1211 (1.6)	22 (1.7)	
LV thrombus		0/60	4/1281 (0.3)	4/1341 (0.3)	0.290
LV Regional wall abnormality		3/59 (5.0)	73/1276 (5.7)	76/1335 (5.7)	0.144
Patent foramen ovale		8/52 (15.3)	210/1132 (18.5)	218/1184 (18.4)	0.544
Aneurysmal Inter atrial septum		2/52 (3.8)	63/1140 (5.5)	65/1192 (5.7)	0.564

6.3.4 Association of AF with Holter ECG parameters

This shall be described for the following parameters

a. Duration of recording and ECG analysis
b. Heart rate parameters
c. Supraventricular ectopic activity
d. Ventricular ectopic activity

The last 3 parameters will be compared for AF and non-AF group with the first 24 hours of recording as well as the whole recording.

a. The total duration of the recording

AF group had a higher median [IQR] 142.17 [78.67-166.28] as compared to the non-AF group, 120.33 [73.30-166.09] but the difference was not statistically significant p=0.410.

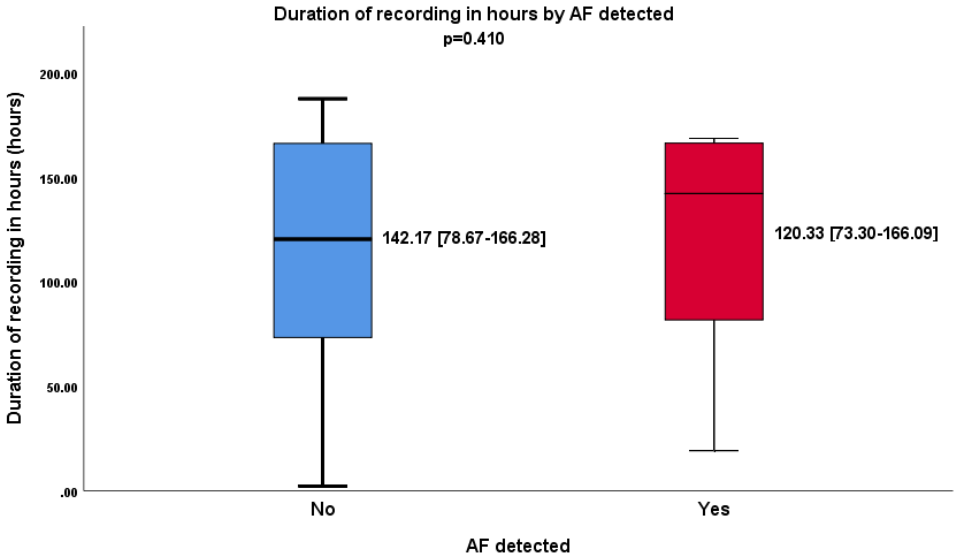


FIGURE 6.5 AF STATUS WITH THE DURATION OF RECORDING

b. Maximum and minimum Heart rate

Maximum and minimum heart rate parameters were only available for the complete duration of recording but not for individual days. There was a significant difference for the maximum heart rate between AF and non-AF group median [IQR] 132.93 [115.00-154.00 and 111.09 [100.00-124.00], p<0.001. There was no difference in the minimum heart rate.

Tachycardia

Tachycardia was seen in the first 24 hours in 33 (41.77%) patients in AF group and 219 (13.50%) in non-AF group, p<0.001 and for the total recording 63 979.74%) in AF group and 424 (26.14%) in the non-AF group, p<0.001.

Bradycardia

Bradycardia was present in 20 (25.31) patients in AF group and 321 (19.79) in the non-AF group, p=0.249. For the total recording bradycardia was seen in 32 (40.50%) patients in the AF group and 515 (31.75%) in the non-AF group, p=0.104.

c. Supraventricular Ectopic (SVE) Activity

Supraventricular ectopic activity is assessed for the first 24 hours as well as the whole duration of the recording.

- Isolated atrial ectopics (count)
- Supraventricular couplet (count)
- Supraventricular ectopic run (count)
- Longest supraventricular ectopic run (in seconds)

All of this data was non- normally distributed and Man-Whitney U test was applied to test the difference between AF and non-AF group for each of these variables.

Isolated supraventricular ectopics (SVE)

For isolated SVE beat counts for the first 24 hours of recording, between AF and non-AF groups, the median [IQR] was 731 [89.00-2523.00] and 46 [13.00-212.25], $p<0.001$. For total recording this was 3425.0 [526.00-13351.00] and 193.50 [57.00-1009.70], $p<0.001$, respectively.

Supraventricular couplets

For supraventricular couple counts for the first 24 hours of recording, between AF and non-AF groups, the median [IQR] was 14 [3.00-143.00] and 2 [0-7.00], $p<0.001$. For total duration of recording this was 137.00 [19.00-756.00] and 7.00 [2.00-28.00], $p<0.001$, respectively.

Supraventricular ectopic run counts

For SVE run counts for the first 24 hours of recording, between AF and non-AF groups, the median [IQR] was 6 [1.00-41.00] and 1 [0-3.00], p<0.001. For total duration of recording this was 34.00 [6.00-186.00] and 3.00 [0.00-11.00], p<0.001, respectively.

Longest supraventricular ectopic run (in seconds)

For longest SVE run for first 24 hours of recording, between AF and non-AF groups, the median [IQR] was 2.81 [1.05-5.48] seconds and 0.97 [0.00-2.35] seconds, p<0.001. For total duration of recording this was 5.51 [2.64-15.04] seconds and 2.14 [0.00-4.24] seconds, p<0.001, respectively.

d. Ventricular ectopic activity

Ventricular ectopic activity is assessed for the first 24 hours as well as the whole duration of the recording.

- Isolated ventricular ectopics (count)
- Ventricular couplet (count)
- Ventricular triplets (count)
- Ventricular ectopic run (count)
- Longest ventricular ectopic run (in seconds)

All of this data was non- normally distributed and Man-Whitney U test was applied to test the difference between AF and non-AF group for each of these variables. Where the median [IQR] is too low, the mean [SD] is reported.

Isolated ventricular ectopics (VE)

For isolated VE beat counts for the first 24 hours of recording, between AF and non-AF groups, the median [IQR] was 77.00 [15.00-831.00] and 17.00 [2.00-151.50], p<0.001. For total duration of recording this was 660.00 [110.00-4070.00] and 73.50 [9.75-728.25], p<0.001, respectively.

Ventricular couplets

For ventricular couplet counts for the first 24 hours of recording, between AF and non-AF groups, the mean [SD] was 29.33 [109.62] and 9.10 [63.70], p<0.001. For the total duration of recording, this was 91.58 [304.00] and 39.26 [296.54], p<0.001, respectively.

Ventricular triplets

For ventricular triplet counts for the first 24 hours of recording, between AF and non-AF groups, the mean [SD] was 1.63 [7.03] and 0.74 [9.56], p<0.001. For the total duration of recording, this was 5.82 [18.14] and 3.20 [37.24], p<0.001, respectively.

Ventricular ectopic run counts

Ventricular ectopic runs were quite infrequent in the whole cohort. Because of this, it is not possible to draw any conclusion for the association between ventricular ectopic runs and AF. For VE run counts for the first 24 hours of recording, between AF and non-AF groups, the mean [SD] was 0.95 [6.60] and 0.30 [4.96], p=0.787. For the total duration of recording, this was 2.15 [12.67] and 1.14 [15.75], p<0.001, respectively.

Longest Ventricular ectopic run (in seconds)

For VE run counts for the first 24 hours of recording, between AF and non-AF groups, the median [IQR] was 2.81 [1.05-5.48] and 0.97 [0.00-2.35], p<0.001. For total duration of recording this was 5.51 [2.64-15.04] and 2.14 [0.00-4.24], p<0.001, respectively,

Pauses and artefacts

During the first 24 hours of recording 5/79 (6.32%) in the AF and 30/1622(1.84%) in the non-AF group had pauses, p=0.021. For the total duration of recording 14/79(17.72) in the AF and 68/1622 (4.19) in the non-AF group had paused, p<0.001.

Presence of Artefact and artefact burden was unrelated to AF detection.

