The clinical epidemiology of atrial fibrillation in a population cohort and methods to identify those at risk of atrial fibrillation



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I dedicate this thesis to my Mum and Dad, my wife Kiran and my kids: Sammar and Zakariya. Without their patience, love and prayers this work would not have been possible.

Declaration

I hereby declare that except where specific reference is made to the work of others, the contents of this thesis are original and have not been submitted in whole or in part for consideration for any other degree or qualification in this, or any other University. This dissertation is the result of my own work and includes nothing, which is the outcome of work done in collaboration, except where specifically indicated in the text. This thesis contains less than 13,000 words including appendices, footnotes & tables and has less than 10 Figures.

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3: The prevalence of atrial fibrillation in a population cohort and its association with valvular heart disease

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Presentations

A) Abstract presentation (Euro-Echo imaging 7th Dec 2018, Milan, Italy)

Oral anticoagulation among patients with atrial fibrillation, the contemporary trends in primary care

B) Abstract presentation (ESC Annual Congress 27th August 2018, Munich, Germany)

The predictors and risk factors of atrial fibrillation in a population cohort and its association with valvular heart disease

C) Abstract presentation (Euro-Echo imaging 7th Dec 2017, Lisbon, Portugal)

The prevalence of atrial fibrillation in a population cohort and its association with VHD

D) Poster presentation (RDM Annual Symposium 6th March 2017, Oxford)

The prevalence of atrial fibrillation in a population cohort and its association with valvular heart disease

Abstract

Study aims and objectives

Atrial fibrillation (AF) is the most common arrhythmia and remains an important cause of cardiovascular morbidity worldwide. The aim of this research is to examine the prevalence of AF alongside its predictors and associated risk factors, oral anticoagulation in AF, the association of AF with valvular heart disease (VHD) and the potential role of BNP as a biomarker for AF in a contemporary, population-based cohort.

Methods

Retrospective analysis of 4009 participants in the OxVALVE study, all of whom were aged 65 years or older, and without a previous diagnosis of VHD.

Results

The prevalence of AF was 7.3%, (12% newly diagnosed). Paroxysmal AF (76%) was the most common type of AF followed by persistent (20%) and permanent AF (3%). Most AF patients were managed with the rate control strategy (46%). The prevalence of AF increased with age increasing from 3.9% among 65-69 years old to 13.2% among participants 80 years of age. Significant associations with AF were observed for: age, male gender, hypertension, hypercholesterolemia, coronary heart disease (CHD), stroke and transient ischemic attack (TIA), left atrial (LA) size, impaired left ventricular (LV) systolic function, and moderate or

severe VHD. LA diameter, significant VHD and systolic blood pressure were independently associated with newly diagnosed atrial fibrillation. Most individuals with AF (87%) had some degree of VHD. AF was significantly associated with the presence and increased severity of mitral and tricuspid regurgitation; and the presence of aortic sclerosis, aortic and pulmonary regurgitation. Serum BNP>20pmol/L was significantly associated with the presence of AF (p = 0.0001) with a high specificity (84%) and negative predictive value (97%).

Conclusion

AF had a high prevalence (7.3%) in this unselected, elderly population cohort. Male gender, hypertension, hypercholesterolemia, coronary artery disease, impaired LV systolic function, left atrial size, significant VHD and the presence of ankle oedema on clinical examination were identified as significant associated risk factors with atrial fibrillation. LA diameter, significant VHD and systolic blood pressure were found to be the independent predictors of newly diagnosed AF. Most of the AF patients had paroxysmal AF and were on the rate control strategy. AF was associated with the presence and severity of VHD. The association of AF with the presence and severity of VHD highlights the importance of echocardiography in subjects with AF regardless of the management strategy: whether rate or rhythm control. Serum BNP can be used as a biomarker to help identify high risk patients with a likely underlying diagnosis of paroxysmal AF meriting longer ambulatory monitoring thereby improving the overall diagnostic yield for AF screening.

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Table of Contents

Abstract 7

List of tables 12

List of figures 13

1 Introduction 14

1.1 Pathophysiology 14

1.2 Population prevalence of AF and the association with Ischaemic strokes 16

1.3 The classification of AF 16

1.4 The rationale for Thesis 19

1.5 Thromboembolic prevention and the association of AF with valvular heart disease 20

1.6 Natriuretic peptides and the potential role in AF 21

2 Methods 23

2.1 Study design 23

2.2 Study population 23

2.3 Baseline data and serum BNP 24

2.4 Echocardiography: 25

2.5 Diagnosis of atrial fibrillation 27

2.6 Statistical analysis 28

3 Results 29

3.1 Baseline characteristics 29
3.2 The population prevalence and patterns of AF 31
3.3 The association between AF and serum BNP 34
3.4 The management of AF (in an elderly community based population cohort) 38
3.5 AF and cardiovascular risk factors 39
3.6 AF and its association with left atrial size & left ventricular systolic function 40
3.7 AF & its association with valvular heart disease 40
3.8 AF & oral anticoagulation 43
3.9 Predictors of newly diagnosed AF 45
4 Discussion 46
4.1 Prevalence of AF 46
4.2 Patterns and management of AF 47
4.3 The association between AF and Serum BNP 48
4.4 Serum BNP, a biomarker for AF 49
4.5 Associated risk factors 51
4.6 Association of AF with VHD 52
4.7 Oral anticoagulation therapy in AF 53
4.8 Independent predictors of new AF 54
4.9 Echocardiographic screening for VHD 55
5 Study Limitations 57

6 Conclusion 60

References 61

Appendix-I 69

Appendix-II 71

Appendix-III 82

List of tables

Table 1: Demographics of study participants with and without (AF) n=4009 30

Table 2: The prevalence of AF according to age, including subjects with New AF (n=4009). 31

Table 3: AF and its association with serum BNP..... 34

Table 4: Measures of diagnostic accuracy, serum BNP as a biomarker for AF..... 35

Table 5: Coronary heart disease and its association with prevalence of AF 39

Table 6: AF and its association with VHD 41

Table 7: Oral anticoagulation in patients with known AF..... 43

Table 8: Independent predictors of new AF (n=36)..... 45

List of figures

Figure 1: Patterns of AF, ESC 2016 guidelines 17

Figure 2: Types of AF, ESC 2016 guidelines 18

Figure 3: The prevalence of AF with age (previously undiagnosed individuals in red)..... 32

Figure 4: Patterns of AF 33

Figure 5: Receiver operating characteristics curve for serum BNP 37

Figure 6: Venn diagram demonstrating the distribution of single and multiple valve abnormalities in subjects with AF..... 42

Figure 7: Oral anticoagulation in subjects with AF 44

1 Introduction

Atrial fibrillation (AF) [I] is the most common sustained cardiac arrhythmia, occurring in 1–2% of the general population [1]. It is also the most common arrhythmia in clinical practice, accounting for approximately one-third of hospitalizations for cardiac rhythm disturbance [2]. Over 2.2 million Americans [2] and 6 million Europeans suffer from this arrhythmia, and its prevalence is estimated to at least double in the next 50 years as the population ages [1]. AF confers a 5-fold increased risk of stroke, and one in five of all strokes are attributed to this arrhythmia. [1] The cost of care of AF patients on health care systems is estimated at 3000 euros per patient per annum with a total burden of 13.5 billion euros in the European Union alone [2].

1.1 Pathophysiology

The pathophysiology of AF involves remodelling of atrial structure and ion channel function as well as the underlying electrophysiological mechanisms of atrial fibrillation initiation and propagation. External stressors such as structural heart disease, hypertension, possibly diabetes, induce a slow but progressive process of structural remodelling in the atria [3]. Activation of fibroblasts, enhanced connective tissue deposition, and fibrosis are the hallmarks of this process. In addition, atrial fatty infiltration, inflammatory infiltrates, myocyte hypertrophy, necrosis, and amyloidosis may also be found among patients with AF [3]. Structural remodelling results in electrical dissociation between muscle bundles and

[I] List of abbreviations: Appendix-I

local conduction heterogeneities, favouring re-entry and perpetuation of the arrhythmia [3]. The functional and structural changes in atrial myocardium and stasis of blood, especially in the left atrial appendage (LAA), generate a prothrombotic state. Furthermore, even short episodes of AF lead to atrial myocardial damage and the expression of prothrombotic factors on the atrial endothelial surface, alongside activation of platelets and inflammatory cells, and contribute to a generalized prothrombotic state. The atrial and systemic activation of the coagulation system can partially explain why short episodes of AF convey a long-term stroke risk [3]. AF provokes a shortening of the atrial refractory period and AF cycle length during the first days of the arrhythmia, largely due to down regulation of the Ca^{2+}-inward current and up regulation of inward rectifier K^{+} currents. Hyperphosphorylation of various Ca^{2+}-handling proteins may contribute to enhance spontaneous Ca^{2+} release events and triggered activity, thus causing ectopy and promoting AF [3]. It has been postulated that a focal source in the pulmonary veins can trigger AF, and ablation of this source can suppress recurrent AF [4]. Another theory suggests that AF can be perpetuated by continuous conduction of several independent wavelets propagating through the atrial musculature in a seemingly chaotic manner. As long as the number of wavefronts does not decline below a critical level, they will be capable of sustaining the arrhythmia [5].

1.2 Population prevalence of AF and the association with Ischaemic strokes

The incidence and prevalence of AF increase with age [1, 2]. The prevalence of AF increases from 0.5% at 40–50 years, to 5–15% at 80 years of age [6, 7, 8, 9]. AF can long remain undiagnosed (silent AF)[10] and many patients with AF never present to hospital [11]. Therefore the "true" prevalence of AF is probably higher.

Occurrence of stroke is common in patients with AF and as a consequence, the risk of death from AF-related stroke is doubled and the cost of care is increased 1.5-fold [1]. Stroke prevention in patients with AF is therefore of paramount importance. International (European Society of Cardiology "ESC", American Heart Association "AHA") guidelines stress the importance of oral anticoagulation (OAC) in patients fulfilling the eligibility criteria; which is based upon the risk factors for thromboembolism, in patients with AF [1, 3, 12, 13].

1.3 The classification of AF

AF is classified into patterns on the basis of presentation, duration, and spontaneous termination of AF episodes into: first (newly) diagnosed, paroxysmal, persistent, persistent long-standing and permanent AF (Figure-1). AF is also classified into various types: focal AF, monogenic AF, polygenic AF, post-operative AF, AF secondary to structural heart disease, AF secondary to mitral stenosis and prosthetic heart valves (previously known as valvular AF) and AF in athletes reflecting different causes of the arrhythmia (Figure-2) as classified in ESC guidelines for management of AF 2016 [3].

AF pattern	Definition
First diagnosed AF	AF that has not been diagnosed before, irrespective of the duration of the arrhythmia or the presence and severity of AF-related symptoms.
Paroxysmal AF	Self-terminating, in most cases within 48 hours. Some AF paroxysms may continue for up to 7 days.[a] AF episodes that are cardioverted within 7 days should be considered paroxysmal.[a]
Persistent AF	AF that lasts longer than 7 days, including episodes that are terminated by cardioversion, either with drugs or by direct current cardioversion, after 7 days or more.
Long-standing persistent AF	Continuous AF lasting for ≥1 year when it is decided to adopt a rhythm control strategy.
Permanent AF	AF that is accepted by the patient (and physician). Hence, rhythm control interventions are, by definition, not pursued in patients with permanent AF. Should a rhythm control strategy be adopted, the arrhythmia would be re-classified as 'long-standing persistent AF'.

