An Observational Study of Natural History of Cardiovascular Diseases

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Abstract

Atherosclerosis is a chronic, progressive, inflammatory disease with a long asymptomatic phase that can be identified by several methods when the disease is still in a subclinical stage. Lifestyle modifications and medical managements such as statin therapy can slow, halt or even reverse the progression of atherosclerotic disease. Whether to screen and treat patients for subclinical atherosclerosis remains controversial.

Demographic data and risk factors were collected retrospectively from 300,000 asymptomatic individuals who attended for self-funding, private cardiovascular screening in the UK and Ireland. Invitations were sent to men and women aged over 50 years in all UK and Ireland postcodes and regions for a cardiovascular health check. Detailed health questionnaire were self-reported by attendees and investigations were completed by trained technicians. Tests included ultrasound screening for AAA, ankle:brachial pressure index (ABPI), carotid duplex imaging for carotid atherosclerosis, electrocardiography for atrial fibrillation and rapid blood test for cholesterol, blood sugar and creatinine levels.

The association between risk factors and prevalence of subclinical atherosclerosis and atrial fibrillation in different subgroups were determined using univariable analysis and odds ratios. After recoding continuous variables that were not normally distributed, significant risk factors were included in a multivariable linear logistic regression analysis in different models establishing two models to identify women at high risk of developing Abdominal Aortic Aneurysm. In addition, Analysis of newly diagnosed cases of Atrial Fibrillation showed a noticeable detection rate of new cases with high

CHA2DS2-VASc score, indicating initiation of anticoagulation for stroke prevention. Moreover, data related to kidney function and cardiovascular risk factors showed significantly higher prevalence of subclinical atherosclerosis among those with stage 3 or worse Chronic Kidney Disease.

A small cohort of participants were prospectively followed up to assess the correlation between asymptomatic Carotid Artery disease and cardiovascular events which established that smoking history and the presence of asymptomatic Carotid artery disease as well as peripheral arterial disease were statistically significant and predictors of cardiovascular event.

These findings highlights the value of ultrasound as a non-invasive and inexpensive tool to identify common and important conditions and sub-clinical atherosclerosis early in order to manage the atherosclerotic process at early stages where individual and healthcare system has the most benefit to achieve.

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List of abbreviations

Abbreviations	Full Descriptions
AAA	Abdominal Aortic Aneurysm
ABI	Ankle-Brachial Index
ABPI	Ankle-Brachial Pressure Index
ACAS	Carotid Endarterectomy for Asymptomatic Carotid Stenosis
ACC	American College of Cardiology
ACCP	American College of Chest Physicians
ACSRS	The Asymptomatic Carotid Stenosis and Risk of Stroke
ACST	The Asymptomatic Carotid Surgery Trial
AF	Atrial Fibrillation
AHA	American Heart Asscoaiation
ASCVD	Atherosclerotic Cardiovascular Disease
ASSIGN	Assessing Cardiovascular Risk Using SIGN Guidelines
ASTEROID	A Study To Evaluate the Effect of Rosuvastatin On Intravascular Ultrasound-Derived Coronary Atheroma Burden
AUC	Area Under the Curve
BMI	Body Mass Index
BMJ	British Medical Journal
BP	Blood Pressure
CAD	Coronary Artery Disease
CAFES-CAVE	Carotid and femoral ultrasound morphology screening and cardiovascular events in low risk subjects
CAS	Carotic Artery Stenosis
CCA	Common Carotid Artery
CEA	Carotid Endarterectomy
CHD	Coronary Heart Disease
CI	Confidence Interval
CKD	Chronic Kidney Disease
CVD	Cardio Vasculr Disease
DOH	Department of Health
EACPR	European Association for Cardiovascular Prevention & Rehabilitation
ECA	External Carotid Artery
ECG	Electrocardiogram
EDV	End Diastolic Velocity
ESC	European Society of Cardiology
ESRD	End Stage Renal Disease
FGF	fibroblast growth factors
GFR	glomerular filtration rate
GP	General Physician
HDL	High density lipoprotein
HLP	Hyperlipidemia
HSE	Health Survey England
HTN	Hypertension
ICA	Internal Carotid Artery
ICREC	Imperial College Research Ethics Committee
IHD	Ischaemic Heart Disease

IL	interleukins
LDL	low density lipoprotein
MACE	Major adverse cardiovascular events
MASS	The Multicentre Aneurysm Screening Study
MCP	monocyte chemotactic protein
MDRD	Modification of Diet in Renal Disease
NASCET	North American Symptomatic Carotid Endarterectomy Trial
NEOERICA	New Opportunities for Early Renal Intervention by Computerised Assessment
NICE	National Institute for Health and Care Excellence
NOAC	Novel Oral Anticoagulants
OAC	Oral Anticoagulant
OCT	Optical coherence tomography
OR	Odds Ratio
PAD	Peripheral Arterial Disease
PCI	Percutaneous Coronary Intervention
PDGF	platelet-derived growth factors
PROCAM	Prospective Cardiovascular Munster Heart Study
PSV	Peak Systolic Velocity
QICKD	Quality Improvement in CKD
RCT	Randomised Control Trial
ROC	receiver operating characteristic
RR	Risk Ratio
SCAF	Stockholm Cohort-study on Atrial Fibrillation
STROBE	The Strengthening the Reporting of Observational Studies in Epidemiology
TCD	Trans Cranial Doppler
TIA	Transient Ischaemic Attack
TIMP	tissue inhibitors of metalloproteinases
TNF	tumour necrosis factor
USPSTF	U.S. Preventive Services Task Force
VEGF	vascular endothelial growth factors
VLDL	very low density lipoprotein
WHO	World Health Organisation
YLL	Years of Life Lost

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Dedication

I dedicate this work to my family specifically my parents and to my lovely wife Dorna and my girls Arta and Tara.