TABLE 6.12 ASSOCIATION OF AF WITH HOLTER ECG VARIABLES			
Variable	**AF detected**	**AF not detected**	**P-value**
Duration of recording, hrs, med (IQR)	142.1 (78.6-166.2)	120.3 (73.3-166.1)	**<0.001**
Max heart rate, bpm, med (IQR)	132.9(115.0-154.0)	111.1(100.0-124.0)	**<0.001**
Tachycardia 1st 24 hrs, n(%)	33 (41.7)	219 (13.5)	**<0.001**
Tachycardia total, n (%)	63 (79.7)	424 (26.1)	**<0.001**
Bradycardia 1st 24 hrs, n(%)	20 (25.31)	321 (19.79)	0.249
Bradycardia total, n (%)	32 (40.5)	515 (31.7)	0.104
Isolated SVE 1st 24 hrs, med (IQR)	731 (3.0-141.0)	46 (13.0-212.2)	**<0.001**
Total SVE, med (IQR)	3425 (526-13351)	193.5 (57-1009.7)	**<0.001**
SVE couplets, 1st 24 hrs, med (IQR)	14 (3.0-143.0)	2 (0-7.0)	**<0.001**
SVE couplet total, med (IQR)	137.0 (19.0-756.0)	7 (2.0-28.0)	**<0.001**
SVE run 1st 24 hrs, med (IQR)	6 (1.0-41.0)	1 (0-3.0)	**<0.001**
SVE run 1st total, med (IQR)	34 (6.0-136.0)	3 (0-11.0)	**<0.001**
Max SVE, sec, 1st 24 hrs, med (IQR)	2.81 (1.05-5.4)	0.97 (0-2.4)	**<0.001**
Max SVE run, sec, total, med (IQR)	5.51 (2.6-15.0)	2.1 (0-4.2)	**<0.001**
Isolated VE, 1st 24 hrs, med (IQR)	77.0 (15.0-831.0)	17.0 (2.0-151.5)	**<0.001**
Isolated VE, 24 hrs, med (IQR)	660.0 (110.0-4070)	73.5 (9.7-728.2)	**<0.001**
VE couplets, 1st 24 hrs, mean (SD)	29.3 (109.6)	9.1 (63.7)	**<0.001**
VE couplets, total, mean (SD)	91.5 (304.0)	39.2 (295.5)	**<0.001**
VE triplets, 1st 24 hrs, mean (SD)	1.63 (7.0)	0.74 (9.5)	**<0.001**
VE triplets, total, mean (SD)	5.8 (18.1)	3.2 (37.2)	**<0.001**
VE run, 1st 24 hrs, mean (SD)	0.95 (6.6)	0.3 (4.9)	**0.787**
VE run, total, mean (SD)	2.15 (12.6)	1.1 (15.7)	**<0.001**
Pauses, 1st 24 hrs, n (%)	5 (6.3)	30 (1.8)	**0.021**
Pauses, Total, n (%)	14 (18.2)	68 (4.2)	**<0.001**

6.4 Logistic regression analysis

All the significant variables from association testing (chi-square, T-Test and Mann Whitney U) will go through Binary Logistic regression analysis.

6.4.1 Binary Logistic regression for clinical variables and imaging data

These results are given in Table 6.13. In summary, each year increase in age was associated with an odds ratio [95% CI, p-value] of 1.07 [1.04-1.09, p<0.001. Age ≥ 70 had OR [95% CI, p-value] of 3.60 [2.16-5.99, p<0.001]. Presence of hypertension, diabetes and renal impairment have odds ratio [95% CI, p-value] of 2.39 [1.18-4.84, p0.015], 1.65 [1.03-2.64, p=0.036] and 3.29 [1.84-5889, p<0.001] respectively.

TABLE 6.13 UNIVARIATE LOGISTIC REGRESSION ANALYSIS FOR CLINICAL AND ECHO DATA

Variables	OR	95% Confidence intervals		P-value
		Lower limit	Upper limit	
Age (per year increase)	1.07	1.04	1.09	**<0.001**
Age ≥ 70	4.04	2.41	6.79	**<0.001**
Hypertension	2.40	1.19	4.86	**0.014**
Diabetes	1.61	1.00	2.60	**0.048**
Renal impairment	3.38	1.89	6.04	**<0.001**
Severe LA dilatation	2.02	1.01	4.03	**0.046**
Severe LV systolic dysfunction	2.12	0.48	9.26	0.315

6.4.2 Binary Logistic regression for Holter ECG data

Each significant Holter ECG variable previously identified in the previous section will be assessed through binary logistic regression.

This includes

1. Maximum heart rate
2. Supraventricular ectopic activity
    a. Isolated ectopics
    b. SVE couplets
    c. SVE runs (number and duration)
3. Ventricular ectopic activity
    a. Isolated ventricular ectopics
    b. Couplets and Triplets

The ventricular runs were not in a considerable proportion of patients to give reliable results and will be omitted from the binary logistic regression analysis.

a. Maximum heart rate and tachycardia episodes:

Every 10 beats per minute increase in the maximum heart rate was associated with an AF OR 1.53 (95% CI 1.41-1.65, $p<0.001$). Patients with 1 or more episode of tachycardia (HR>100) were more likely to have AF, had an OR 4.46 (95% CI 2.77-7.16, $p<0.001$). For a cut-off of maximum HR ≥125/min, the OR for AF was 5.61 (95% CI 3.45-9.11, $p<0.001$)

b. Supraventricular ectopic activity parameters

Just the presence of SVE ectopic was not associated with AF. Moreover, there was no meaningful correlation with a unit increase in SVE ectopic activity with AF detection. Optimal cut off for isolated SVE ectopic was identified by observing the ROC curve through maximum sensitivity and minimum 1-specificity.

For isolated SVE ectopics, the cut-off was found to be ≥ 66/day. ≥66 SVE ectopics per first 24 hours were associated with OR 6.32 (95% CI 3.51-11.37, p<0.001) for AF.

SVE couplets if present in the first 24 hours, has an odds ratio of 3.72 95% (95% CI 1.85-7.55, p<0.001) for AF detection. After applying a cut-off for ≥ 3 SV couplets, the OR becomes 5.67 (95% CI 3.20-10.06, P<0.001).

SVE runs if present, in the first 24 hours, has an odds ratio of 3.07 (95% CI 1.78-5.31, p<0.001) for AF detection. After applying a cut-off for ≥ 25 SVE couplets, the OR becomes 10.66 (95% CI 6.15-18.47, P<0.001). For SVE runs lasting for ≥ 2.5 seconds the OR for AF detection is 5.00 (95% CI 3.13-7.98, P<0.001)

c. Ventricular ectopic activity parameters

Just the presence of VE was no significant. For isolated VE ectopics, the optimal cut-off was found to be ≥ 36/day. ≥36 VE ectopics per day were associated with OR (95% CI, p-value) 2.89 (1.79-4.68, p<0.001) for AF. Presence of VE couplets and triplets had an OR (95% CI, p-value) of 2.57 (1.62-4.06, p<0.001) and 3.23 (1.85-5.64, p<0.001) respectively.

d. Pauses

Presence of pauses did not have any significant association with AF through the logistic regression analysis, OR 2.85 (95% CI 0.98-8.32, p=0.054).

These results are summarised in Table 6.14 and Figure 6.6

TABLE 6.14 UNIVARIATE LOGISTIC REGRESSION ANALYSIS FOR HOLTER ECG VARIABLES				
Variables	**OR**	**95% Confidence intervals**		**P-value**
		Lower limit	**Upper limit**	
Maximum HR (for 10 bpm increase)	1.53	1.41	1.65	**<0.001**
Maximum HR ≥ 125//min	5.61	3.45	9.11	**<0.001**
Tachycardia 1 episode or more	4.46	2.77	7.16	**<0.001**
≥66 SVE/day	6.32	3.51	11.37	**<0.001**
SVE Couplets	3.74	1.85	7.55	**<0.001**
≥3 SVE Couplets	5.67	3.20	10.06	**<0.001**
SVE runs	3.07	1.78	5.31	<0.001
≥25 SVE runs	10.66	6.15	18.47	**<0.001**
SVE runs ≥ 2.5 sec	5.00	3.13	7.98	**<0.001**
≥ 36 VE/day	2.89	1.79	4.68	**<0.001**
VE Couplets	2.57	1.62	4.06	**<0.001**
VE Triplet	3.23	1.85	5.64	**<0.001**
Pauses	2.85	0.98	8.32	**0.931**

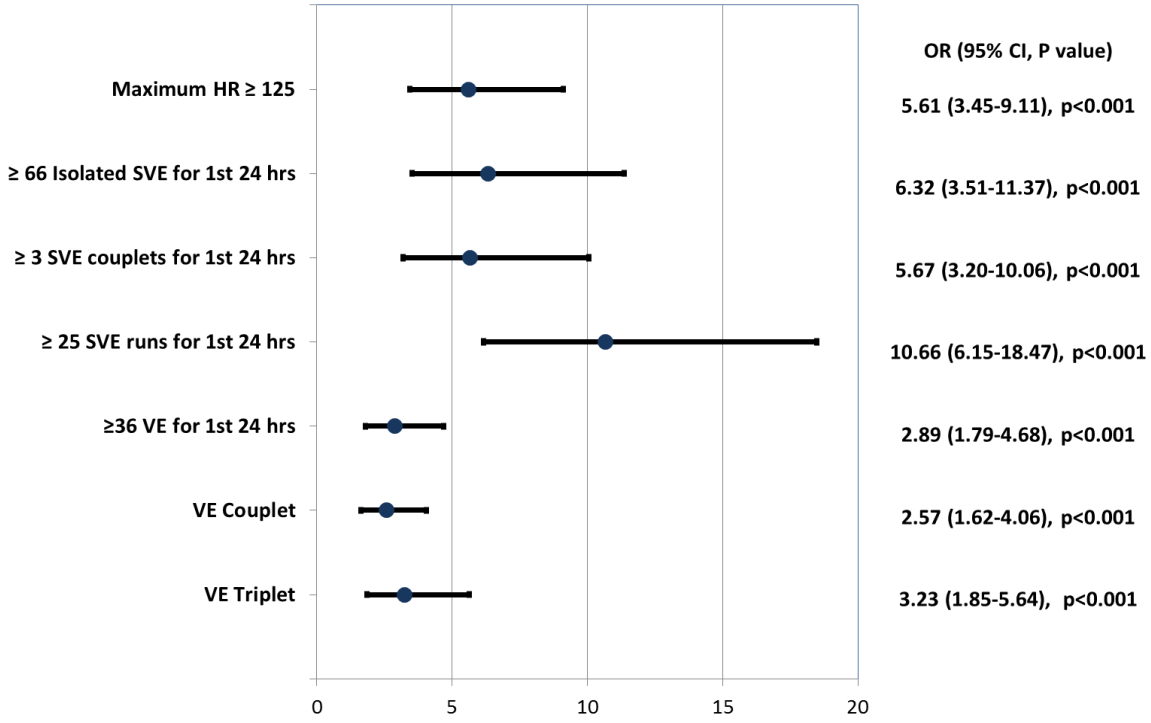


FIGURE 6.6 ODDS RATIOS FOR INDIVIDUAL HOLTER ECG PARAMETERS WITH AF DETECTION

6.4.3 Multivariate Logistic regression

Multivariate logistic regression was performed Holter ECG variables and clinical variables. This included Age≥70, ≥66 SVE/day, ≥25 SVE runs/day and ≥36 VE/day, hypertension, diabetes and renal impairment and severe LA dilatation, using the Enter method. The results concluded that age ≥ 70, ≥66 SVE/day, ≥25 SVE runs/day and severe LA dilatation were independently predictive of AF. These results are described in Table 6.15 and Figure 6.7.