Figure 1: Patterns of AF, ESC 2016 guidelines

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AF type	Clinical presentation	Possible pathophysiology
AF secondary to structural heart disease	AF in patients with LV systolic or diastolic dysfunction, long-standing hypertension with LVH, and/or other structural heart disease. The onset of AF in these patients is a common cause of hospitalization and a predictor of poor outcome.	Increased atrial pressure and atrial structural remodelling, together with activation of the sympathetic and renin-angiotensin system.
Focal AF	Patients with repetitive atrial runs and frequent, short episodes of paroxysmal atrial fibrillation. Often highly symptomatic, younger patients with distinguishable atrial waves (coarse AF), atrial ectopy, and/or atrial tachycardia deteriorating in AF.	Localized triggers, in most cases originating from the pulmonary veins, initiate AF. AF due to one or a few re-entrant drivers is also considered to be part of this type of AF.
Polygenic AF	AF in carriers of common gene variants that have been associated with early onset AF.	Currently under study. The presence of selected gene variants may also influence treatment outcomes.
Post-operative AF	New onset of AF (usually self-terminating) after major (typically cardiac) surgery in patients who were in sinus rhythm before surgery and had no prior history of AF.	Acute factors: inflammation, atrial oxidative stress, high sympathetic tone, electrolyte changes, and volume overload, possibly interacting with a pre-existing substrate.
AF in patients with mitral stenosis or prosthetic heart valves	AF in patients with mitral stenosis, after mitral valve surgery and in some cases other valvular disease.	Left atrial pressure (stenosis) and volume (regurgitation) load are the main drivers of atrial enlargement and structural atrial remodelling in these patients.
AF in athletes	Usually paroxysmal, related to duration and intensity of training.	Increased vagal tone and atrial volume.
Monogenic AF	AF in patients with inherited cardiomyopathies, including channelopathies.	The arrhythmogenic mechanisms responsible for sudden death are likely to contribute to the occurrence of AF in these patients.

Figure 2: Types of AF, ESC 2016 guidelines

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1.4 The rationale for Thesis

AF remains under-diagnosed, as it is often asymptomatic. Up to 30% of patients with AF are unaware of their diagnosis and 25% of those with AF-associated stroke have no prior diagnosis of AF [14]. Moreover studies have shown that AF is paroxysmal in 30% of patients with stroke and therefore may not appear on a single 12 lead ECG [14]. Because of the rather poor sensitivity of single standard ECG for paroxysmal AF, 24-hour ECG recording (Holter) is often used, allowing the detection of previously unrecognized AF in stroke patients. Further extending the ECG recording time from 24hr Tape to a 7 day event recorder [15] further increases the AF detection among patients with a normal 12 lead ECG and 24-hour ECG recording by >5% [16, 17, 18, 19]. Similarly the implantable loop recorder devices have shown to further improve the ability to diagnose AF [16]. A systematic review including studies with Holter diagnosis of PAF/A-flutter in patients with ischemic stroke suggested that screening consecutive patients with Holter monitoring shall identify new AF/atrial flutter in approximately one in 20 patients [20].

It is therefore very important to identify high risk patients likely to have an underlying diagnosis of AF, to increase pre-test probability and to reduce the number of patients needing longer monitoring times.

1.5 Thromboembolic prevention and the association of AF with valvular heart disease

The recommendations for commencement of oral anticoagulation (OAC) therapy among AF patients are dependent upon the types of AF as well as the overall risk of thromboembolism.

The advent of direct oral anticoagulants (DOACs) and the recommendation of DOAC use for stroke prevention in patients with AF [12, 13, 21] have opened new horizons for thromboembolic risk prevention.

AF frequently accompanies valvular heart disease (VHD) [22, 23, 24]. LA dilatation is an early manifestation of progressive mitral valve disease, and the presence of paroxysmal or permanent AF is an accepted indication for early percutaneous or surgical mitral intervention [25]. AF is also frequently seen in later stages of aortic valve disease when LV dilatation and elevated end-diastolic pressure exert secondary effects on LA function [1]. The presence of mitral stenosis and mitral regurgitation is associated with both the incidence and prevalence of AF.[26, 27] The OxVALVE Population Cohort Study is the first population based study of VHD worldwide and demonstrates both the prevalence of undiagnosed and known VHD in older people and the contemporary clinical and epidemiological characteristics of VHD. The initial results of OxVALVE study showed that previously undetected VHD affects 1 in 2 of the elderly population and is more common in lower socioeconomic classes. Furthermore it showed that clinically significant VHD is three times more common in individuals with current or previous AF [28].

1.6 Natriuretic peptides and the potential role in AF

Natriuretic peptides are the most widely used markers of myocardial strain and are primarily synthesised in the heart and regulated by myocardial stress in response to volume or pressure overload. They include B-type natriuretic peptide (BNP) and the N-terminal fragment of its prohormone (NT-proBNP), atrial natriuretic peptide (ANP), adrenomedullin and the midregional fragment of the prohormone (MR-proANP). These prohormones are released under conditions of haemodynamic stress and processed into biologically active natriuretic peptides, which induce vasodilation, natriuresis and diuresis [29]. A major landmark was reached approximately 15 years later, the 1990s, when B-type natriuretic peptide (BNP) was shown to provide physicians with the ability to diagnose congestive heart failure in the primary care setting [30]. The prognostic properties of BNP and its inactive part, N-terminal pro BNP (NT-proBNP), were thereafter described and validated rapidly in patients with heart failure, stable and acute coronary artery disease, as well as among patients with VHD including arotic stenosis (AS), aortic regurgitation (AR) and mitral regurgitation (MR) [29, 31, 32].

Previous Studies have shown BNP and NTpro-BNP levels to be elevated in patients with both new and prevalent AF [33, 34, 35, 36]. Various large randomised trials involving NOACs have also proposed NT-proBNP to be a marker of prognosis among patients with AF [37, 38, 39].

Most of the previous studies on natural history of AF are hospital based [22, 24] and the majority of population-based studies are more than 10 years old [40, 41, 42, 43, 44, 45]. Recent studies seem to focus on natural history of AF in the context of heart failure or intra-cardiac devices [46, 47, 48].

In this study we endeavour to understand the burden of AF including its population prevalence, various patterns and treatment of AF in the community setting in an elderly (age >65) asymptomatic contemporary, population cohort; [28] and to define its predictors (in particular BNP), associated risk factors, proportion of AF patients meriting and receiving anticoagulation therapy, and the association of AF with VHD.

2 Methods

2.1 Study design

A retrospective observational study, using data from existing OxVALVE population cohort study. This study was designed to identify undiagnosed VHD in the community but included measures that could be used for the diagnosis of AF and many potentially associated factors.

2.2 Study population

The epidemiological and clinical data of 4009 OxVALVE study participants was analysed. The purpose, design, methods and initial results of OxVALVE study have been published previously [28, 49]. In summary subjects aged 65 years and older without known VHD who were registered with one of the 7 primary care medical centres were invited to participate. Younger subjects were excluded since (i) previous retrospective studies have demonstrated that the prevalence of VHD is low in those aged <65 years and (ii) uptake of community screening was likely to be low in those with work or family commitments. The participating medical centres were representative of the local population demographics and selected for the availability of accurate patient databases with comprehensive search facilities. Subjects with a previous diagnosis of VHD (identified using relevant National Health Service diagnostic Read codes) were not included in the study but their diagnostic data were collected to derive total prevalence. Exclusion criteria included terminal illness and immobility or general frailty precluding attendance (as judged by the general practitioner/family physician). Potential study participants are identified from practice lists by the practices themselves—all patient identifiable information was held by the GPs until

participants consent to take part in the study. The Oxfordshire population aged 65 years and over consisted of 103742 adults in the 2011 census (45% men), with ethnicity as follows: Caucasian 97.8%, Asian 1.1%, African-American 0.6%, mixed ethnicity 0.3%, other ethnicity 0.1%. Potential participants were invited by letter with a single follow-up reminder to non-responders. Those declining participation were asked to fill in a brief response indicating their reasons to allow detection of study bias. All participants provided written informed consent [49].

2.3 Baseline data and serum BNP

All the study participants had their full medical history (inclusive of drug history), clinical observations (blood pressure, heart rate, heart rhythm, height, weight, ankle oedema), and symptoms recorded prior to having a limited cardiovascular physical examination followed by undergoing screening echocardiography. Study participants also underwent venepuncture and EDTA plasma samples are collected for serum B-type natriuretic peptide (BNP) analysis and these were frozen prior to analysis for up to 3 days following centrifugation and separation. BNP analyses utilised the Siemens ADVIA Centaur analyser (Siemens Healthcare Diagnostics, Frimley, UK) in accordance with manufacturer's recommendations. Sample registration and tracking were collated using Sapphire V.5.1 (LabVantage, Somerset, New Jersey, USA). The demographics and associated risk factors of subjects with AF were calculated from these data. [II]

[II] Case report form used for data collection: Appendix II

2.4 Echocardiography:

The echocardiographic data of the participants with AF was analysed to assess association between AF and VHD. This includes both single valve and mixed valve disease, right and left sided disease and the severity of the valve disease. Echocardiography was performed by the British Society of Echocardiography (BSE) accredited sonographers or physicians using a Vivid-Q portable machine (Vingmed-General Electric, Horton, Norway)—the same pool of operators also perform visit 2 scans. BSE accreditation is directly comparable to European Association of Cardiovascular Imaging accreditation in transthoracic echocardiography (with which there is reciprocal recognition). A two-beat clip for each image was stored in sinus rhythm, while a five-beat clip was acquired in patients with irregular rhythm (usually atrial fibrillation). Measurements were not recorded immediately following an ectopic beat. When assessing regurgitation with colour flow Doppler, the Nyquist limit was set to 50–60 cm/s. For views of each valve, the colour gain was optimised until just before 'speckling' occurs.

In addition to standard acquisition protocols, the following images/measurements were obtained (corresponding views listed in brackets):

- Zoomed images of the aortic valve, aortic root and ascending aorta, along with any regurgitation (parasternal long and short axis).
- Diastolic function assessment (to include mitral valve inflow, pulmonary vein flow and pulsed wave (PW) tissue Doppler imaging (TDI) of the septal and lateral walls).
- Tissue velocity imaging (TVI) 2D loop of left ventricle.

- Continuous wave Doppler through aortic, mitral and tricuspid valves to demonstrate presence/absence of any regurgitation (apical five/four/three and two-chamber views, as appropriate).

Left ventricular ejection fraction was assessed using the Teichholz calculation if left ventricular systolic function is qualitatively normal, accompanied by experienced visual assessment of overall systolic function. Abnormal systolic function lead to a formal biplane volumetric assessment of ejection fraction, classified as follows: normal ≥60%, mildly impaired 45–59%, moderately impaired 35–44% and severely impaired <35%. A high threshold for normality was chosen to ensure that a large proportion of participants underwent volumetric assessment.

Valve anatomy and physiology are assessed in accordance with BSE criteria for stenosis and regurgitation, [50] which were adapted from internationally recognised guidelines [51, 52]. Aortic valve sclerosis is defined by the presence of all of the following echocardiographic features:

- Focal areas of thickening and increased cusp echogenicity (calcification)—minor leaflet tip thickening in itself is insufficient and abnormal cusp echogenicity must be demonstrated.
- Normal or near normal cusp mobility.
- Maximum aortic valve transvalvular velocity less than or equal to 2.5 m/s.

These criteria are minor modifications of the European Association of Echocardiography/American Society for Echocardiography guidelines [52]. A calcified or thickened aortic valve with transvalvular velocity greater than 2.5 m/s is diagnosed as aortic stenosis. Extrapolating from the American Society of Echocardiography guidelines, [51] we define mild (as opposed to trivial or 'physiological') valvular regurgitation if the regurgitant

jet has a clear origin and is visible in more than one view on colour Doppler. Trivial mitral regurgitation required the presence of normal mitral valve anatomy and a regurgitant jet that extends less than 1 cm into the left atrium at Nyquist limit 50–60 cm/s in all views. . "Significant" VHD referred to VHD of more than mild severity i.e. at least mild valvular stenosis or moderate plus valvular regurgitation, as defined by the International guidelines [51, 52].

2.5 Diagnosis of atrial fibrillation

Participants with a previous (known) diagnosis of AF were identified in the OxVALVE study using the NHS Read codes in the GP databases. New (previously undiagnosed) AF was identified in the OxVALVE study participants without a previous diagnosis of AF, by real-time analysis of the cardiac rhythm during echocardiography, in addition to retrospective analysis of the recorded ECG. Analysis of the recorded ECG was performed on at least 6 image loops, with each loop containing at least 5 recorded beats. This was supplemented by assessment of the pulse wave Doppler trace of mitral inflow [53]. The real-time assessment was performed by highly specialised accredited cardiac physiologists with expertise in analysing ambulatory heart rhythm monitoring devices, in addition to echocardiography. Subjects with atrial flutter were also identified using the above process, supplemented by 2D and M-Mode motion of mitral valve leaflets [54] and were excluded from AF cohort. Rolling review with blinded re-reporting of a random sample of approximately 15% of scans by the pool of BSE accredited sonographers and physicians was undertaken for quality assurance and to ensure consistency of reporting across sites. Reproducibility between the original assessment and that delivered by the group was reported using Cohen's κ coefficient. An

independent blinded cardiologist reviewed scans, when differences in reporting emerged [49]. I confirmed the diagnosis subsequently by reviewing the transthoracic echocardiogram studies of all the subjects with known and new AF and atrial flutter. No diagnostic discrepancies were found between the echocardiographers and myself, confirming good inter-observer agreement. The responsible General Practitioners (GPs) of all the study participants with newly diagnosed AF & atrial flutter were made aware of the diagnosis by the study team and the subjects were subsequently managed accordingly by their GPs. The prevalence of AF and proportion of individuals with new AF were calculated from these data.