TABLE 6.15 MULTIVARIATE LOGISTIC REGRESSION ANALYSIS FOR ALL VARIABLES				
Variable	**OR**	**95% Confidence intervals**		**P-value**
		Lower limit	**Upper limit**	
Age ≥ 70	2.20	1.27	3.87	**0.005**
≥66 isolated SVE/1st 24 hrs	2.72	1.42	5.20	**0.002**
≥25 SVE runs/1st 24 hrs	5.95	3.27	10.83	**<0.001**
≥ 36 VE/1st 24 hrs	1.58	0.94	2.65	**0.084**
Hypertension	1.67	0.78	3.56	**0.180**
Diabetes	1.38	0.82	2.30	**0.217**
Renal insufficiency	1.84	0.98	3.46	**0.057**
Severe LA dilatation	2.08	0.99	4.33	**0.050**

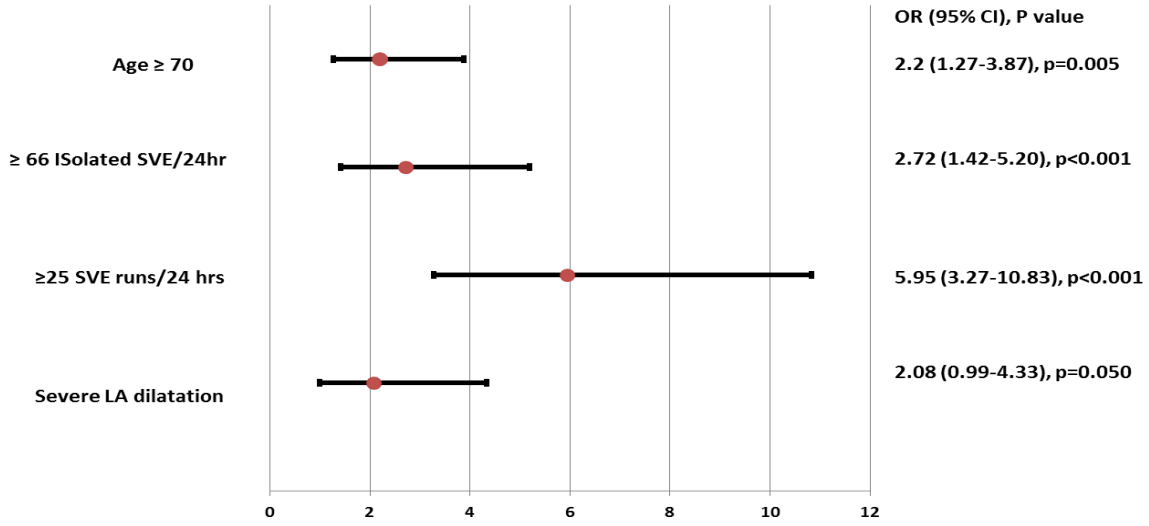


FIGURE 6.7 ODDS RATIOS FOR SIGNIFICANT VARIABLES PER MULTIVARIATE REGRESSION

6.5 Model performance

The area under the curve (C statistic) for the multivariate model was 0.81 (95% CI 0.77-0.85, p<0.001) with individual C-statistics for each variable mentioned in Figure 6.8 and Table 6.16.

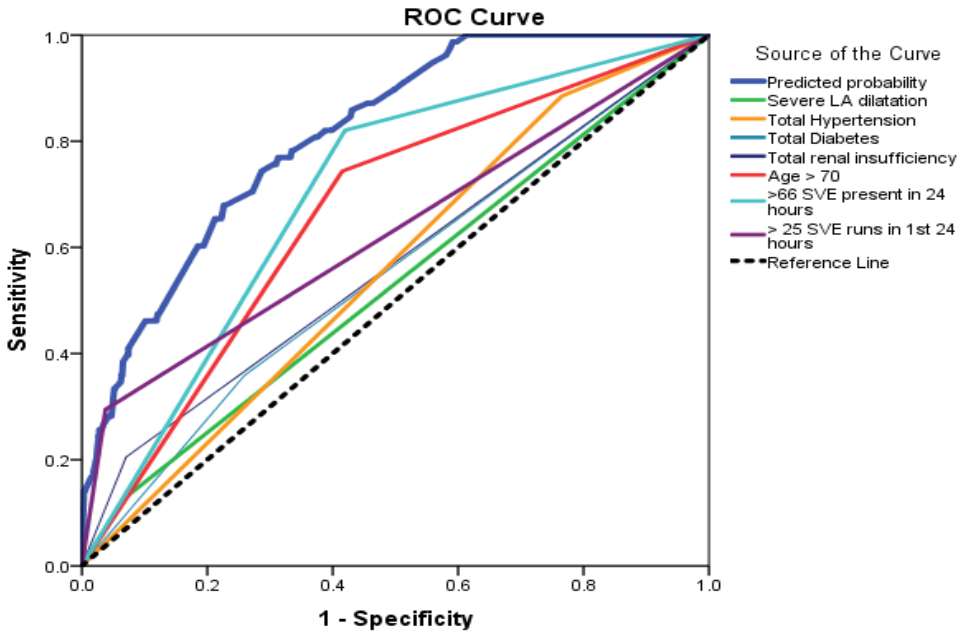


FIGURE 6.8 AREA UNDER THE CURVE FOR COMBINED MODEL

TABLE 6.16 AUC VALUES FOR INDIVIDUAL VARIABLES AND COMBINED MODEL

Variable(s)	Area	95% CI Interval		P-value
		Lower	Upper	
Combined model	0.812	0.770	0.854	**<0.001**
Age ≥ 70	0.664	0.606	0.723	**<0.001**
≥66 SVE/1st 24 hrs	0.700	0.647	0.754	**<0.001**
≥25 SVE/1st 24 hrs	0.629	0.555	0.702	**<0.001**
≥ 36 VE/1st 24 hrs	0.629	0.567	0.691	**<0.001**
Hypertension	0.560	0.500	0.620	**0.074**
Diabetes	0.550	0.482	0.617	**0.136**
Renal impairment	0.567	0.497	0.638	**0.044**
Severe LA dilatation	0.530	0.461	0.598	**0.374**

7 INTERPRETATION OF RESULTS

This chapter aims to provide an overview of the results of both the cohorts together.

7.1 A general overview of the 2 cohorts

The two cohorts presented in this work are very relevant in their context. The SWBH cohort which comes from a retrospective observational registry. This dataset was more focused on AF detection in an all-comer cohort. This makes it unique as the patients had various cardiovascular risk factors and not only ischemic stroke) predisposing them to the risk of AF. Hence the results for AF detection and AF risk factor analysis are relevant to a general population of patients undergoing 7-day Holter monitoring for any indication. In comparison, the MonDAFIS cohort is from a randomised trial on stroke survivors. This means that the results are more applicable for that patient group. The work was done based on hypothesis previously described in the introduction and methods sections. The analysis of the hypothesis testing will be given here. Also some similarities in clinical risk factors and Holter ECG findings between the two groups will be discussed as well.

7.2 Results of the Hypotheses

7.2.1 The hypotheses related to the SWBH dataset

a. AF is more likely to be present in patients symptomatic with palpitations.

30 (71.4%) patients with AF had palpitations as the main underlying symptom as compared to 211 (48.6%) patients without AF, $p<0.001$. The cut off for p-value is taken as 0.05. This rejects the null hypothesis and accepts the main hypothesis. Furthermore, univariate logistic regression analysis showed palpitations to be associated with AF with OR 3.44 (95% CI 1.65-

7.18). Multivariate logistic regression retained the association of palpitations with AF, OR 2.86 (95% CI 1.33-10.44), p=0.015.

b. AF detection increases in the presence of underlying cardiovascular risk factors like increasing age, hypertension, diabetes, coronary artery disease, hypercholesterolemia and previous stroke or TIA.

The result of this hypothesis can be summarised in the table 7.1 below

TABLE 7.1 AF ASSOCIATION WITH BASELINE CHARACTERISTICS AND COMORBIDITIES

Variable	Total (n=476)	AF Detected	AF Not detected	P-value
Age, years, mean (SD)	56.4 (17.0)	69.81 (12.2)	53.1 (16.7)	**<0.001***
Hypertension, n (%)	173(36.3)	32 (76.1)	141 (32.4)	**<0.001***
Diabetes, n (%)	78 (16.3)	11 (26.2)	67 (18)	0.072
Coronary artery disease, n (%)	102 (21.4)	17 (40.4)	85 (19.5)	**0.002***
Hypercholesterolemia, n (%)	177 (37.1)	17 (40.4)	160 (36.8)	0.644
History of stroke or TIA, n (%)	111 (23.3)	23 (54.7)	88 (20.2)	**<0.001***

This shows that AF is associated with higher mean age, and more presence of hypertension, coronary artery disease and history of previous stroke or TIA. There was no significant association of AF with diabetes and hypercholesterolemia.

On univariate logistic regression analysis the OR (95% CI, p-value) for AF vs hypertension coronary artery disease and previous stroke was 6.65 (95% CI 3.17-13.90, p<0.001), 2.79 (95% CI 1.44-5.40, p=0.002) and 4.76 (95% CI 2.48-9.12, p<0.001), respectively.

On multivariate logistic regression the OR (95% CI, p-value) for hypertension was 2.45 (95% CI 1.08-8.61, p=0.034) and stroke/TIA was 4.14 (95% CI 1.81-13.01, p=0.001).

c. Presence of excessive supraventricular ectopic (SVE) activity is associated with more AF.

AF group compared to the non-AF group had a higher median number of isolated SVE and supraventricular ectopic runs at 1275.0 (IQR 426.0-5937.7) vs 341.0 (IQR 96.5-1989.5), p<0.001 and 33.0 (IQR 15.0-45.7) vs 4.0 (IQR 2.5-7), p<0.001, respectively. This rejects the null hypothesis and accepts the main hypothesis.

Univariate logistic regression analysis showed that patients with ≥50 SVE ectopics/24 hour recording were more likely to have AF detected, OR 15.7 (95% CI 6.4-38.2), p<0.001.

7.2.2 The hypotheses related to the MonDAFIS dataset

a. Higher age and concomitant cardiovascular conditions (hypertension, diabetes, coronary artery disease, heart failure, chronic kidney disease) are associated with AF.

The result for this hypothesis are previously given in Table 6.8 and can be summarised in the table 7.2 below.

The p-value is taken as significant at <0.05. The results show shows that age, hypertension, diabetes and renal insufficiency are associated with newly detected AF.

TABLE 7.2 ASSOCIATION OF AGE AND COMORBIDITIES WITH AF				
Variable	**Total (n=1714)**	**AF Detected (n=78)**	**No AF (n=1636)**	**P-value**
Clinical Parameters				
Age, years, median (IQR)	67 (57.0-76.0)	76 (69.0-79.0)	66 (57.0-76.0)	**<0.001***
Hypertension, n (%)	1314 (76.7)	69 (88.4)	1245 (76.1)	**0.012***
Diabetes, n (%)	449 (26.1)	28 (35.8)	421 (25.7)	**0.046***
Coronary artery disease, n (%)	199 (11.6)	14 (17.9)	185 (11.3)	0.074
PVD, n (%)	68 (4.0)	4 (5.1)	64 (3.8)	0.591
Heart failure, n(%)	50 (2.9)	3 (3.8)	47 (2.9)	0.618
History of stroke or TIA, n (%)	331 (19.3)	18 (23.1)	313 (19.1)	0.389
Renal insufficiency, n (%)	132 (7.7)	16 (20.5)	116 (7.1)	**<0.001***

Furthermore, univariate logistic regression showed that the odds ratio (OR) for AF detection increases per each 10-year increase in age by 1.5 (95% CI 1.4-1.9, p<0.001), hypertension 2.4 (95% CI 1.2-4.8), p<0.001 and diabetes 1.6 (95% CI 1.0-2.6, p=0.048).

b. Echocardiographic findings of dilated left atrium and/or left ventricular dysfunction is associated with underlying AF

There was a significant difference between AF and non-AF groups for their left atrial size. Mild dilatation of LA was seen in 27 (44.2) and 419 (37.4) and severely dilated LA was seen in 10 (14.1) and 111 (9.9), p=0.018, respectively.

There was also a significant difference for the left ventricular systolic function. The mild to moderate LV systolic dysfunction was seen in 17 (27.8) and 147 (12.1) and severely impaired LV systolic function was seen in 2 (3.2) and 20 (1.6), p=0.001, respectively.

The rejects the null hypothesis and accepts the main hypothesis that echocardiographic findings of dilated left atrium and left ventricular dysfunction is associated with underlying AF.

Furthermore, on univariate logistic regression severe LA dilatation had a higher OR of AF detection at 2.02 (95% CI 1.01-4.03), p=0.046.

c. A higher isolated supraventricular ectopic count in the first 24 hour period is associated with paroxysmal AF.

The median isolated SVE beat count for the first 24 hours of recording, was significantly higher for AF group at 731 (IQR 89.00-2523.00) vs the non-AF group at 46 (IQR 13.00-212.25), p<0.001. ≥66 SVE ectopics per first 24 hours were associated with AF, OR 6.32 (95% CI 3.51-11.37, p<0.001).

This rejects the null hypothesis and accepts the main hypothesis that a higher isolated supraventricular ectopic activity in the first 24 hour period is associated with paroxysmal AF.

d. Higher counts and duration of supraventricular ectopic runs in the first 24 hours of recording is associated with underlying AF.

The median SVE run counts for the first 24 hours of recording for AF group was 6 (IQR 1.00-41.00) and 1 (IQR 0-3.00), p<0.001. For longest SVE run for first 24 hours of recording, for AF group, the median was 2.81 (IQR 1.05-5.48) seconds and for non-AF group 0.97 (IQR 0.00-2.35) seconds, p<0.001.

SVE runs if present, in the first 24 hours, has OR 3.07 (95% CI 1.78-5.31, p<0.001) for AF detection. For ≥ 25 SVE couplets, the OR for AF detection is 10.66 (95% CI 6.15-18.47, P<0.001). For SVE runs lasting for ≥ 2.5 seconds the OR for AF detection is 5.00 (95% CI 3.13-7.98, P<0.001)

This rejects the null hypothesis and accepts the main hypothesis that a higher count and duration of supraventricular ectopic runs in the first 24 hours of recording is associated with underlying AF.

e. Excessive ventricular ectopic activity in the first 24 hour period is associated with paroxysmal AF.

For median isolated VE beat count in the first 24 hours, for the AF group was 77.0 (IQR 15.0-831.0) and for the non-AF group was 17.0 (IQR 2.0-151.5), p<0.001.

For isolated VE ectopics, ≥36 VE ectopics per day were associated with OR (95% CI, p-value) 2.89 (1.79-4.68, p<0.001) for AF. Presence of VE couplets and triplets had an OR (95% CI, p-value) of 2.57 (1.62-4.06, p<0.001) and 3.23 (1.85-5.64, p<0.001) respectively.

This rejects the null hypothesis and accepts the main hypothesis that a higher count of ventricular ectopic runs in the first 24 hours of recording is associated with underlying AF.

7.3 Comparison of AF detection

In the SWBH cohort, the overall AF detection rate was 8.8% but it was 9.3% in stroke survivors. The pick-up rate of AF for the interventional arm of the MonDAFIS trial using the 7-day event monitor was 4.6%. This apparent difference can be explained by the fact that in the SWBH cohort the high AF detection was driven by patients with palpitations and stroke who constituted 50% and 15 % of the total cohort respectively.

7.4 Comparison of comorbidities

Generally, patients in MonDAFIS cohort were predominantly male and had more hypertension, diabetes. Coronary artery disease was more prevalent in the SWBH cohort. History of stroke/TIA was taken as the one before the index event in the MonDAFIS cohort which was comparable across the cohorts. Moreover, there was a significantly higher median age for AF group in both the SWBH and MonDAFIS group as compared to the non-AF group. With regards to the symptoms, palpitations and syncope were also more prevalent in the SWBH group but the dizziness was seen more frequently in the MonDAFIS group. In general hypertension and older age were commonly associated with AF detection across both cohorts. Previous stroke/TIA and coronary artery disease were associated with AF in the SWBH cohort but this association was not seen in the MonDAFIS group. Conversely, diabetes was associated with more AF in the MonDAFIS cohort.

It is also important to highlight the difference in data collection for both groups as SWBH dataset came from a retrospective observational registry looking at patient records. MonDAFIS, however, had systematic data collection as part of a clinical trial. Due to this alongside other important differences in the patient population, apart from numerical comparison, no further statistical tests were performed to compare the two datasets.

The figure below highlights the important differences between the two groups.