2.6 Statistical analysis

Continuous variables are provided as mean +/- standard deviation and categorical variables are provided as numbers and percentages. Unpaired t-test was used to analyse the relationship between continuous variables while the Chi-squared (X^2) test was used to analyse the relationship between categorical variables. Multiple Logistic regression models were constructed and stepwise rejection of variables was performed using a significance threshold level of $p < 0.05$ in order to analyse the predictors of new AF. 10 (0.2%) out of 4009 participants had no left atrial (LA) diameter and left ventricular ejection fraction measurements due to poor acoustic windows resulting in difficult image acquisition. The data of these 10 participants were also included in the final analysis as the rest of demographics, clinical and echocardiographic variables were available for interpretation.

3 Results

3.1 Baseline characteristics

The mean age of participants with AF was higher than those with no AF, (75.9 +/- 6.4 years vs 72.7 +- 5.92 years, p<0.0001) (Table-1). AF was more common among males as compared to females (176(59.7%) vs 119(40.3%), p=0.03). Subjects with AF were found to be more symptomatic in terms of NYHA (New York Heart Association) functional class 3-4 when compared to those with no AF: 18 (6.1%) vs 76 (2.0%), p <0.0001. Significantly higher proportion of individuals with AF had pacemaker implantation as compared to those with no AF (4.1% vs 0.6%, p<0.0001). No significant difference was found between the heart rate, blood pressure (both systolic and diastolic) and body mass index among the participants with AF when compared to those with no AF. No significant difference between the blood pressure among subjects with AF and those with no AF can be explained by the fact that our study is based upon an elderly >65, asymptomatic population cohort; a large proportion of which were known hypertensive (45%, 1807/4009) and were already established on appropriate antihypertensive medications. The presence of ankle oedema however on clinical examination was found to be significantly associated with AF (79 (26.8%) vs 505 (13.6%), p<0.0001) (Table-1).

Table 1: Demographics of study participants with and without (AF) n=4009

	Atrial fibrillation	No Atrial fibrillation	p-value
No of participants	295 (7.3%)	3714 (92.6%)	
New AF	36 (0.8%)	-	
Age	75.9 +- 6.4	72.7 +- 5.92	<0.0001
Gender			
Male	176 (59.7%)	1781 (48.0%)	0.03
Female	119 (40.3%)	1933 (52.0%)	
Smoking status			
Smoker	10 (3.4%)	255 (6.9%)	
Ex-smoker	129 (43.7%)	1495 (40.3%)	
Non smoker	156 (52.9%)	1961 (52.8%)	
NYHA Class			
I/II	277 (93.8%)	3637 (98.0%)	
III/IV	18 (6.1%)	76 (2.0%)	<0.0001
History			
Hypertension	177 (60.0%)	1630 (43.9%)	0.002
Hypercholesterolemia	145 (49.2%)	1370 (36.9%)	0.008
Diabetes	36 (12.2%)	422 (11.4%)	
Angina	47 (15.9%)	262 (7.1%)	<0.0001
Percutaneous coronary intervention	21 (7.1%)	132 (3.6%)	0.006
Coronary artery bypass grafting	15 (5.1%)	54 (1.5%)	<0.0001
Myocardial infarction	33 (11.2%)	157 (4.2%)	<0.0001
Stroke/TIA	40 (13.6%)	204 (5.5%)	<0.0001
Permanent pacemaker	12 (4.1%)	22 (0.6%)	<0.0001
Rheumatic fever	9 (3.1%)	75 (2.0%)	
Clinical examination			
Heart rate (beats/min)	73.5 +- 14.0	72.7+- 11.9	
Body mass index (kg/m2)	27.9 +- 5.17	27.5 +- 4.8	
Ankle oedema	79 (26.8%)	505 (13.6%)	<0.0001
Systolic blood pressure	142.7 +- 23.4	143.1 +- 19.9	
Diastolic blood pressure	81.4 +- 12.7	80.0 +- 11.3	
Echocardiogram			
LVEF (%)	65 +- 11	66 +- 9	
LA size (2D) cm	4.1 +- 0.7	3.6 +- 0.5	<0.0001
Significant VHD	67 (22.7%)	218 (5.8 %)	<0.0001
LVEF >55%	258 (87.4%)	3473 (93.5%)	
<55%	37 (12.5%)	241 (6.5%)	0.0005

Continuous variables are presented as numbers and percentages and categorical variables are presented as mean +- standard deviation. Unpaired t-test & Chi-squared (X^2) test used to assess statistical relationship between continuous & categorical variables respectively. p-value of <0.05 was deemed statistically significant. Only those p-values of statistical significance are quoted.

3.2 The population prevalence and patterns of AF

The total prevalence of AF in our population cohort was 7.3% (295/4009). 36 out of 295 subjects were diagnosed with new AF, making it 12% (36/295) of the AF and 0.8% of the total cohort (Table-1). The prevalence of AF increased with age in keeping with the previous studies. This includes both the total prevalence: increasing from 3.9% among 65-69 years old to 13.2% among participants 80 years or more of age; as well as the prevalence of newly diagnosed (new AF): 0.9% among 65-69 years old to 1.8% among subjects 80 years or more of age (Table-2, Figure-3).

88% (259/295) of study participants with AF had known AF. 60% (155/259) of subjects with known AF patients were found to be in sinus rhythm where as the 40% (104/259) were in AF. Among patients with known AF: 76% (197/259) had paroxysmal AF, 20.5% (53/259) had persistent AF whereas 3.5% (9/259) had permanent AF (Figure-4).

Table 2: The prevalence of AF according to age, including subjects with New AF (n=4009)

Age (Years)	AF Prevalence (n) %	Newly diagnosed AF (n) %
65-69	58/1454 (3.9%)	13/1454 (0.9%)
70-74	76/1168 (6.5%)	7/1168 (0.6%)
75-79	79/767 (10.3%)	5/767 (0.6%)
80+	82/620 (13.2%)	11/620(1.8%)

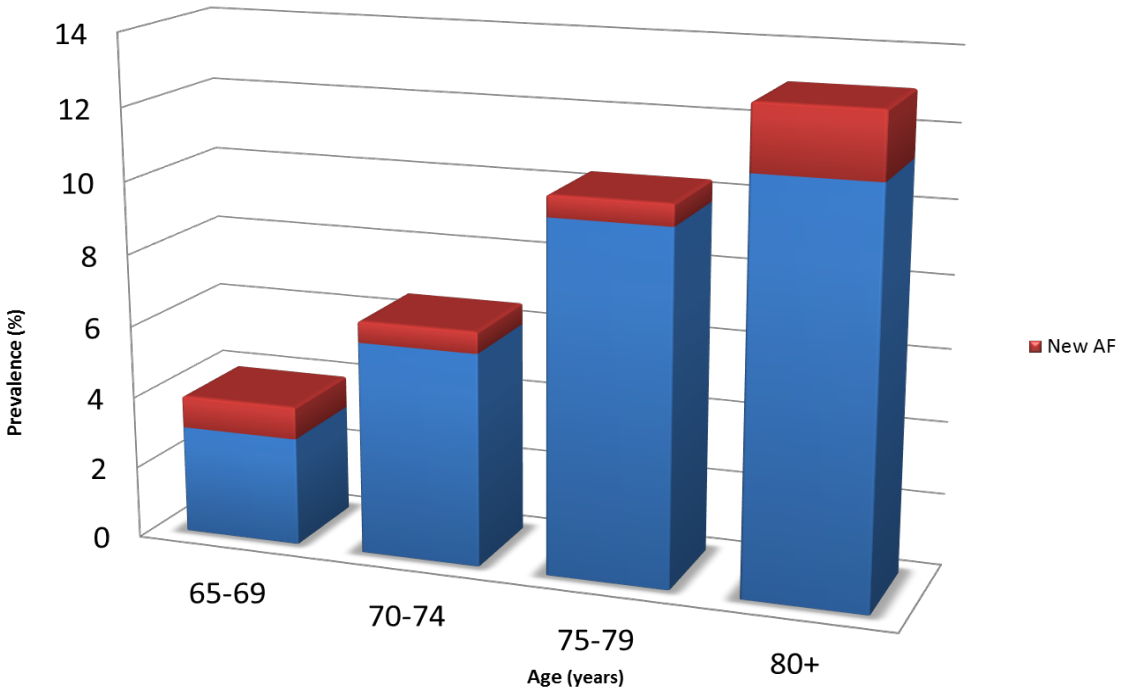


Figure 3: The prevalence of AF with age (previously undiagnosed individuals in red).

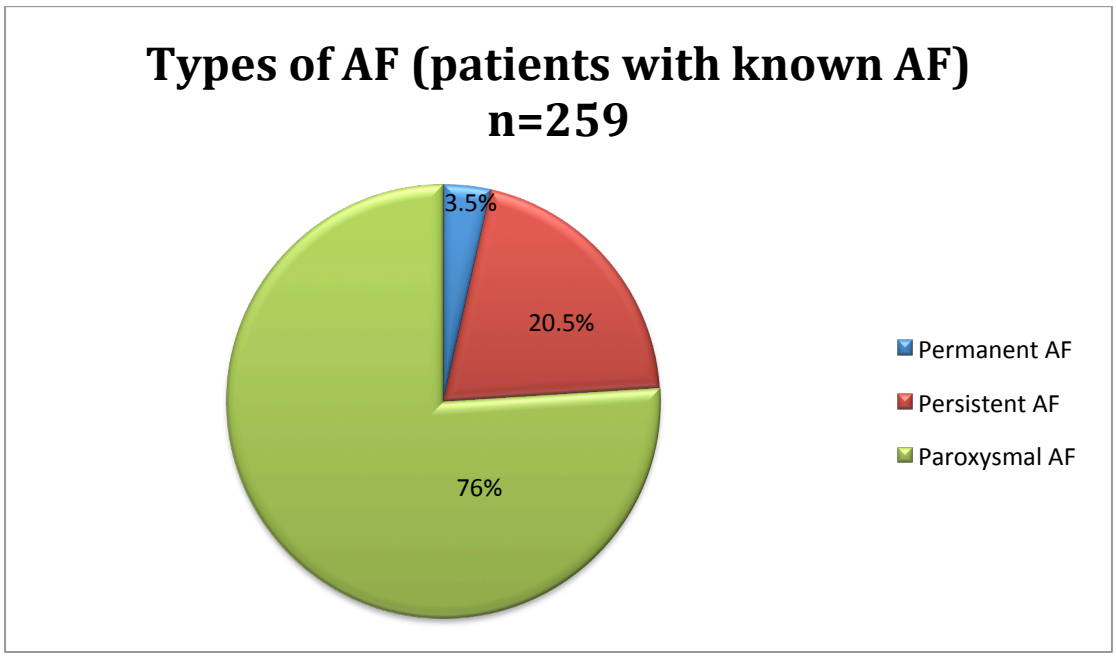


Figure 4: Patterns of AF

3.3 The association between AF and serum BNP

Overall 35% (1416/4009) study participants had their serum BNP analysed; among which 92% (1307/1416) had no AF and 8% (109/1416) had AF.

71% (78/109) subjects with AF had a serum BNP >20pmol/L as compared to only 16% (208/1307) with no AF; showing a significant association between raised serum BNP >20pmol/L and AF (p-value <0.0001) Table-3

A serum BNP level >20pmol/L had sensitivity of 71% (95% CI 62-80%), specificity of 84% (95% CI 82-86%), positive likelihood ratio 4.5 (95% CI 3.8-5.3), negative likelihood ratio 0.34 (0.25-0.46), positive predictive value of 27% (95% CI 24-31%) and a negative predictive value of 97% (95% CI 96-98%) for diagnosing AF.

Receiver operated characteristic (ROC) curve showed an area under the curve of (AUC) of 0.69 (95% CI 0.62-0.75) suggesting serum BNP to be a useful biomarker for AF (Table-4, Figure-5).

Table 3: AF and its association with serum BNP

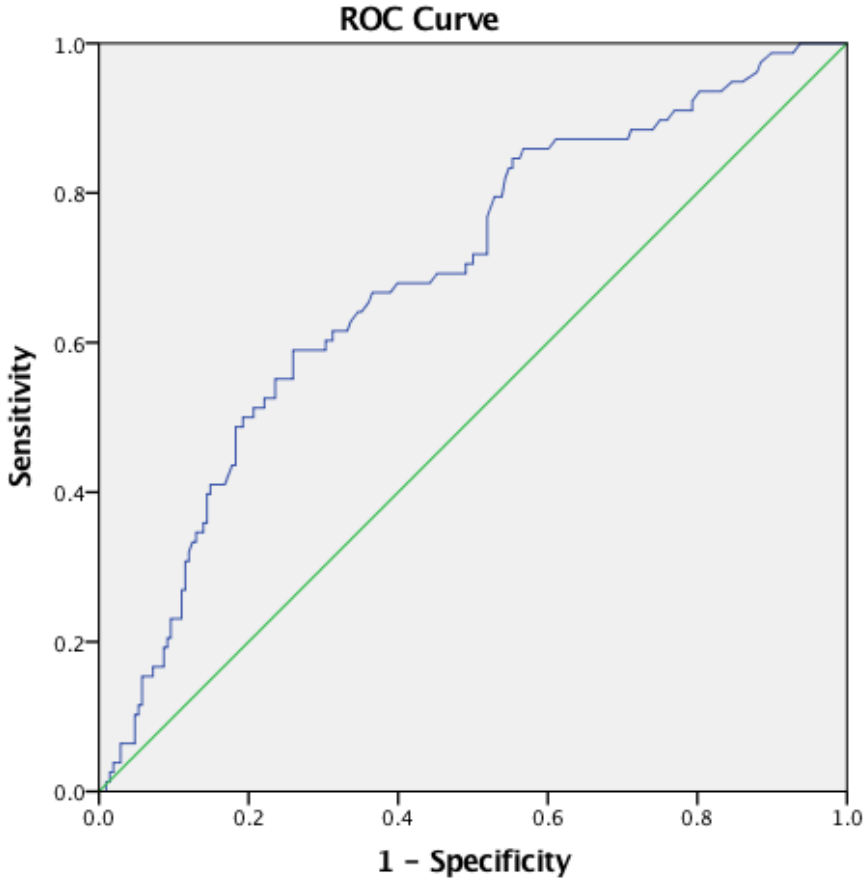
	AF	**No AF**	**Total**
Total no of subjects with BNP	109	1307	**1416**
Patients with BNP>20 pmol/L	78	208	**286**
Total	**187**	**1515**	**1702**

The two-tailed P value is less than 0.0001 (Fisher's Exact Test)

Table 4: Measures of diagnostic accuracy, serum BNP as a biomarker for AF

	AF				
BNP	**Present**	**n**	**Absent**	**n**	**Total**
Positive	True Positive	a = 78	False Positive	c = 208	a + c= **286**
Negative	False Negative	b = 31	True Negative	d = 1099	b + d= **1130**
Total		a + b = **109**		c + d = **1307**	

Statistic	Formula	Value	95% CI
Sensitivity	$\frac{a}{a+b}$	71.56%	62.12% to 79.79%
Specificity	$\frac{d}{c+d}$	84.09 %	81.99% to 86.03%
Positive Likelihood Ratio	$\frac{Sensitivity}{1-Specificity}$	4.50	3.79 to 5.34
Negative Likelihood Ratio	$\frac{1-Sensitivity}{Specificity}$	0.34	0.25 to 0.46
Disease prevalence	$\frac{a+b}{a+b+c+d}$	7.70% (*)	6.36% to 9.21%
Positive Predictive Value	$\frac{a}{a+c}$	27.27% (*)	24.00% to 30.81%
Negative Predictive Value	$\frac{d}{b+d}$	97.26 % (*)	96.34% to 97.95%
Accuracy	$\frac{a+d}{a+b+c+d}$	83.12% (*)	81.07% to 85.04%


ROC Curve
Sensitivity
1 – Specificity
0.0
0.2
0.4
0.6
0.8
1.0

Area Under the Curve

Test Result Variable(s): Serum BNP

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.689	.035	.000	.621	.757

The test result variable(s): BNP RESULT has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Figure 5: Receiver operating characteristics curve for serum BNP

3.4 The management of AF (in an elderly community based population cohort)

A) 51%, (132/259) of patients with known AF were on rate control medical therapy:

1) 75%, (99/132) either on Beta-blockers or Beta-blockers + Digoxin

2) 15%, (20/132) on digoxin only

3) 10%, (13/132) Diltiazem 7, Verapamil 6

B) 9%, (23/259) were on rhythm control medical therapy, including:

1) Class 1-C Anti-Arrhythmic (Flecainide 2) 5%, 2/23

2) Class 3 Anti-Arrhythmic (Sotalol 13, Amiodarone 8) 91%, 21/23

C) 32%, (82/259) were on neither the rate control nor the rhythm control medical therapy

D) Only 5%, (13/259) underwent DC-Cardioversions and 3%, (9/259) underwent catheter ablation for AF

3.5 AF and cardiovascular risk factors

Hypertension was found to be a significant cardiovascular risk factor associated with the prevalence of AF when compared to those with no AF (177 (60%) vs 1630 (43.9%), p=0.002) (Table-1). Similarly hypercholesterolemia (145 (49.2%) vs 1370 (36.9%), p=0.008) (Table-1) and cumulative coronary heart disease (including subjects with angina, previous myocardial infarction/percutaneous coronary intervention/coronary artery bypass grafting) 116 (39.3%) vs 605 (16.3%), p<0.0001 were found to be significant cardiovascular risk factors associated with AF (Table-5). Smoking and diabetes were not found to be significantly associated with the prevalence of AF.

Table 5: Coronary heart disease and its association with prevalence of AF

Coronary heart disease	**Atrial fibrillation n = 295**	**No Atrial fibrillation n = 3714**	**p-value**
Angina	47 (15.9%)	262 (7.1%)	<0.0001
Percutaneous coronary intervention	21 (7.1%)	132 (3.6%)	0.006
Coronary artery bypass grafting	15 (5.1%)	54 (1.5%)	<0.0001
Myocardial infarction	33 (11.2%)	157 (4.2%)	<0.0001
Total	116 (39.3%)	605 (16.3%)	<0.0001

Chi-squared (X^2) test is used to assess the statistical relationship between categorical variables

3.6 AF and its association with left atrial size & left ventricular systolic function

Increased left atrial size (in cm): 4.1+-0.7 vs 3.6+-0.5, p<0.001 and impaired left ventricular (LV) systolic function LVEF<55%: 37 (12.5%) VS 241 (6.5%), p 0.0005 were significantly associated with the prevalence of AF (Table-1)

3.7 AF & its association with valvular heart disease

Significant VHD was more common and was significantly associated with the prevalence of AF when compared to those with no AF (67 (22.7%) vs 218 (5.8%) p<0.0001) (Table-1). Most of the individuals with AF had some degree of VHD: 258/295 (87%). Mixed valve disease was more common in subjects with AF as compared to single valve disease (Figure-6). The prevalence of AF was significantly associated with the presence and increased severity of mitral regurgitation (p<0.0001), tricuspid regurgitation (p<0.0001), presence of aortic sclerosis (p=0.01), aortic regurgitation (p=0.008) and pulmonary regurgitation (p=0.006) (Table-6). No significant association was found between history of rheumatic fever and the prevalence of AF.

Table 6: AF and its association with VHD

VHD	Severity	AF (n = 295)	No AF (n = 3714)	p-value
MR	Mild-	98 (33.2%)	874 (23.5%)	0.006
	Mild/moderate	7 (2.4%)	68 (1.8%)	
	Moderate-	20 (6.8%)	43 (1.2%)	<0.0001
	Moderate/severe	3 (1.0%)	5 (0.1%)	
	Severe	1 (0.3%)	1 (0.0%)	
MS	Mild-	-	8 (0.2%)	
	Mild/moderate	-	1 (0.0%)	
	Moderate-	-	-	
	Moderate/severe	-	1 (0.0%)	
AR	Mild-	46 (15.6%)	499 (13.4%)	
	Mild/moderate	7 (2.4%)	54 (1.5%)	
	Moderate-	10 (3.4%)	47 (1.3%)	0.008
	Moderate/severe	-	3 (0.1%)	
	Severe	-	-	
AS	Mild-	2 (0.7%)	24 (0.6%)	
	Mild/moderate	-	-	
	Moderate-	2 (0.7%)	16 (0.4%)	
	Moderate/severe	-	1 (0.0%)	
	Severe	-	6 (0.2%)	
AoScl		170 (57.6%)	1677 (45.1%)	0.01
TR	Mild-	93 (31.5%)	971 (26.1%)	
	Mild/moderate	20 (6.8%)	63 (1.7%)	<0.0001
	Moderate-	18 (6.1%)	35 (0.9%)	<0.0001
	Moderate/severe	2 (0.7%)	3 (0.1%)	
	Severe	8 (2.7%)	3 (0.1%)	
TS		0	0	
PS	Mild	0	1 (0.0%)	
PR	Trace/Mild	119 (40.3%)	1092 (29.4%)	0.006
	Mild/moderate	-	-	
	Moderate	1 (0.3%)	20 (0.5%)	
MAC		46(15.6%)	482 (12.9%)	

MR = mitral regurgitation, MS = mitral stenosis, AR = aortic regurgitation, AS = aortic stenosis, TS = tricuspid stenosis, TR = tricuspid regurgitation, PR = pulmonary regurgitation, PS = pulmonary stenosis, AoScl = aortic sclerosis, MAC = mitral annular calcification. Chi-squared (X^2) test used to calculate p-value for categorical variables.

Total number of patients with atrial fibrillation: 295
Number of participants with atrial fibrillation and no valvular heart disease = 37 (12.5%)

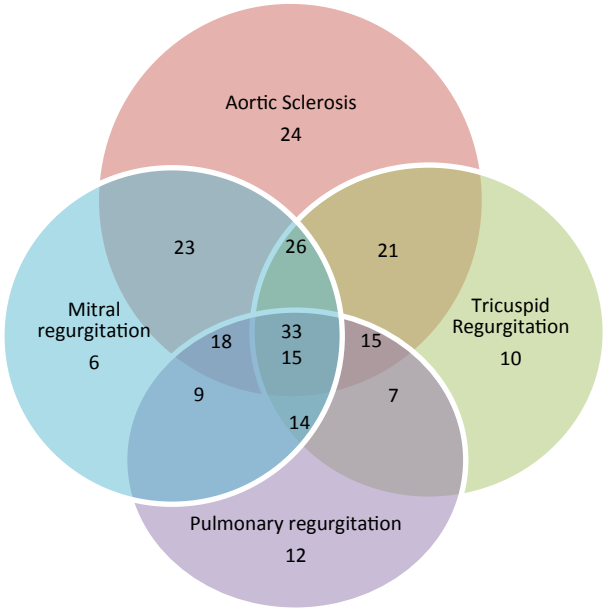


Figure 6: Venn diagram demonstrating the distribution of single and multiple valve abnormalities in subjects with AF. The area of each circle is proportionate to the number of participants with different manifestations of valvular heart disease. Numbers denote the number of participants in each group. The diagram excludes aortic stenosis (n=4), mitral stenosis (n=0), aortic regurgitation (n=63), tricuspid and pulmonary stenosis (n=0) [III]

[III] Key for single and mixed VHD: Appendix-III

3.8 AF & oral anticoagulation

205/259 (79.1%) subjects with known AF had a CHA_2DS_2VASC score of 2 or more and therefore merited anticoagulation on the basis of current guidelines. Only 100/259 (38.6%) subjects however received appropriate oral anticoagulation therapy. 98/100 (98%) of those on anticoagulation were on Warfarin and only 2/100 (2%) were on direct oral anticoagulants (DOACs) at the time of entry into the study (August 2009 – January 2013). 75/259 (28.9%) subjects were on Aspirin only. 84/259 (32.4%)received neither Aspirin nor Warfarin (Table-7, Figure-7)