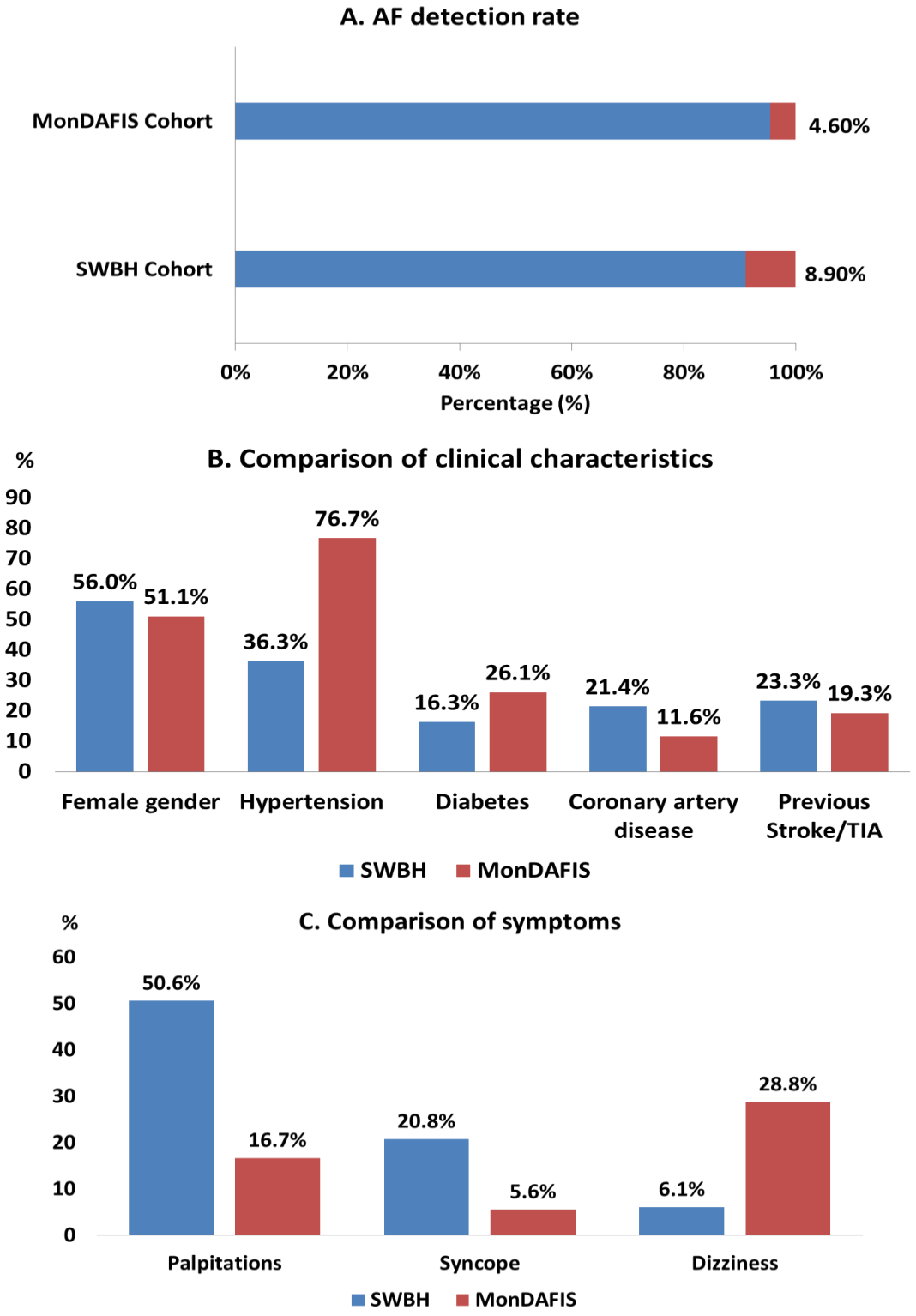
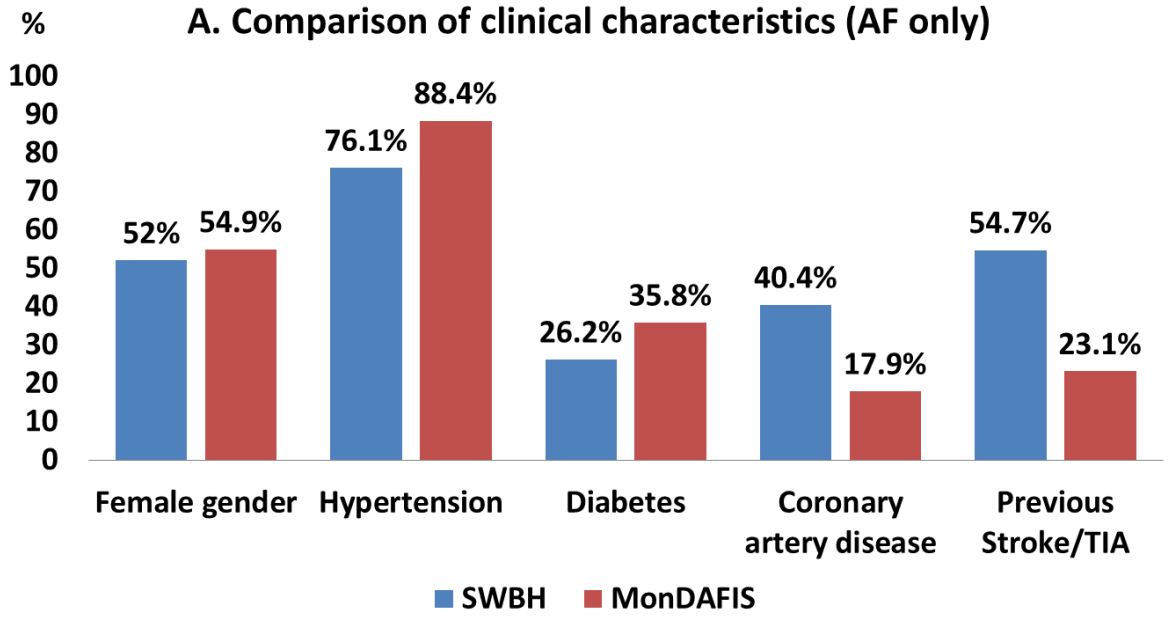


FIGURE 7.1 COMPARISON BETWEEN OVERALL SWBH AND MONDAFIS COHORTS A. AF DETECTION, B. COMMON CLINICAL CHARACTERISTICS, C. SYMPTOMS



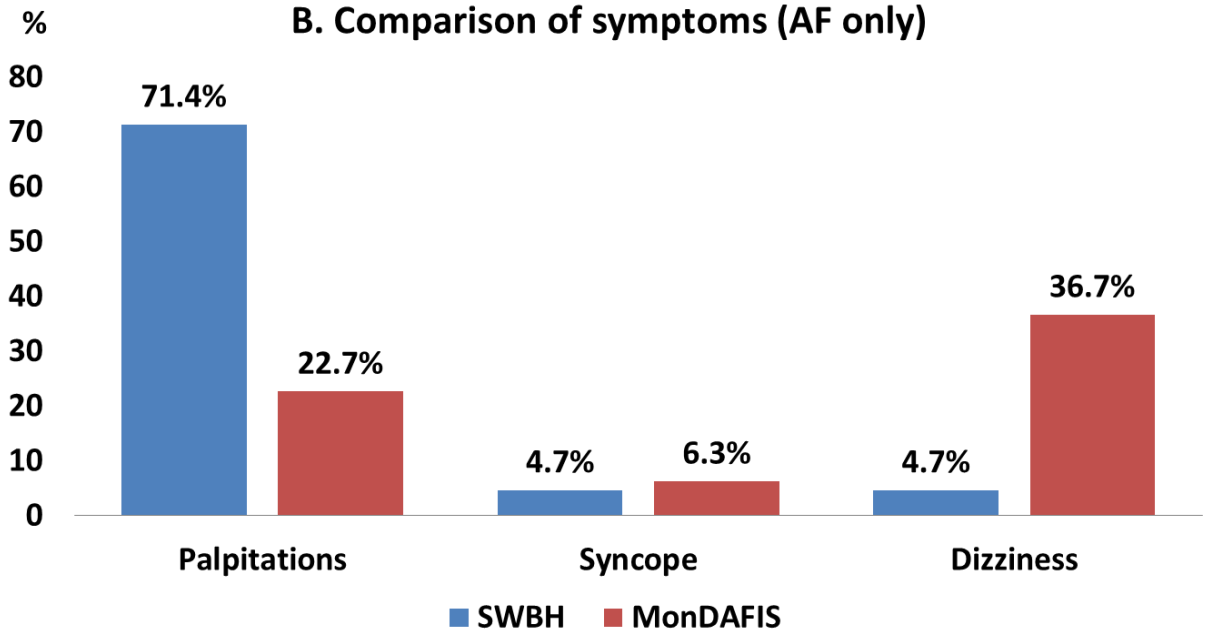


FIGURE 7.2 COMPARISON BETWEEN AF GROUPS FOR SWBH AND MONDAFIS COHORTS A. COMMON CLINICAL CHARACTERISTICS, B. SYMPTOMS

7.5 Comparison of Holter ECG findings

AF group had a higher maximum heart rate in both SWBH and MONDAFIS datasets. Also, the AF group was more likely to have isolated supraventricular ectopics (SVE), supraventricular ectopic runs and sinus pauses. The cut-offs may be slightly different between various studies but this could be due to a complex interplay of in the study design, patients characteristics and comorbidities and type of ECG recording technology.

Ventricular ectopics were associated with AF in the MonDAFIS but not in the SWBH group. However, this significance of ventricular ectopic activity was not seen in multivariate analysis.

7.6 Summary of findings

In general, despite the differences in the demographics and the clinical presentation of the two groups, there was a general trend of patients with AF detected being older and more likely to be hypertensive. Also, the AF group was more likely to be associated with higher SVE beat counts and SVE runs per 24-hour recording.

A detailed account of these findings with reference to the previous relevant research will be explained in the discussion.

8 DISCUSSION

8.1 Sample size

A total of 3470 patients were randomised for the MonDAFIS trial with 1714 in the interventional (prolonged ECG monitoring arm) after applying exclusion criteria. Compared to this, the EMBRACE trial compared conventional 24-hour Holter ECG monitoring with 30-day event monitoring and randomised 577 patients with 287 in the long term monitoring arm.[208] The FIND-AF study (observational) looked at the detection of AF in 7-day Holter monitoring and had 281 patients.[209] FIND-AF $_{randomised}$ which compared 24-hour Holter ECG with 10-day Holter at baseline, 3 months and 6 months had 398 patients.[210] Crystal-AF which compared implantable loop recorder for patients with cryptogenic stroke vs standard ECG monitoring based on physician's discretion randomised within 3 months of index event had 441 patients in total with 221 in the loop recorder arm.[211] Another multicentre German study (IDEAS) for detection rate of AF by 72-Hour continuous in-hospital ECG monitoring in patients with acute stroke recruited 1135 patients. This makes MonDAFIS the single largest head to head trial comparing different ECG monitoring strategies in stroke patients for any amount of monitoring duration and further increases the relevance of results from this study. The complete SWBH registry had 584 patients for 3 years. The final dataset had a total of 476 patients after applying relevant exclusion criteria. This a respectable testing volume for a teaching hospital. One point to note here is that there was no patient screening before offering this test but this was left at the discretion of the requesting physician. This meant that some of these patients may have had shorter durations of ECG monitoring before the requesting physician deemed it necessary to perform a 7-day holter ECG monitoring.