Table 7: Oral anticoagulation in patients with known AF

Oral anticoagulation in patients with known AF (n=259)	
CHA_2DS_2VASC Score of 2 or more	205 (79.1%)
On aspirin only	75 (28.9%)
On anticoagulants	100 (38.6%)
On warfarin	98 (98.0%)
On both aspirin and warfarin	5
DOACs	2 (2.0%)
Not on aspirin or anticoagulants	84 (32.4%)

DOACs = Direct oral anticoagulants

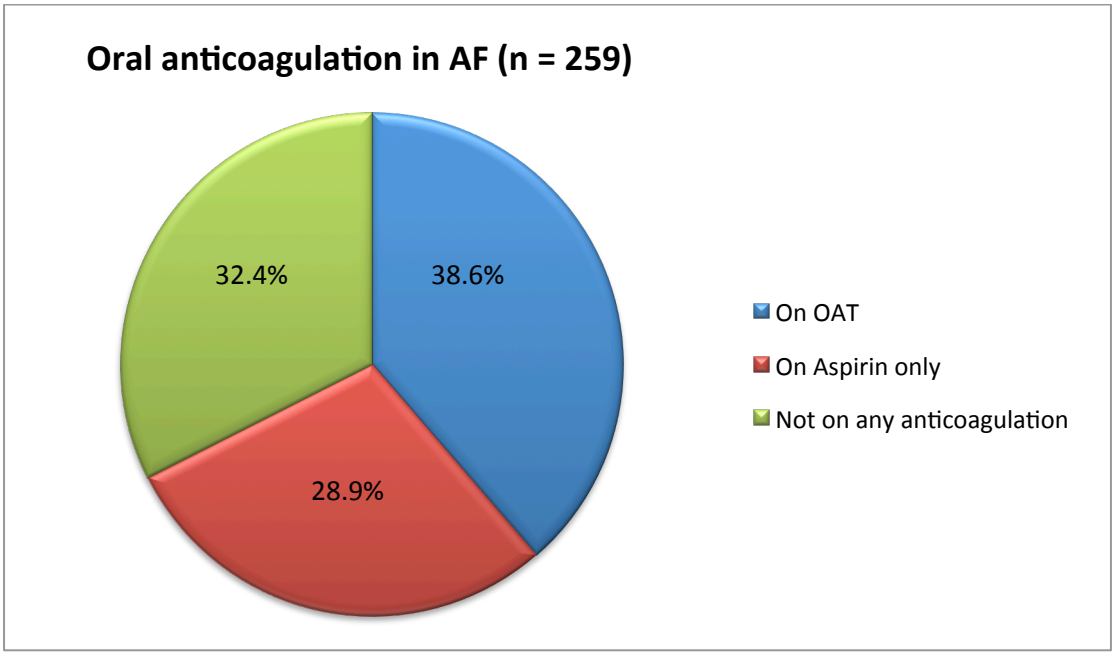


Figure 7: Oral anticoagulation in subjects with AF

3.9 Predictors of newly diagnosed AF

Logistic regression analysis showed LA diameter (p<0.0001), significant VHD (p=0.03) and systolic blood pressure (p=0.01) to be independent predictors of newly diagnosed AF (Table-8).

Table 8: Independent predictors of new AF (n=36)

Variable	Frequency	Multivariate logistic regression analysis (p-value)	OR 95% CI
LA diameter (cm)	4.2 +- 0.7	<0.0001	3.62 (3.43-3.82)
Systolic BP (mmHg)	134.5 +- 19.3	0.01	0.97 (0.95-0.99)
Significant VHD	4 (10.8%)	0.03	3.27 (1.12-9.54)

OR= odds ratio, LA = left atrium, BP= blood pressure, CI = confidence interval, NAF = newly diagnosed atrial fibrillation. Continuous variables are given as mean+- standard deviation and categorical variables are given as numbers and percentages.

4 Discussion

Using data from the large prospective OxVALVE cohort study based on elderly population, my study presents the epidemiological characteristics of AF in a contemporary population cohort. My study not only describes the patterns, management, population prevalence, predictors, correlates and the associated risk factors for AF, but also the association of AF with BNP and VHD. Furthermore the study shows trends concerning the use of oral anticoagulation therapy (OAT) among subjects with AF in primary care as well as the potential role of serum BNP as a biomarker for AF.

4.1 Prevalence of AF

My study shows an AF population prevalence of 7.3%, 12% of which was previously undiagnosed. This represents a higher prevalence when compared to the average prevalence among similar age groups in previous studies such as “Cardiovascular health study” a population based longitudinal study involving 5201 subjects 65 years or more of age, showing a population prevalence of 5.5% [41]. Similarly the population based cross-sectional “ATRIA study” involving 17,974 subjects with AF showed a population prevalence of 6.3% among subjects 65 years of more of age [7]. The prevalence of AF increased steadily with age from 3.9% among 65-69 years to 6.5% among 70-74 years old, 10.3% among 75-79 years old and finally rising to 13.2% among participants 80 years or more. Similar trends have been observed in the previous studies [1, 6, 7, 8, 9, 41, 42, 55].

4.2 Patterns and management of AF

AF can frequently be asymptomatic and therefore silent AF remains common. Paroxysmal AF remains a common pattern of AF as shown in various large population based studies [56, 57, 58, 59, 60]. The results from my study confirm PAF to be the most common pattern being 76% (197/259) of the total no of patients with known AF, while persistent AF was 20% (53/259) had persistent AF with permanent AF being among 3.5% (9/259) only.) AF can be managed either with the rate or rhythm control strategy. The majority of AF patients (46%, 119/259) in my study were managed with rate control strategy with either a beta-blocker or a combination of beta-blockers and digoxin (83%, 99/119) or digoxin (17%, 20/119) alone. This may well be owing to the fact that most of these patients were clinically well and asymptomatic and therefore unaware of underlying AF.

14% (36/259) of the AF patients in my study were managed with rhythm control medical therapy. Most of them 58%, (21/36) being on Class-3 Anti-Arrhythmic (potassium channel blockers) followed by Class-4 Anti-Arrhythmic (Calcium channel blockers) 36%, (13/36) and only 5% (2/36) being on Class-1C Anti-Arrhythmic (Sodium channel blockers).

Rather surprisingly 40% (104/259) of the AF patients in my study were on neither the rate nor the rhythm control medical therapy. This may once again be owing to the fact that these patients had PAF and were asymptomatic and therefore didn't merit, rate or rhythm control medical therapy. Similarly a lower percentage of patients 5% (13/259) undergoing DCCV is perhaps owing to the fact that only 20% of the known AF patients had persistent and only 3.5% had permanent AF; with the rest having PAF. Only 5% of patients (13/259) underwent catheter ablation for AF which may well be once again owing either being asymptomatic or having good symptom control on either rate or rhythm control medical therapies.

4.3 The association between AF and Serum BNP

The role of natriuretic peptides in patients with atrial fibrillation (AF) was assessed initially by studies conducted during the first years of 2000. These studies were predominantly of descriptive nature evaluating differences of natriuretic peptide levels, BNP and NT-proBNP, in patients with AF as compared with matched controls, as well as the relationship between natriuretic peptides and sinus rhythm versus AF [32]. During the last years, the prognostic properties of NT-proBNP were extended to patients with AF. Several of the landmark non-vitamin K antagonist oral anticoagulant (NOAC) trials had advanced biomarker programmes within the main study. The strong association between the level of NT-proBNP and outcomes in AF was initially reported from the RE-LY trial based on 6189 patients in 2012 [38]. The data showed that when comparing the highest quartile levels of NT-proBNP with those of normal concentrations, the risk of stroke or systemic embolism was doubled, and for cardiovascular mortality fivefold higher, in models adjusting for known risk factors. No significant association was seen for major bleeding. These results were subsequently validated and expanded in the very large biomarker cohort (n=14 892) from the ARISTOTLE trial which showed that the level of NT-proBNP was continuously and independently associated with the individual events of total and ischaemic stroke, total and cardiovascular death but not with myocardial infarction or bleeding [39]. Similar association between the NT-proBNP level and outcomes was later also shown in the ENGAGE AF-TIMI 48 biomarker cohort (n=4880) [61]. Similarly recently published data from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) II registry once again verified the association between BNP/NT-proBNP levels and cardiovascular death and composite

adverse events in a non-clinical trial AF population [62]. These findings suggested that NT-proBNP and other biomarker measurements might be of clinical value for prognostication and decision support in patients with AF. Therefore there is an argument for measuring the natriuretic peptide level as part of the routine evaluation of patients with AF [31].

The result from my research however showed that overall 35% (1416/4009) study participants had their serum BNP analysed; among which 92% (1307/1416) had no AF and 8% (109/1416) had AF. 71% (78/109) subjects with AF had a serum BNP >20pmol/L as compared to only 16% (208/1307) with no AF; showing a significant association between raised serum BNP >20pmol/L and AF (p-value <0.0001) Table-3. Owing to the cross-sectional nature of my study it was not possible to analyse the burden of cardiovascular mortality and morbidity among these patients however this can later be analysed in the follow-up phase of OxVALVE study.

4.4 Serum BNP, a biomarker for AF

AF remains under-diagnosed, as it is often asymptomatic. Clinical examination, 12 Lead ECG and 24 hr ambulatory monitoring are recommended as the first line investigations for screening patients with a likely underlying diagnosis of AF [3}. However up to 30% of patients with AF are unaware of their diagnosis and 25% of those with AF-associated stroke have no prior diagnosis of AF [14]. Moreover studies have shown that AF is paroxysmal in 30% of patients with stroke and therefore may not appear on a single 12 lead ECG [14]. Because of the rather poor sensitivity of single standard ECG for paroxysmal AF, 24-hour

ECG recording (Holter) is often used, allowing the detection of previously unrecognized AF in stroke patients. Further extending the ECG recording time from 24hr Tape to a 7 day event recorder [15] further increases the AF detection among patients with a normal 12 lead ECG and 24-hour ECG recording by >5% [16, 17, 18,19]. Similarly the implantable loop recorder devices have shown to further improve the ability to diagnose AF [16]. A systematic review including studies with Holter diagnosis of PAF/A-flutter in patients with ischemic stroke suggested that screening consecutive patients with Holter monitoring shall identify new AF/atrial flutter in approximately one in 20 patients [20]. Previous Studies have shown BNP and NTpro-BNP levels to be elevated in patients with both new and prevalent AF [33, 34, 35, 36, 63].

It is therefore important to identify high risk patients likely to have an underlying diagnosis of AF, to increase pre-test probability and to reduce the number of patients needing longer monitoring times. The results of my study showed that the subjects with a serum BNP level >20pmol/L had sensitivity of 71% (95% CI 62-80%), specificity of 84% (95% CI 82-86%), positive likelihood ratio 4.5 (95% CI 3.8-5.3), negative likelihood ratio 0.34 (0.25-0.46), positive predictive value of 27% (95% CI 24-31%) and a negative predictive value of 97% (95% CI 96-98%) for diagnosing AF. Receiver operating characteristic (ROC) curve showed an area under the curve of (AUC) of 0.69 (95% CI 0.62-0.75) which statistically is considered as borderline although still similar to guideline recommended risk scores such as the CHA_2DS_2-VASc [63, 64]. Serum BNP>20pmol/L is significantly associated with the presence of both new and known AF ($p = 0.0001$) with a high specificity (84%) and negative predictive value (97%). Serum BNP can therefore be used as a biomarker to identify among high risk patients (elderly, hypertensive with concomitant VHD, CHD etc.) and negative first line investigations (12 lead ECG, Clinical examination +- 24hr monitoring) to identify the ones that are likely to

have an underlying diagnosis of AF and therefore would merit long term monitoring (with 48-72 hr ambulatory monitors, 5 day event monitors, implantable loop recorders etc. which are all much more expensive investigations as compared to serum BNP which is extensively used in primary care for screening in heart failure and costs around 20-25£) which would not only improve the diagnostic yield for AF but could also thereby help reduce the mortality and morbidity among these patients and perhaps the overall cost of managing these AF patients down the line .