8.2 Duration of recording and analysis

For the MonDAFIS trial, the patients in the interventional arm were started on 7-Holter monitoring within 24 hours of admission in the stroke unit.[207] It is pertinent to mention that this was in the setting of a clinical trial with strict consideration of continuation of monitoring for as long as possible up to a maximum of 7-days and to keep interruptions and artefacts to a minimum. Despite this, the median duration of total recording was 120.48 hours and the median duration of actual analysed recording was 96.78 hours. This is 28% and 37% less than the intentional duration of the recording of 166 hours. A total of 886 (52%) patients completed at least 5 days of recording. In comparison, in observational FIND-AF, 68% of patients managed to complete the recording for 5 days or more.[209] In real life, with patients having 7-day Holter ECG recording in the community or even in this hospital, the performing physician should take into account at least some loss of ECG data during 7-day ECG monitoring for one-third to half of their patients. In prolonged monitoring, this could be due to lead detachment which could be accidental or for tests, artefacts, patient non-compliance or faulty equipment. Implantable loop recorders although can although provide an option of longer durations of monitoring but this does depend on patient preference to go through the procedure of an implantable device and also involves a risk of infection and patient discomfort. In CRYSTAL AF, around 2% of patients developed an infection at the implantable loop recorder site.[211]

8.3 The detection rate of AF

Pickup rate of AF, especially in stroke survivors, has been a subject of interest in many studies, comparing various durations and types of Holter ECG. As expected, longer monitoring duration increases AF detection.[212] In observational Find-AF the overall pick up rate of AF in 224 stroke patients was 12.5% over 7-days of continuous Holter monitoring in unselected stroke patients.[209] In FIND-AF $_{randomised}$ the pickup rate of AF in the intensive monitoring arm which offered 10-day ECG monitoring at baseline, 3 months and 6 months picked up 14% new AF as compared to the control group.[210] But if the results for each day of monitoring are split for the first 7-days of Holter monitoring in the first cycle the overall AF detection was around 8%. For EMBRACE trial, the overall detection rate of AF was 16.1% in the interventional arm and 3.2% in the control arm. However, for the first 1 week of recording out of a total of 4 weeks, the detection of new AF was 7.2%. The detection of new AF in IDEAS study is quite comparable to our work at 4.3%. In Crystal AF trial the detection rate of paroxysmal AF in cryptogenic stroke for the first 6 months was 1.7% in the control arm with usual Holter ECG monitoring in comparison to 8.9% AF through implantable loop recorders. After 12 months the difference was 2% and 12% respectively.[211] The pick-up rate of AF for the interventional arm of the MonDAFIS trial using the 7-day event monitor was 4.6% which is higher than the non-invasive monitoring arm in Crystal AF. It is interesting to note that on a closer look at the detection rate of AF for each month, in CRYSTAL AF even with implantable loop recorders the detection rate of AF for the first month was 3.4% which increased as the monitoring duration was increased beyond this to 6 months (8.9%) and 12 months (12%).

For the SWBH cohort, the overall AF detection rate was 8.8% but it was 9.3% in stroke survivors. This is comparable to the work by Grond et al (4.3%, 72-hour monitoring)[7], FIND-AF (12.5%, 10 days monitoring)[213] and FIND-$AF_{randomised}$ (14%).[210]

Our work also justifies routine access of primary care physicians in requesting 7-day Holter ECG monitoring as the pick-up rates among hospital and primary care physicians were similar. Here an important question arises: Whether open access to ECG monitoring can provide an alternative approach to increase the detection of unknown AF? Current guidelines recommend pulse palpation followed by an ECG in patients with an irregular pulse in populations >65 years to detect AF [214,215]. Pulse palpation can be replaced by a blood pressure machine. [216,217] Systematic prolonged ECG monitoring is recommended in stroke survivors. Also, community-based ECG screening programmes using patient-operated devices can identify patients with silent AF, especially when elderly populations are screened, for example, those aged 75 years or more.[218-220] Such population-based screening programmes require a specific infrastructure that is currently confined to a research environment or not available at all.

The following table summarises the important trials using various ECG monitoring methods and the relevant detection rate of AF.

Table 8.1 Comparison of various studies with regards to AF detection methods								
Trial Name	**Lead author**	**Journal**	**Year**	**Trial methodology**	**n**	**Follow up**	**Endpoint**	**Results**
Find AF Observational[209]	Stahrenberg	Stroke	2010	Prospective observational Acute stroke patients Cardiomem – 7d IP for 24 hours, remaining recording at home	281	Cross-sectional	New AF	New AF 4.8% for 24 hours vs 6.4% for 48 hours vs 12.5% for 7 day
IDEAS[38]	Rizos	Stroke	2012	Prospective observational Acute stroke patients 24 Hrs Holter and vs additional 72 hrs CEM. The aim was to see if the addition of aCEM picks up more AF	496	Cross-sectional	New AF (30 seconds)	New AF 8.2% AF correctly identified by 34.1% of 24 hr Holter in 34.1% vs 65.9% of CEM vs 92.7% of aCEM.
-	Higgins[221]	Stroke	2013	Randomised within 14 days of acute stroke. Standard Monitoring (12 lead ECG, 24 hr Holter) vs additional monitoring that includes Standard Plus 7 day event monitoring	100	Follow up at 4 weeks and 3 months	New AF for 20 seconds	New AF 4-week follow up 4% (standard) vs 12 % (intervention) 3 month follow up 10% (standard) vs 22 %(intervention) 82% completed all 7 days of recording in the intervention arm

Trial Name	Lead author	Journal	Year	Trial methodology	n	Follow up	Endpoint	Results
-	Grond[7]	Stroke	2013	Prospective cohort Acute Stroke or TIA monitored at Hospital. All had 72 hr Holter	1135	Hospital stay	New AF (30 seconds)	New AF 4.3% (72 hrs) vs 2.3% (for 1st 24 hrs)
Find AF Randomised	Wachter[210]	Neurology	2017	Randomised Stroke patients 10-day Cardiomem at 0,3 and 6 months vs 24 hours Holter ECG. 1st intervention initiated within the index admission.	398	12 months	New AF (30 seconds)	New AF 13.5% in Intervention group vs 6.1% of control.
EMBRACE[24]	Gladstone	NEJM	2014	Multicenter, Randomised trial Cryptogenic stroke patients 24 hours Holter ECG vs 30-day Event recorder	572	90 days	AF 30 seconds	New AF 16.1% (30-day event recorder) vs 3.2% (24-hour Holter) Incremental increase as 24 hrs -2.2% 1 week - 7.4% 2 weeks - 11.6% 3 weeks - 12.3% 4 weeks - 14.8%
CRYSTAL-AF[211]	Sanna	NEJM	2014	Randomised control trial Cryptogenic Stroke Implantable loop Recorder vs 24 hrs tape	441	6 months and 12 months	**Primary** AF at 6 months **Secondary** AF at 12 months	New AF 6 months - 1.4% vs 8.9% 12 months - 2% vs 12.4% 36 months - 30% in ILR group

8.4 Baseline Characteristics

8.4.1 Age:

It was found that patients with AF were more likely to be older. For MonDAFIS cohort the median age for AF group was 76 [69-79] years compared to non-AF group 66 [57-76] years, p<0.001. Also, each 10-year increase in age increased the risk of AF by 1.70 [95% CI 1.40-1.90] p<0.001, and age ≥ 70 was an independent predictor of AF with OR of 2.20 [95% CI 1.27-3.87], p=0.005. SWBH cohort showed similar results with mean [SD] age of AF vs non-AF group as 69.81 [12.2] and 53.10 [16.70], p<0.001 respectively and each 10-year increase in age was associated with OR of 1.80 [1.60-2.10], p<0.001.

This older age associated with the detection of new AF is consistent with other reports[30,222]. There is also evidence older age is associated with prevalent AF.[51,223] Furthermore, a study by Suissa *et al* showed which risk of AF with age more than 62 had an OR of 11 [95% CI 5-26] and a large observational study by Verdecchia *et al* in which patients who developed AF tended to be older.[30,222] Overall the cut off age beyond which there is a significant rise of risk of underlying AF is not clear.[51,223] However, based on current work the risk of AF beyond 70 years is significant. A recent study based on validation of various clinical factors as risk predictors of AF as part of a HOVAC score (that includes hypertension, coronary artery disease, peripheral vascular disease, obesity and age ≥75) has also suggested age 75 and beyond as an important clinical predictor of AF.[224] Another risk score, STAF has suggested a lower cut-off for age at 62 for patients with cryptogenic stroke.[225]

8.4.2 Gender

Atrial fibrillation as shown by many studies is multifactorial and the role of gender is not exactly clear. STAF score developed to look for clinical risk factors of AF found female gender as an independent predictor of AF. CHA_2DS_2VASc score proposed by some to identify patients at higher risk of incident AF also identified female gender as a high-risk group.[192] There was no significant difference in detection of underlying AF based on the gender in the SWBH or MonDAFIS cohort.