4.5 Associated risk factors

Similar to previous studies [7, 9, 41, 42, 55] AF was more common among men as compared to women (59.7% vs 40.3%). The subjects with AF were older (mean age: 75.9 +- 6.4 vs 72.7 +- 5.92, $p<0.0001$) and more symptomatic in terms of NYHA functional class-3, 4 when compared with those without AF (6.1% vs 2.0%, $p<0.0001$). As expected, a higher rate of historical stroke and TIA was observed among participants with AF when compared to those without AF (13.6% vs 5.5%, $p<0.0001$). The presence of ankle oedema on clinical examination ($p<0.0001$) was also found to be an important correlate of AF. This may well be iatrogenic (secondary to anti-hypertensive therapy e.g. calcium channel blockers: 64/295, 21.6% subjects with AF were taking calcium channel blockers including 31.6% of those with AF and ankle oedema) or possibly secondary to hypertension, leading to diastolic dysfunction. A higher proportion of subjects with AF had undergone permanent pacemaker implantation (4.1% vs 0.6%, $p<0.0001$) when compared with those with no AF. This could well be related to fact that the subjects with AF and poor chronotropic response often

undergo AV nodal ablation and backup pacing as a part of “pace and ablate” strategy [1,2, 13].

Hypertension (p=0.002), hypercholesterolemia (p=0.008), coronary heart disease (p<0.0001), LA size (p<0.0001), impaired LV systolic function (p=0.0005) & significant VHD (p<0.0001) were found to be significant risk factors associated with AF. Moreover diabetes, rheumatic fever, smoking & body mass index were found not to be significant risk factors associated with AF in my study.

4.6 Association of AF with VHD

AF frequently accompanies valvular heart disease [22, 23, 24]. Left atrial dilatation is an early manifestation of progressive mitral valve disease, and the presence of paroxysmal or permanent AF is an accepted indication for early percutaneous or surgical mitral intervention [25]. AF is also frequently seen in later stages of aortic valve disease when LV dilatation and elevated end-diastolic pressure exert secondary effects on LA function [1]. The presence of mitral stenosis and mitral regurgitation is associated with both the incidence and prevalence of AF [26, 27]. The recently published results of OxVALVE study (based upon the first 2500 study participants) showed that significant VHD was three times more common among patients with AF [28]. My study validates this: showing significant VHD to be almost three times common among subjects with AF when compared with those without AF [67(22.7%) vs 218(5.8 %), p-value <0.0001]. Indeed most of the study participants with AF (87%) were found to have some degree of VHD (87%). This is likely to be related to either LA dilatation as a direct consequence of VHD e.g. mitral stenosis, mitral regurgitation or secondary LA dilatation as a result of diastolic dysfunction due to LV volume and pressure overload (e.g. aortic regurgitation, aortic stenosis). My study showed that the

prevalence of AF was significantly associated with the presence and increased severity of mitral regurgitation ($p<0.0001$), tricuspid regurgitation ($p<0.0001$), presence of aortic sclerosis ($p=0.01$), aortic regurgitation ($p=0.008$) and pulmonary regurgitation ($p=0.006$). No significant association was found between aortic and mitral stenosis and the prevalence of AF. It has to be taken into account that none of our AF subjects had mitral stenosis & only four (1.4%) had aortic stenosis. The small number of aortic stenosis subjects in this study could be related to the fact that the murmur of aortic stenosis is distinct, radiates to carotids and is easier to diagnose on auscultation as compared to other murmurs, possibly leading to exclusion of these subjects from this study [65, 66, 67]. As would be expected in an elderly population cohort, age related degenerative mixed valve disease was more common in subjects with AF as compared to single valve disease.

4.7 Oral anticoagulation therapy in AF

AF confers a fivefold increased risk of stroke and its prevention in patients with AF is therefore extremely important. Oral anticoagulant (OAC) therapy reduces the risk of stroke by at least 64% and is recommended for all except for those at a truly low risk and those whose perceived bleeding risk outweighs the benefits of treatment [3].

International guidelines stress the importance of oral anticoagulation (OAC) in patients fulfilling eligibility criteria [1, 12, 13, 3]. The rate of stroke in AF patients without concomitant VHD ranges from less than 2 to more than 10 strokes per 100 patient-years [68] and it is as high as 17–18% in patients with mitral stenosis or prosthetic valves [69]. The current recommendations for OAC therapy among AF patients however depend upon the origin and type of AF [12, 13]. The advent of direct oral anticoagulants (DOACs) and the recommendation of DOAC use for stroke prevention in patients with AF [12] have provided

more flexible options for stroke prevention for patients with AF. Warfarin (Vitamin-K antagonist) remained the only recommended oral anticoagulant for patients with AF in context of prosthetic valves or mitral stenosis until very recently ESC recognised the current evidence and recommended the use of DOACs in aortic valve disease and mitral regurgitation (only) [21].

My study showed that the 205 (79.1%) participants with known AF had a CHA_2DS_2VASC of 2 or more and therefore merited oral anticoagulation on the basis of current guidelines. However only 100 (38.6%)received appropriate oral anticoagulation therapy (OAT). 98 (98%) subjects received Warfarin and 2 (2%)received DOACs. 75 (28.9%) subjects received Aspirin alone and 84 (32.4%) subjects received neither Aspirin nor any form of anticoagulation. Minimal use of DOACs for oral anticoagulation in our study can be explained by the fact that OxVALVE study started in 2009 and DOACs were not widely available moreover ESC guidelines only recommended the use of DOACs in NVAF in 2012 [12].

4.8 Independent predictors of new AF

My study showed LA size, systolic blood pressure and the presence of significant VHD to be the independent predictors of newly diagnosed (new) AF. Furthermore subjects with dilated LA and the presence of significant VHD were found to be three times more likely to develop new AF. LA size & hypertension have been shown predict AF in previous studies [70, 71, 72, 73]. Significant VHD likely to be related to the aetiology and pathophysiology of AF as previously discussed. [1, 22, 23, 24, 25]

4.9 Echocardiographic screening for VHD

Valvular heart disease (VHD) is common and a major indication for imaging. Echocardiography is the first-line imaging technique for diagnosis, assessment, and serial surveillance for VHD. VHD is known to be under-detected with implications for prognosis for moderate-to-severe disease, so there is an argument for screening high-risk populations [74]. The OxVALVE study showed the prevalence of undetected moderate or severe VHD is 6.4%, with a total prevalence (including those already diagnosed) of 10–11%, whereas mild VHD was detected in a large proportion (44%) of subjects aged ≥65 [28]. Recent ESC guidelines have suggested that screening echocardiography should be offered to those with a likely pathological murmur or any murmur associated with a cardiac symptom. Echocardiographic screening has also been suggested in elderly patients after hip fracture as finding significant AS can lead to modifications in anaesthetic technique and perioperative care [74]. Indeed the results from my recently published research paper based upon OxVALVE study participants confirm that cardiac auscultation alone has a poor accuracy in diagnosing valvular heart disease among asymptomatic subjects [75].
The findings of the OxVALVE study [28], alongside other recent studies, suggest a significant association of AF with VHD for both all grades and significant VHD, which may be a suitable pre-screening indicator. The recent ESC guidelines also recommended echocardiographic screening in patients with AF even in the absence of a murmur or cardiac symptoms [74], as there are several useful parameters that echocardiography can provide.

My study showed that significant VHD was almost three times common among subjects with AF when compared with those without AF [67(22.7%) vs 218(5.8 %), p-value <0.0001]

and most of the study participants with AF (87%) were found to have some degree of VHD. AF can therefor be considered a silent marker of VHD

5 Study Limitations

The OxVALVE study only included participants who were 65 years of age or older therefore the results cannot be generalised to younger age groups.

The number of participants with newly diagnosed AF was small and therefore predictors of new AF are based upon a small sample size (n=36), limiting the power to detect risk factors with small effect size. Furthermore confounding factors such as age, other co-morbidities (e.g. hypertension, diabetes), medications etc. have to be taken into account during the interpretation of these results.

The incidence of AF could not be calculated as the study is based upon cross-sectional data. Long-term follow up of the OxVALVE cohort has commenced, which will allow us to calculate AF incidence in the future alongside cardiovascular mortality and morbidity among AF patients with raised serum BNP.

The sampling of BNP in only a subset of the entire cohort might introduce selection bias.

BNP is available as a point of care analysis and is already widely used in clinical practice for heart failure, so the clinical application is already in place and the method could easily be applied for AF screening. However, the proposed cut-off point of BNP of 20pmol/L needs to be validated externally before implementation in clinical practice.

A new AF or atrial flutter diagnosis in my study was based upon real-time assessment of the cardiac rhythm during echocardiography by highly trained physiologists, in addition to analysis of the recorded ECG during the scan (equivalent to a standard 12 Lead ECG), and the diagnosis was not made on ambulatory ECG monitoring.
Therefore it is possible that subjects with undiagnosed paroxysmal AF (found to be in sinus rhythm during the study) could be missed, owing to the assessment at a single time-point in the study. The duration of AF could also not be accurately determined due to the cross-sectional nature of the study.

The minimal use of DOACs for oral anticoagulation in our study can be explained by the fact that OxVALVE study started in 2009 and DOACs were not widely available moreover ESC guidelines only recommended the use of DOACs in AF in 2012 [12].

My study showed that 28.9% of the AF subjects received Aspirin alone and 32.4% subjects received neither Aspirin nor any form of anticoagulation. This may well be due to subjects having a higher bleeding risk scores. (E.g. HASBLED, ABC risk scores etc.) It was however difficult to calculate the risk scores to confirm this owing to limited data availability as well as the cross-sectional nature of the study.

My Thesis is based on retrospective, cross-sectional data gathered from OxVALVE study. The primary aim of OxVALVE study was echocardiographic screening for VHD rather than AF. Therefore although the echocardiographic guidelines for screening patients in AF were followed; they may not have been strictly adhered with for all the scans.

My study did not show a significant association between (undiagnosed) aortic and mitral stenosis and the prevalence of AF as a result of low numbers – none of our AF subjects had mitral stenosis and only four (4/295, 1.4%) had aortic stenosis.

6 Conclusion

Data from the large contemporary OxVALVE population cohort study showed a high prevalence of AF in this unselected, elderly population, including a significant proportion (12%) with previously undiagnosed AF. The prevalence of AF increased significantly with age, in line with previous studies. Male sex, hypertension, hypercholesterolemia, coronary artery disease, impaired LV systolic function, LA size, significant VHD and the presence of ankle oedema on clinical examination were identified as significant factors associated with AF. The prevalence of AF was significantly associated with the presence and increased severity of mitral and tricuspid regurgitation and the presence of aortic sclerosis, aortic and pulmonary regurgitation. The high prevalence of significant VHD highlights the need for routine cardiac imaging in patients with AF. The association with degenerative VHD re-emphasises that as life expectancy continues to increase, AF is likely to be one of the more pressing medical conditions in the years to come. LA size, significant VHD and systolic blood pressure were identified as the independent predictors of newly diagnosed AF. PAF was found to be most common followed by persistent and permanent AF in my study respectively. Most of the AF patients were managed by rate control strategy. Serum BNP was found to be significantly associated with the presence of both new and known AF ($p = 0.0001$) with a high specificity and negative predictive value. Serum BNP can therefore possibly be used as a screening biomarker to identify high risk patients having a likely underlying diagnosis of AF and therefore would merit long term monitoring; which would help improve the diagnostic yield for AF screening. Future prospective studies would however be needed to validate this.