8.4.3 Echo data and Comorbidities

a. LV function, LA size and valvular heart disease,

It is well known that atrial fibrillation is associated with impaired left ventricular systolic and diastolic function.[226-229] Although in MonDAFIS a significant association between heart failure syndrome and new AF was not seen, there was a significant association of severely impaired LV systolic function with AF on association testing. This difference was not however seen on univariate logistic regression analysis for LV systolic dysfunction.

There is sufficient evidence to suggest that increasing left atrial size is strongly associated with AF in many studies.[230-234] In the MonDAFIS cohort, severely dilated LA was associated with new AF detection and this was replicated on logistic regression. Severely dilated LA was one of the independent predictors of AF on multiple logistic regression.

Interestingly LA appendage thrombus was seen in 10 patients but AF was not detected in any of these patients. This shows a high likelihood of underlying AF but the 7-day Holter ECG was unable to pick up AF in these patients. This highlights the importance of prolonged ECG

monitoring beyond 7 days in some high-risk patients if the initial monitoring fails to pick up AF.

Results from the SWBH cohort showed that left-sided valvular heart disease was associated with silent AF in univariate logistic regression with an OR of 5.2 [2.6-10.3]. This is comparable to a prior report from a large observational study which also identified mitral regurgitation (MR) and aortic stenosis (AS) as predictors of AF in univariate analysis. Only, AS was independently associated with AF.[235] A Japanese study has shown increased LA size ≥ 3.8 cm and any mitral valvular disease as independent predictors of AF in patients with ischemic stroke.[236]

b. Hypertension

Hypertension has long been considered as an important risk factor for AF due to its effect on LV size and function and LA remodelling.[30,31] The study from Zhao et al for validation of HOVAC score for prediction of AF, allocated 2 points for the presence of hypertension as a predictor of AF, alongside valvular disease, coronary artery disease and age 75.[224] The MonDAFIS cohort showed a significant association with AF with OR 2.39 [95% CI 1.18-4.84] which was also seen in the SWBH cohort OR 6.65 [3.17-13.90].

c. Coronary Artery disease

Coronary artery disease is frequently associated with risk of underlying AF. Nucifora *et al* found a significant difference through multi-slice coronary CT that showed 41% obstructive coronary artery disease in the AF group as compared to 27% in the non-AF group.[70] It is also part of the HAVOC score of clinical risk predictors for AF.[224]

The history of previous myocardial infarction or percutaneous coronary intervention was assessed as evidence of coronary artery disease in this cohort. There was no significant difference between AF and non-AF groups for the presence of coronary artery disease in the MonDAFIS. This is in contrast to the results from the SWBH dataset in which coronary artery disease was an important risk factor for AF. This difference can be explained by patient demographics as well as the fact that patient in MonDAFIS cohort was already high-risk due to confirmed stroke/TIA.

d. Diabetes Mellitus

There is conflicting and limited evidence of an association of risk of AF with underlying diabetes mellitus. In a very large Danish registry there was an increased risk of developing AF especially in younger patients with diabetes. [237] Results from the VALUE trial with high-risk hypertensive patients showed that patients with new-onset diabetes with pre-existing hypertension had a higher incidence of developing AF.[238] In the MonDAFIS cohort diabetes was associated with AF with an OR of 1.65 [95% CI 1.03-2.64, p=0.036]. On the other hand for the SWBH cohort, there was no significant difference between the AF and non-AF group. This difference could be due to stringent criteria for diagnosing diabetes for patients enrolled in a clinical trial but in the SWBH cohort which could have missed some patients with subclinical diabetes due to the observational nature of the study.

e. AF-related Symptoms

In the SWBH dataset, palpitations were the most common symptom associated with underlying AF at 12.5%. They were seen in 22% of AF patients compared to 16% non-AF in the MonDAFIS group. However, this difference was not statistically significant. some prior

reports have associated palpitations with AF [239] while others found a more ephemeral nature of presenting symptoms.[83] Another cross-sectional study has shown only 26% of patients with AF to have symptoms.[240] It is previously reported that females have more symptoms and poorer quality of life with AF. [241] Generally the symptoms can be wide-ranging and sometimes can be just a decrease in effort tolerance. Association of symptoms with AF is a complex interplay of the presence of tachycardia, female gender, race and any psychological distress.[242] Although the SWBH cohort showed a positive correlation between palpitations and the presence of AF, in general, the presence of AF-related symptoms has no proven correlation with underlying AF.

f. Renal insufficiency

A population cohort study of more than three thousand patients has shown that renal insufficiency leads to a higher risk of prevalent AF.[243] Presence of renal insufficiency has a bearing on the choice of oral anticoagulation for AF as well as increased cardiovascular mortality and bleeding risk.[244] On univariate logistic regression there renal impairment (eGFR <60 ml/min) was associated with AF with OR 3.29 [1.84-5.89]. This was not however seen for multivariate logistic regression.

8.5 Holter ECG findings

8.5.1 Heart rate parameters

A large cross-sectional study of more than 11 thousand 24-hour Holter monitors showed that higher maximum heart rate was strongly associated with underlying AF however this effect was blunted by concomitant use of beta-blockers.[240] Abnormal heart rate variability (HRV) has long been cited as having an important association with AF.[123,245] This could be

due to impaired vagal tone or cholinergic response.[246] There was no reliable data to compare HRV parameters with the risk of AF.

In the MonDAFIS dataset, AF was found to be a higher maximum heart rate with a heart rate of ≥ 125 /min (OR 7.13 [95% CI 4.33-12.04]). This association of a higher maximum heart rate and a higher mean heart rate with AF was also seen in the SWBH cohort. Heart rate, however, could be affected by paroxysmal AF episodes and could lead to a cause-effect bias. Hence in the combined Model, maximal heart rate parameters were not included due to risk of introduction of bias in the multivariate model prediction.

8.5.2 Excessive supraventricular ectopic activity

There is a definite role of excessive supraventricular ectopic activity in initiating sustained atrial arrhythmia like AF in patients with previous stroke, post-operative or even healthy individuals.[114,117,247] ASSERT trial even showed an increased risk of stroke with atrial tachyarrhythmias detected with implantable cardiac devices which underlines the importance of such short atrial runs which are not marked as AF.[248] In the MonDAFIS group, ≥ 66 SVE ectopics/day and ≥ 25 SVE runs/ day were independently predictive of AF in stroke patients. Excess supraventricular ectopy was equally found to be an independent predictor of AF in the SWBH cohort which showed ≥ 50 SVE ectopics/day or any duration of SVE run to be predictive of AF. A study done by Larsen et al showed that SVE ectopics at much higher number ≥ 30/hour and SVE run lasting for more than 20 beats were associated with AF.[249] Another group also showed more than 29 SVE/hour and a supraventricular run more than 10 beats in 24 hours as having a significant association with AF in patients with cerebral ischemia.[250] This is a higher threshold for excessive supraventricular ectopic. While this could

be quite specific for their group, it may not be as sensitive in a large MonDAFIS cohort. Regardless of the cut-offs for the excessive supraventricular ectopic activity, it was associated with unknown AF, comparable to prior analyses [28,117,251]

8.5.3 Excessive ventricular ectopic activity

Ventricular ectopic activity is a marker of LV systolic dysfunction and left heart disease.[252] LV systolic dysfunction, in turn, is associated with AF.[226] In the MonDAFIS dataset, excessive VEs although showed association with AF through binary logistic regression. In multiple regression, however, it did not have an independent association with AF. There was no association of ventricular ectopic activity with AF in the SWBH cohort. There is no direct large study to look for the association of ventricular ectopy with AF but such work is desirable.

8.5.4 Pauses

Sinus node disease, identified by sinus pauses [253], has been linked to underlying AF.[254,255] In the SWBH dataset, sinus pauses had a significant association with AF through univariate logistic regression. Although sinus pauses were not part of the multivariate model, there is evidence to suggest that it could be associated with unknown AF, confirming findings from a previous study.[256]

8.6 Limitations

The main limitation applicable to the whole work is the differences in the population cohort and the research methodology between the two groups. This prevents a statistical analysis across the two groups. Moreover, despite best efforts to keep the data collection, analysis and presentation without any bias, it is still pertinent to point out that some bias could be introduced in various steps for the SWBH and MonDAFIS work.

8.6.1 Limitation related to SWBH dataset

1. Sample Size:

Sample size remains an important limitation in this cohort. After screening more than 500 patients and 476 patients were included in the final cohort which was reasonable for a busy teaching hospital. The sample size also had an effect on the relatively wide confidence intervals for the calculated odds ratios, although this improved by bootstrapping the data.

2. Cause-Effect and selection Bias:

AF group had a longer duration of monitoring which could introduce a confounding bias. For example, this could be simply because patients with stroke or those with symptoms were better motivated to wear the monitor for longer. To rectify this the multivariate model was adjusted for the duration of the recording.

Older patients usually have a higher incidence of comorbidities. The AF group was significantly older as compared to the non-AF group. This could also lead to a selection bias. However, this perceived effect persisted in the multivariate model indicating a strong correlation of the model with AF. Another source of selection bias could be introduced as

these patients may have been considered as a higher risk for AF by the test requesting physician due to their comorbidities like previous stroke or presence of palpitations as indicated by a predominance of these indications. Some of these patients may have had a prior 24 or 48 hour Holter ECG as well. This data was however not consistently available.