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Appendix-I

List of abbreviations

AF: Atrial fibrillation

VHD: Valvular heart disease

LV: Left ventricle

EF: Ejection fraction

LA: Left atrium

VAF: Valvular atrial fibrillation

NVAF: Non-valvular atrial fibrillation

NAF: Newly diagnosed atrial fibrillation

OAC: Oral anticoagulation

TIA: Transient ischemic attack

DOACs: Direct oral anticoagulants

NYHA: New York Heart Association

PCI: Percutaneous coronary intervention

CABG: Coronary artery bypass grafting

BP: Blood pressure

AS: Aortic stenosis

AR: Aortic regurgitation

MS: Mitral stenosis

MR: Mitral regurgitation

TR: Tricuspid regurgitation

TS: Tricuspid stenosis

PR: Pulmonary regurgitation

PS: Pulmonary stenosis

AoScl: Aortic sclerosis

MAC: Mitral annular calcification

ECG: Electrocardiogram

GP: General practitioner

ESC: European Society of Cardiology

AHA: American Heart Association

ROC curve: Receiver operated characteristic curve

AUC: Area under the curve

BNP: B type natriuretic peptide

NT-proBNP: N-terminal pro BNP

PAF: Paroxysmal atrial fibrillation

OAT: Oral anticoagulation therapy

CRF: Case report form

Appendix-II

Case report form (CRF) template used for data collection

View CRF Details

Name:	Contact
Description:	Orinigal Version
OID:	F_CONTACT

Version(s)

Version Name	oid	Description	Status	Revision Notes	Action
v02	F_CONTACT_V02	Orinigal Version	available	SR 29/01/2010	
v01	F_CONTACT_V01	Orinigal Version	available	SR 29/01/2010	

Items

Name	Item_OID	Description	Data Type	Version(s)	Integrity Check
Address	I_CONTA_ADDRESS	Address	character string	v01,v02	OK
Aged_65_or_Over	I_CONTA_AGED_65_OR_OVER	Is the Participant aged 65 or over?	character string	v01,v02	OK
Alt_Address	I_CONTA_ALT_ADDRESS	Alternative Address	character string	v01,v02	OK
Alt_First_Name	I_CONTA_ALT_FIRST_NAME	Alternative First Name	character string	v01,v02	OK
Alt_Last_Name	I_CONTA_ALT_LAST_NAME	Alternative Last Name	character string	v01,v02	OK
Alt_Postcode	I_CONTA_ALT_POSTCODE	Alternative Post Code	character string	v01,v02	OK
Alt_relationship	I_CONTA_ALT_RELATIONSHIP	Relationship	character string	v01,v02	OK
Alt_Telephone_home	I_CONTA_ALT_TELEPHONE_HOME	Alternative Telephone home	character string	v01,v02	OK
Alt_Telephone_mobile	I_CONTA_ALT_TELEPHONE_MOBILE	Alternative Telephone mobile	character string	v01,v02	OK
Alt_Title	I_CONTA_ALT_TITLE	Title	character string	v01,v02	OK

consent_bloods_analysis	I_CONTA_CONSENT_BLOODS_ANALYSIS	Bloods may be used for DNA analysis	integer	v02	**OK**
consent_bloods_future	I_CONTA_CONSENT_BLOODS_FUTURE	Blood & urine may be stored for use in future studies inc. genetics	integer	v02	**OK**
consent_bloods_research	I_CONTA_CONSENT_BLOODS_RESEARCH	Bloods may be used for genetic research	integer	v02	**OK**
consent_contact_details	I_CONTA_CONSENT_CONTACT_DETAILS	Information may be used for contact details and for health status tracking	integer	v02	**OK**
consent_future_studies	I_CONTA_CONSENT_FUTURE_STUDIES	May be approached for future studies	integer	v02	**OK**
consent_level	I_CONTA_CONSENT_LEVEL	Consent Level	integer	v01	**OK**
Email_Address	I_CONTA_EMAIL_ADDRESS	Email Address	character string	v01,v02	**OK**
First_Name	I_CONTA_FIRST_NAME	First Name	character string	v01,v02	**OK**
Informed_Consent_Given	I_CONTA_INFORMED_CONSENT_GIVEN	Has the Participant given informed consent?	character string	v01,v02	**OK**
Initials	I_CONTA_INITIALS	Initials	character string	v01,v02	**OK**
Last_Name	I_CONTA_LAST_NAME	Last Name	character string	v01,v02	**OK**
Middle_Name	I_CONTA_MIDDLE_NAME	Middle Name	character string	v01	**OK**
Postcode	I_CONTA_POSTCODE	Post Code	character string	v01,v02	**OK**
Preferred_Contact_Method	I_CONTA_PREFERRED_CONTACT_METHOD	Contact Preference	character string	v01,v02	**OK**
Prev_History_VHD	I_CONTA_PREV_HISTORY_VHD	Does the participant have a previous history of valvular heart disease?	character string	v01,v02	**OK**

Telephone_Home	I_CONTA_TELEPHONE_HOME	Telephone Home	character string	v01,v02	**OK**
Telephone_Mobile	I_CONTA_TELEPHONE_MOBILE	Telephone Mobile	character string	v01,v02	**OK**
Telephone_Work	I_CONTA_TELEPHONE_WORK	Telephone Work	character string	v01,v02	**OK**
Title	I_CONTA_TITLE	Title	character string	v01,v02	**OK**

View CRF Details

Name:	Screening
Description:	Orinigal Version
OID:	F_SCREENING

Version(s)

Version Name	oid	Description	Status	Revision Notes	Action
v02	F_SCREENING_V02	Reqesuted changes	available	Medat 14/08/2014	
v01	F_SCREENING_V01	Orinigal Version	available	Update from SR first draft	

Items

Name	Item_OID	Description	Data Type	Version(s)	Integrity Check
ACEI	I_SCREE_ACEI	ACEI	character string	v01,v02	**OK**
ACEI_Details	I_SCREE_ACEI_DETAILS	ACEI Details	character string	v01,v02	**OK**
Angina	I_SCREE_ANGINA	Angina	character string	v01,v02	**OK**
Angina_Details	I_SCREE_ANGINA_DETAILS	Angina Details	character string	v01,v02	**OK**
Angiography	I_SCREE_ANGIOGRAPHY	Angiography	character string	v01,v02	**OK**
Angiography_Details	I_SCREE_ANGIOGRAPHY_DETAILS	Angina Details	character string	v01,v02	**OK**
Ankle_Oedema	I_SCREE_ANKLE_OEDEMA	Ankle Oedema	character string	v01,v02	**OK**

Ankle_Oedema_Details	I_SCREE_ANKLE_OEDEMA_DETAILS	Ankle Oedema Description	character string	v01,v02	**OK**
Anti_arrhythmics	I_SCREE_ANTI_ARRHYTHMICS	Anti-arrhythmics	character string	v01,v02	**OK**
Anti_arrhythmics_Details	I_SCREE_ANTI_ARRHYTHMICS_DETAILS	Anti-arrhythmics details	character string	v01,v02	**OK**
Anticoagulant	I_SCREE_ANTICOAGULANT	Anti-coagulant	character string	v01,v02	**OK**
Anticoagulant_Details	I_SCREE_ANTICOAGULANT_DETAILS	Anti-coagulant	character string	v01,v02	**OK**
ARB	I_SCREE_ARB	ARB	character string	v01,v02	**OK**
ARB_Details	I_SCREE_ARB_DETAILS	ARB Details	character string	v01,v02	**OK**
Asprin	I_SCREE_ASPRIN	Aspirin	character string	v01,v02	**OK**
Asprin_Details	I_SCREE_ASPRIN_DETAILS	Aspirin Details	character string	v01,v02	**OK**
asthma	I_SCREE_ASTHMA	Asthma	character string	v02	**OK**
asthma_copd_curr	I_SCREE_ASTHMA_COPD_CURR	asthma or COPD current problem	character string	v02	**OK**
Atrial_Fibrillation	I_SCREE_ATRIAL_FIBRILLATION	Atrial Fibrillation	character string	v01,v02	**OK**
Atrial_Fibrillation_Details	I_SCREE_ATRIAL_FIBRILLATION_DETAILS	Atrial Details	character string	v01,v02	**OK**
Beta_Blockers	I_SCREE_BETA_BLOCKERS	Beta-blockers	character string	v01,v02	**OK**
Beta_Blockers_Details	I_SCREE_BETA_BLOCKERS_DETAILS	Beta-blockers details	character string	v01,v02	**OK**
BP_Diastolic	I_SCREE_BP_DIASTOLIC	Blood pressure diastolic	integer	v01,v02	**OK**
BP_Systolic	I_SCREE_BP_SYSTOLIC	Blood pressure systolic	integer	v01,v02	**OK**
BSA	I_SCREE_BSA	BSA	floating	v01,v02	**OK**
CA_Channel_Blocker	I_SCREE_CA_CHANNEL_BLOCKER	Ca Channel Blockers	character	v01,v02	**OK**

			string		
CA_Channel_Blocker_Details	I_SCREE_CA_CHANNEL_BLOCKER_DETAILS	Ca Channel Blockers Details	character string	v01,v02	**OK**
CABG	I_SCREE_CABG	CABG	character string	v01,v02	**OK**
CABG_Details	I_SCREE_CABG_DETAILS	CABG Details	character string	v01,v02	**OK**
CCS	I_SCREE_CCS	CSS	character string	v01,v02	**OK**
chronic_kidney_disease	I_SCREE_CHRONIC_KIDNEY_DISEASE	Chronic kidney disease	character string	v02	**OK**
chronic_kidney_disease_details	I_SCREE_CHRONIC_KIDNEY_DISEASE_DETA	Chronic kidney disease - details	character string	v02	**OK**
close_rel_heart_disease	I_SCREE_CLOSE_REL_HEART_DISEASE	Close relative under 60 suffers from heart disease or stroke	character string	v02	**OK**
close_rel_heart_disease_details	I_SCREE_CLOSE_REL_HEART_DISEASE_DET	Close relative under 60 suffers from heart disease or stroke - details	character string	v02	**OK**
close_rel_valve_disease	I_SCREE_CLOSE_REL_VALVE_DISEASE	Close relative suffers from valve disease	character string	v02	**OK**
close_rel_valve_disease_details	I_SCREE_CLOSE_REL_VALVE_DISEASE_DET	Close relative suffers from valve disease - details	character string	v02	**OK**
Comments	I_SCREE_COMMENTS	Comments	character string	v01,v02	**OK**
copd_emphysema	I_SCREE_COPD_EMPHYSEMA	Chronic obstructive airways disease (COPD/emphysema)	character string	v02	**OK**
Country_of_Birth	I_SCREE_COUNTRY_OF_BIRTH	Country of Birth	character string	v01,v02	**OK**
CVA_TIA	I_SCREE_CVA_TIA	CVA/TIA	character string	v01,v02	**OK**
CVA_TIA_Details	I_SCREE_CVA_TIA_DETAILS	CVA/TIA Details	character string	v01,v02	**OK**
Diabetes	I_SCREE_DIABETES	Diabetes	character string	v01,v02	**OK**
Diabetes_Type	I_SCREE_DIABETES_TYPE	Diabetes Details	character	v01,v02	**OK**

			string		
Diuretic	I_SCREE_DIURETIC	Diuretic	character string	v01,v02	**OK**
Diuretic_Details	I_SCREE_DIURETIC_DETAILS	Diuretic Details	character string	v01,v02	**OK**
echo_ao_scler	I_SCREE_ECHO_AO_SCLER	Ao Sclerosis	integer	v01,v02	**OK**
echo_ar	I_SCREE_ECHO_AR	AR	integer	v01,v02	**OK**
echo_as	I_SCREE_ECHO_AS	AS	integer	v01,v02	**OK**
echo_bi_aov	I_SCREE_ECHO_BI_AOV	Bicuspid AoV	integer	v01,v02	**OK**
echo_ef	I_SCREE_ECHO_EF	Echo EF	integer	v01,v02	**OK**
echo_mr	I_SCREE_ECHO_MR	MR	integer	v01,v02	**OK**
echo_ms	I_SCREE_ECHO_MS	MS	integer	v01,v02	**OK**
echo_pr	I_SCREE_ECHO_PR	PR	integer	v01,v02	**OK**
echo_ps	I_SCREE_ECHO_PS	PS	integer	v01,v02	**OK**
echo_report	I_SCREE_ECHO_REPORT	Echo Report	file	v01,v02	**OK**
echo_rhythm	I_SCREE_ECHO_RHYTHM	Rhythm	character string	v01,v02	**OK**
echo_tr	I_SCREE_ECHO_TR	TR	integer	v01,v02	**OK**
echo_ts	I_SCREE_ECHO_TS	TS	integer	v01,v02	**OK**
Ethnic_Origin	I_SCREE_ETHNIC_ORIGIN	Ethnic Origin	character string	v01,v02	**OK**
Ethnic_Origin_other	I_SCREE_ETHNIC_ORIGIN_OTHER	Ethnic Origin - other	character string	v02	**OK**
exsmoker_cigs_per_day	I_SCREE_EXSMOKER_CIGS_PER_DAY	Ex-Smoker - Cigs per day	integer	v02	**OK**
exsmoker_years_smoked	I_SCREE_EXSMOKER_YEARS_SMOKED	Ex-Smoker - Years smoked	integer	v02	**OK**
exsmoker_years_stopped	I_SCREE_EXSMOKER_YEARS_STOPPED	Ex-Smoker - Years stopped	integer	v02	**OK**
Follow_Up_In_5	I_SCREE_FOLLOW_UP_IN_5	5 year follow up	character string	v01,v02	**OK**
Follow_Up_Required	I_SCREE_FOLLOW_UP_REQUIRED	Clinical study follow up	character string	v01,v02	**OK**
gp_auscul_aoritc_regurg	I_SCREE_GP_AUSCUL_AORITC_REGURG	Aortic regurgitation	character string	v02	**OK**
gp_auscul_aortic_sclerosis	I_SCREE_GP_AUSCUL_AORTIC_SCLEROSIS	Aortic sclerosis	character string	v02	**OK**
gp_auscul_cerain_diagnosis	I_SCREE_GP_AUSCUL_CERAIN_DIAGNOSIS	How certain are you of your diagnosis	character	v02	**OK**

			string		
gp_auscul_comments	I_SCREE_GP_AUSCUL_COMMENTS	Comments	character string	v02	**OK**
gp_auscul_heart_sound	I_SCREE_GP_AUSCUL_HEART_SOUND	How well can you hear the heart sounds	integer	v02	**OK**
gp_auscul_make_diagnosis	I_SCREE_GP_AUSCUL_MAKE_DIAGNOSIS	Are you prepared to make a diagnosis on the basis of auscultation	character string	v02	**OK**
gp_auscul_mitral_regurg	I_SCREE_GP_AUSCUL_MITRAL_REGURG	Mitral regurgitation	character string	v02	**OK**
gp_auscul_mitral_stenosis	I_SCREE_GP_AUSCUL_MITRAL_STENOSIS	Mitral stenosis	character string	v02	**OK**
gp_auscul_murmor_category	I_SCREE_GP_AUSCUL_MURMOR_CATEGORY	Category of Murmur	character string	v02	**OK**
gp_auscul_murmur	I_SCREE_GP_AUSCUL_MURMUR	Murmur	character string	v02	**OK**
gp_auscul_other	I_SCREE_GP_AUSCUL_OTHER	Other	character string	v02	**OK**
gp_auscul_refer_echo	I_SCREE_GP_AUSCUL_REFER_ECHO	Would you refer an asymptomatic patient for an echocardiogram on the basis of your auscultation	character string	v02	**OK**
gp_auscul_tricuspid_regurg	I_SCREE_GP_AUSCUL_TRICUSPID_REGURG	Tricuspid regurgitation	character string	v02	**OK**
Heart_rate	I_SCREE_HEART_RATE	Heart Rate	integer	v01,v02	**OK**
Heart_rhythm	I_SCREE_HEART_RHYTHM	Rhythm	character string	v01,v02	**OK**
Height	I_SCREE_HEIGHT	Height	integer	v01,v02	**OK**
Hyperlipidaemia	I_SCREE_HYPERLIPIDAEMIA	Hyperlipidaemia	character string	v01,v02	**OK**
Hyperlipidaemia_Details	I_SCREE_HYPERLIPIDAEMIA_DETAILS	Hyperlipidaemia	character string	v01,v02	**OK**
Hypertension	I_SCREE_HYPERTENSION	Hypertension	character string	v01,v02	**OK**
Hypertension_Details	I_SCREE_HYPERTENSION_DETAILS	Hypertension details	character string	v01,v02	**OK**

inhalers	I_SCREE_INHALERS	Inhalers	character string	v02	**OK**
inhalers_details	I_SCREE_INHALERS_DETAILS	Inhalers - details	character string	v02	**OK**
inhalers_reliever	I_SCREE_INHALERS_RELIEVER	Inhalers - Reliever	character string	v02	**OK**
inhalers_steroids	I_SCREE_INHALERS_STEROIDS	Inhalers - Preventer/steroid inhaler (brown/red/yellow/orange colour)	character string	v02	**OK**
inhalers_steroids_dose	I_SCREE_INHALERS_STEROIDS_DOSE	Inhalers - steroid - dose of steroid	integer	v02	**OK**
inhalers_steroids_freq	I_SCREE_INHALERS_STEROIDS_FREQ	Inhalers - steroid - frequency	character string	v02	**OK**
inhalers_steroids_name	I_SCREE_INHALERS_STEROIDS_NAME	Inhalers - steroid - name	character string	v02	**OK**
inhalers_steroids_name_other	I_SCREE_INHALERS_STEROIDS_NAME_OTHE	Inhalers - steroid - Other	character string	v02	**OK**
inhalers_steroids_puffs	I_SCREE_INHALERS_STEROIDS_PUFFS	Inhalers - steroid - puffs	character string	v02	**OK**
Length_of_Residence_in_UK	I_SCREE_LENGTH_OF_RESIDENCE_IN_UK	Length of residence in UK	integer	v01,v02	**OK**
Lipid_Lowering_Agent	I_SCREE_LIPID_LOWERING_AGENT	Lipid-lowering agent	character string	v01,v02	**OK**
Lipid_Lowering_Agent_Details	I_SCREE_LIPID_LOWERING_AGENT_DETAIL	Lipid-lowering agent details	character string	v01,v02	**OK**
lung_disease_other	I_SCREE_LUNG_DISEASE_OTHER	Lung disease - other	character string	v02	**OK**
lung_disease_other_details	I_SCREE_LUNG_DISEASE_OTHER_DETAILS	Lung disease - other - details	character string	v02	**OK**
lung_test_feno	I_SCREE_LUNG_TEST_FENO	FeNO (ppb)	character string	v02	**OK**
lung_test_fev	I_SCREE_LUNG_TEST_FEV	FEV (litres)	character string	v02	**OK**
lung_test_fvc	I_SCREE_LUNG_TEST_FVC	FVC (litres)	character string	v02	**OK**
lung_test_pef	I_SCREE_LUNG_TEST_PEF	PEF (litres/min)	charact	v02	**OK**

			er string		
lung_test_quality	I_SCREE_LUNG_TEST_QUALITY	Quality	character string	v02	**OK**
marital_status	I_SCREE_MARITAL_STATUS	Marital Status	character string	v02	**OK**
MI	I_SCREE_MI	MI	character string	v01,v02	**OK**
MI_Details	I_SCREE_MI_DETAILS	MI Details	character string	v01,v02	**OK**
Nitrates	I_SCREE_NITRATES	Nitrates	character string	v01,v02	**OK**
Nitrates_Details	I_SCREE_NITRATES_DETAILS	Nitrates Details	character string	v01,v02	**OK**
Number_Pregnancies	I_SCREE_NUMBER_PREGNANCIES	Number of pregnancies	integer	v01,v02	**OK**
NYHA_Class	I_SCREE_NYHA_CLASS	NYHA Class	character string	v01,v02	**OK**
oral_steroids	I_SCREE_ORAL_STEROIDS	Oral steroids	character string	v02	**OK**
oral_steroids_details	I_SCREE_ORAL_STEROIDS_DETAILS	Oral steroids - details	character string	v02	**OK**
Other_Anti_Platelet	I_SCREE_OTHER_ANTI_PLATELET	Other anti-platelet	character string	v01,v02	**OK**
Other_Anti_Platelet_Details	I_SCREE_OTHER_ANTI_PLATELET_DETAILS	Other anti-platelet details	character string	v01,v02	**OK**
Other_Cardiac_History	I_SCREE_OTHER_CARDIAC_HISTORY	Other	character string	v01,v02	**OK**
Other_Cardiac_History_Details	I_SCREE_OTHER_CARDIAC_HISTORY_DETAI	Other Details	character string	v01,v02	**OK**
Other_Cardiac_Medication	I_SCREE_OTHER_CARDIAC_MEDICATION	Other medications	character string	v01,v02	**OK**
Other_Cardiac_Medication_Details	I_SCREE_OTHER_CARDIAC_MEDICATION_DE	Other Medications Details	character string	v01,v02	**OK**
Other_Residence1	I_SCREE_OTHER_RESIDENCE1	Non-UK Country 1	character string	v01,v02	**OK**

Other_Residence1_Period	I_SCREE_OTHER_RESIDENCE1_PERIOD	Length of residence in non-UK country 1	integer	v01,v02	**OK**
Other_Residence2	I_SCREE_OTHER_RESIDENCE2	Non-UK Country 2	character string	v01,v02	**OK**
Other_Residence2_Period	I_SCREE_OTHER_RESIDENCE2_PERIOD	Length of residence in non-UK country 2	integer	v01,v02	**OK**
Other_Residence3	I_SCREE_OTHER_RESIDENCE3	Non-UK Country 3	character string	v01,v02	**OK**
Other_Residence3_Period	I_SCREE_OTHER_RESIDENCE3_PERIOD	Length of residence in non-UK country 3	integer	v01,v02	**OK**
Pacemaker	I_SCREE_PACEMAKER	Pacemaker Details	character string	v01,v02	**OK**
Pacemaker_Details	I_SCREE_PACEMAKER_DETAILS	Pacemaker	character string	v01,v02	**OK**
PCI	I_SCREE_PCI	PCI	character string	v01,v02	**OK**
PCI_Details	I_SCREE_PCI_DETAILS	PCI Details	character string	v01,v02	**OK**
Pregnancy_Problems	I_SCREE_PREGNANCY_PROBLEMS	Have you experienced any problems during pregnancy	character string	v01,v02	**OK**
Pregnancy_Problems_Details	I_SCREE_PREGNANCY_PROBLEMS_DETAILS	Details of pregnancy difficulty	character string	v01	**OK**
Pregnancy_Problems_haemor	I_SCREE_PREGNANCY_PROBLEMS_HAEMOR	Pregnancy problems - Post-partum haemorrhage/bleeding after birth	character string	v02	**OK**
Pregnancy_Problems_heart	I_SCREE_PREGNANCY_PROBLEMS_HEART	Pregnancy problems - Heart problems	character string	v02	**OK**
Pregnancy_Problems_hyperten	I_SCREE_PREGNANCY_PROBLEMS_HYPERTEN	Pregnancy problems - Hypertension/hig pressure	character string	v02	**OK**
Pregnancy_Problems_miscarriage	I_SCREE_PREGNANCY_PROBLEMS_MISCARRI	Pregnancy problems - Miscarriage	integer	v02	**OK**
Pregnancy_Problems_other	I_SCREE_PREGNANCY_PROBLEMS_OTHER	Pregnancy problems - other	character string	v02	**OK**
Pregnancy_Problems_pre_eclamp	I_SCREE_PREGNANCY_PROBLEMS_PRE_ECLA	Pregnancy problems - Pre-eclampsia	character string	v02	**OK**
Pregnancy_Problems_premature	I_SCREE_PREGNANCY_PROBLEMS_PREMATUR	Pregnancy problems - Premature baby	character string	v02	**OK**

Pregnancy_Problems_small	I_SCREE_PREGNANCY_PROBLEMS_SMALL	Pregnancy problems - Small size baby	character string	v02	**OK**
Previous_Pregnancies	I_SCREE_PREVIOUS_PREGNANCIES	Have you been pregnant	character string	v01,v02	**OK**
Rheumatic_Fever	I_SCREE_RHEUMATIC_FEVER	Rheumatic Fever	character string	v01,v02	**OK**
Rheumatic_Fever_Details	I_SCREE_RHEUMATIC_FEVER_DETAILS	Rheumatic Fever Details	character string	v01,v02	**OK**
rheumatoid_arthritis	I_SCREE_RHEUMATOID_ARTHRITIS	Rheumatoid arthritis	character string	v02	**OK**
smoker_cigs_per_Day	I_SCREE_SMOKER_CIGS_PER_DAY	Smoker - cigarettes per day	integer	v02	**OK**
smoker_years	I_SCREE_SMOKER_YEARS	Smoker - Years	integer	v02	**OK**
Smoking_Status	I_SCREE_SMOKING_STATUS	Smoking Status	character string	v01,v02	**OK**
Syncope	I_SCREE_SYNCOPE	Syncope	character string	v01,v02	**OK**
Syncope_Details	I_SCREE_SYNCOPE_DETAILS	Syncope Details	character string	v01,v02	**OK**
Weight	I_SCREE_WEIGHT	Weight	integer	v01,v02	**OK**

Appendix-III

AF & VHD Numbers & Key (n = 295)

(Excluded from Venn Diagram)

MS	0
AS	4
AR	63
PS	0
TS	0
No VHD	37

Individual VHD in AF Cohort

MR	6
TR	10
PR	12
AoScl	24

Mixed VHD in AF Cohort

AoScl, TR, MR, PR	33
AoScl, TR, MR	26
AoScl, TR, PR	15
MR, PR, TR	14




AoScl, TR
21
AoScl, MR
23
AoScl, PR
18
MR, TR
15
TR, PR
7
MR, PR
9