3. Recall Bias:

Some part of the data was based on the history provided by the patient, which can introduce recall bias, like the description of symptoms of palpitations, dizziness, syncope etc. To counter this, the history of various symptoms associated with the presenting complaint was cross-checked with the GP or referring physician's clinic letter.

4. AF Pick-up rate for less than 7-day ECG recording

Due to the method of data collection, an AF detection for the whole duration of monitoring was recorded. Hence, the pick-up rate of AF with for individual days is not available to assess incremental daily pick up of AF. For the same reason, the differences between the sub-7-day and 7-day cohorts referred for ECG monitoring at SWBH is not possible to investigate.

8.6.2 Limitation related to MONDAFIS dataset

Some of the limitations related to the conduct of the study have been mentioned in the Methods section describing the relevant errors in the workflow and the ways through which these were addressed. Other limitations are mentioned here.

1. Admission-rate bias:

This is could lead to a special form of selection bias. It is known that AF leads to severe stroke. This means more patients with AF presenting to stroke centres as those without AF

may have less debilitating symptoms and they either go un-noticed and do not present to hospital at all or present late to primary care. An effort was made to negate this by giving a fixed proportion to the different levels of stroke centres to include a wide range of patients.

2. The validity of results for patients with ischemic stroke and TIA:

The design of the study meant that the study population was very specific and involved patients presenting with acute ischemic stroke or TIA. This may lead to the inference that the ECG and clinical variables found to have a significant association with AF are relevant to that specific patient group only. In real practice, these ECG and clinical variables are individually known to be associated with AF. The important thing with this work is that it combines the relevant variables, previously identified separately through various studies in one group with high predictive power to identify patients at risk of AF.

3. Missing or unavailable data

The variables available for analysis were mostly similar to the initial analysis plan but some variables could not be transcribed when ECG data files were merged to create a complete data spreadsheet. These include daily total trends for heart rate variability, mean heart rate and beat counts. Similarly while the numbers of events like supraventricular ectopics, ventricular ectopics etc. are of importance, of equal interest, would have been the availability of daily proportion of these events compared to total beat count. This information also was not available for analysis.

One other important limitation was that only 52% of patients completed at least 5 days of Holter monitoring and those who completed 7-days of monitoring was 36%.

Similarly, the echo data was no available for roughly one-third of the patients. Moreover, the variables used were categorical which could be less sensitive than continuous data measurements.

Also, the MonDAFIS cohort had a relatively mild stroke population with a median NIHSS score of 3 (IQR 2-4), who are less likely to have had cardioembolic/ large vessel stroke. A classification of these stroke types based on their presentation of clinical stroke diagnosis (OCSP classification or equivalent) or likely aetiology (TOAST classification or equivalent) should be considered. The TOAST classification is available within the trial, but not yet released to be included in this manuscript.

4. Observer bias:

The quality of ECG data is as good as the person analysing the data. This is an inherent problem in all studies related to the analysis of complicated data which involves human input on top of software analysis. This can make it error-prone and can introduce inter-observer and even intra-observer bias. To standardise this, it was ensured that all working stations were standardised with the same definitions for highlighting each ECG event, for example, AF, supraventricular ectopic, ventricular ectopic etc. Each event was individually confirmed by experienced personnel who had all received training at the same level to perform the analysis. Each case was further assessed by cardiology physician (myself) confirm the quality of the analysis. Finally, for difficult or complicated findings the opinion of Professor of Cardiology (PK) was sought to adjudicate the matter. All AF episodes were independently confirmed by external validation as well. Due to this multi-step process, the observer bias was kept to a minimum.

5. Data migration and transcription:

Presence of multiple centres for data collection, data analysis in the core-lab and a different coordinating centre meant that there needed to be a major effort to ensure that the data quality is not affecting by data generation, migration and transcription. This could theoretically lead to loss of data and indeed a few patient ECG recordings were damaged during this process. To this end, secure servers were used to transmit the files between the study centres, core lab and the coordinating centre (Charité). The ECG files were then stored in Sentinel servers in the University of Birmingham and data transmission was carried out in bulk after each quarter to coordinating centre in Germany. This could lead to the following potential problems:

e. More than 1 ECG data file for a patient due to repeat analysis.
f. Transmission of an older version of the ECG data files to the study coordinating centre.
g. Presence of more than 1 recording for the same patient as the recording was split into two halves, leading to 2 ECG files.

These issues were extensively discussed at the trial steering committee and a major validation effort was undertaken to check a 10% sample from all the patients to ensure that the ECG data available in the trial database is the exact representation of the final ECG data analysed. This led to a 100% validation success. With regards to more than 1 ECG data files, the first half of the recording was used for all further analyses to prevent the introduction of false data.

8.7 Conclusions

1. Duration of ECG monitoring and open access

SWBH study suggests that open access to prolonged ECG monitoring has a high diagnostic yield in patients with various symptoms, opening up an alternative approach to increase the detection of unknown AF. Comparable AF detection rates between cardiology and primary care also complement the argument for an open access service. Open access to ECG monitoring has the advantage of using existing health infrastructure but is limited to populations with symptoms. In the all-comer patient cohort, 7-day Holter ECG monitoring yields a significant AF detection rate, suggesting that this is a useful diagnostic tool for similar populations without known AF in primary and secondary care. The SWBH data the wider use of systematic ECG monitoring to allow early initiation of therapy for AF, particularly stroke prevention, e.g. as part of an integrated approach to AF care.

Prolonging ECG monitoring beyond 24-72 hours significantly increases the detection of AF in the high-risk population. Further ECG monitoring, beyond 7-days, is suggested to look for AF in clinically high-risk patients as identified by ou the multivariate model, especially, if they have evidence of significant supraventricular ectopy on prior monitoring.

2. Clinical predictors of AF:

Age ≥70 especially with a history of stroke is a very important risk factor for AF and should be taken into account for any future prediction models. Across both studies, common cardiovascular risk factors increase the likelihood of underlying AF however there could be subtle differences due to difference in population dynamics and type of patients going through the Holter monitoring

Presence of symptoms especially palpitations is an independent predictor of AF in an all-comer population but this effect is not seen in stroke patients. Further work is needed to clarify this association.

3. ECG predictors of AF

Supraventricular ectopic activity is the single most important Holter ECG predictor of AF in stroke patients as well as in general patient population. The cut-offs may be slightly different between various studies but this could be due to a complex interplay of in the study design, patients characteristics and comorbidities and type of ECG recording technology.

The main aim is to use the data from the MONDAFIS trial to not only come up with a positive predictive model but also develop criteria outlining negative predictive variables. This will help ensure that resources are utilised in the best possible way in a setting of a limited supply of technical expertise and facilities of long term ECG monitoring.

4. Importance of current findings

Our findings, especially from the MonDAFIS, are very relevant and particularly interesting as it combines the work from various previous studies and trials into one big group and identifies the relevant predictors of AF with a combined model of patient demographics, comorbidities, echo findings and Holter ECG variables. The overall predictive power of these variables is also very significant with an AUC of 0.81. This has great potential in identifying high-risk patients with ischemic stroke, in whom AF has not been identified yet.

8.8 What this work adds to existing evidence

The 2016 ESC AF guidelines highlighted some gaps in evidence suggesting further research work regarding major health modifiers causing AF.[11] This work aims to address that gap in the evidence.

An effort was made to highlight important demographic and clinical baseline characteristics which increase the risk of finding incidental AF. In both groups advancing age and underlying hypertension was seen to be strongly associated with AF. Furthermore, in the all-comer patient population advancing age some other risk factors like the previous stroke, coronary artery disease and presence of palpitations increased the detection of AF. In the stroke survivors in the MonDAFIS group, the presence of diabetes and renal insufficiency were important risk factors.

One key message from ESC is the use of ECG screening in older stroke survivors[11]. This work leads to the argument that for such patients especially if they are hypertensive and symptomatic with palpitations, there should be a higher suspicion of underlying AF. This risk stratification can be further fine-tuned if the patient has echocardiographic evidence of left-sided valvular disease, significant LV impairment, LA dilatation and Holter ECG evidence of significant atrial ectopic activity. In these patients, prolonged ECG monitoring beyond 7 days should be considered if initial systematic monitoring fails to identify AF.

8.9 Future work

1. With regards to SWBH dataset more patients are required for further studies especially to assess specific Holter ECG variables as incident AF predictors in an all-comer population. To this end, these findings will need validation in other, external larger patient cohorts.

2. The variables identified through this work can lead to an AF predictive risk score (with internal and external validation) especially for stroke survivors, with no clear diagnosis of AF on 7-day Holter despite having high-risk features. In future, I intend to perform a validation of these identified factors on a large population-based registry such as BBC-AF. This should include a combination of patients' baseline characteristics as well as the proposed Holter ECG predictive factors, echocardiographic parameters identified in this work. It is highly desirable to have such a score as it will help rule out very low-risk patients to reduce the costs and patient inconvenience of long term ECG monitoring for this group of patients.

3. Recently patient operated portable ECG recording devices and smartwatches to detect AF have generated interest.[39-41] In general, the sensitivity of heart rate based AF and photoplethysmography is low. Even ECG electrode-based AF detection methods are based on the algorithms and currently require a physician to diagnose a recorded AF episode.[42] Future will require refinement of detection algorithms to improve the diagnostic accuracy of these devices.

4. Use of machine learning for artificial intelligence (AI) based convolutional neural networking may have a role in the future to predict AF.[257] However this technology needs to be carefully assessed before it can be made publically available for such purpose.

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