Statement of originality

This is to certify that this is my original work, performed within the Imperial College London and does not overlap with any other institutes or departments and has not submitted for any other degree or other purposes.

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Part of this research has been presented in the Veith Symposium in the United States of America and published in The British Journal of Surgery.

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Presentations and publications arising from this study

Oral presentation:

- Chronic kidney disease and cardiovascular comorbidities, 26th World Congress of 'International union of angiology' Sydney, Australia, Aug 2014.

- Screening For AAAs In Women: When Should They Be Screened And When Should They Not Be, VEITH symposium, Nov 2015.

Publications:

- **M Chabok**, A Nicolaides et al, Risk factors associated with increased prevalence of abdominal aortic aneurysm in women, ***British Journal of Surgery, 2016 Jun 22. doi: 10.1002/bjs.10179***

- Giannoukas AD, **Chabok M**, Spanos K, Nicolaides A, Screening for Asymptomatic Carotid Plaques with Ultrasound, ***Eur J Vasc Endovasc Surg. 2016 May 19. pii: S1078-5884(16)30053-3. doi: 10.1016/j.ejvs.2016.04.013***

- **M Chabok**, A Nicolaides et al, Prevalence of Abdominal Aortic Aneurysms and Iliac Aneurysms in a UK population of 50,000 women, accepted for publication in ***Vascular Investigations and Therapy Journal***

Chapter 1 Introduction and Background

1.1 Cardiovascular Disease

Cardiovascular disease (CVD) affects the lives of millions of people and is one of the largest causes of death and disability in the UK and globally[1]. Cardiovascular disease which comprises heart attacks (myocardial infarction), angina and strokes, is ranked as the number one cause of mortality and is a major cause of morbidity worldwide[2]. Huge improvements have been made in the prevention and treatment of CVD over the last decade but CVD remains a leading cause of morbidity and mortality, despite improvements in outcomes[1]. However, comparisons with other countries show that England could still do better in improving CVD mortality rates[3].

CVD is one of the leading contributors to the global disease burden. The single most common cardiovascular disease is ischaemic heart disease including myocardial infarction (MI, heart attacks) and angina. Most CVD in England is caused by atherosclerosis[4]. Despite the enormous burden of CVD, many patients remain undiagnosed and untreated. In the future, a continuing downward trend in CVD mortality will depend on further improvements in population health and CVD treatment[4].

Cardiovascular Disease Outcomes Strategy published by Department of Health calls for improving outcomes for people with or at risk of cardiovascular disease by reducing premature mortality rates for CVD by improving prevention, diagnosis and treatment, bringing all services up to the standards of the best. Improving cardiovascular outcomes require further sustained and coordinated action to prevent disease and to manage it better when it does occur[3]. To prevent disease and improve

health, it is essential to understand why diseases arise, and conversely why, in many cases, they do not.

As outlined by National Institute for Health and Care Excellence (NICE), the overall aim of treatment is to prevent the occurrence of a cardiovascular event by reducing modifiable risk factors through lifestyle changes and drug management[5]. To do this, it is necessary to study the distribution of natural history of disease in populations and to identify the agents responsible; effective strategies can then be planned.

1.2 Risk Factors

The concept of 'risk' can be confusing because the term is applied in several different ways. In one sense it may be used to describe the likelihood or probability of a certain disease being present ('diagnostic risk'). More commonly the term is used to denote the likelihood of serious harm, particularly death, resulting from the patient's illness ('prognostic risk'). Here, risk assessment is closely intertwined with the diagnostic evaluation because the potential for harm depends in large part on the underlying diagnosis[6].

The risk of cardiovascular disease is greater in men, patients over 50 years of age, patients with a family history of cardiovascular disease, and in certain ethnic backgrounds such as South Asians. Cardiovascular disease also has several important, and potentially modifiable, risk factors such as hypertension, abnormal lipids, obesity, diabetes mellitus, and psychosocial factors such as depression, anxiety and social isolation. Low physical activity, poor diet, smoking, and excessive alcohol intake are

also risk factors[5].

The incidence of CVD is largely explained by several modifiable risk factors increasing the risk of future CVD events and contribute to an estimated 90% of the population attributable risk fraction of ischaemic heart disease and stroke worldwide[7].

CVD is multi-factorial in its causation and lifestyle changes are the basis of any treatment strategy, with patients often requiring behavioural counselling. Those unable to achieve or maintain adequate risk reduction through lifestyle changes alone or those at high risk may benefit from pharmacotherapy[2].

The case-control study is usually the first type of epidemiological study conducted to determine which agent, host, or environmental factors are associated with the occurrence of a disease. Factors found to be associated with disease are called risk factors. Identification of risk factors can lead to increased understanding of the disease process and possibly enactment of disease control measures long before more detailed information about the cause of the disease can be confirmed[8].

In apparently healthy persons, CVD risk is most frequently the result of multiple interacting risk factors. Figure 1.1 shows the most common and traditional modifiable and non-modifiable risk factors for cardiovascular disease. The effects of known risk factors can vary enormously from one population to another, and there is still substantial uncertainty as to how important these are in different settings and as to how their importance is changing with time. By understanding the medical, social and

ethical factors that affect community health, solutions to public health problems could be developed.

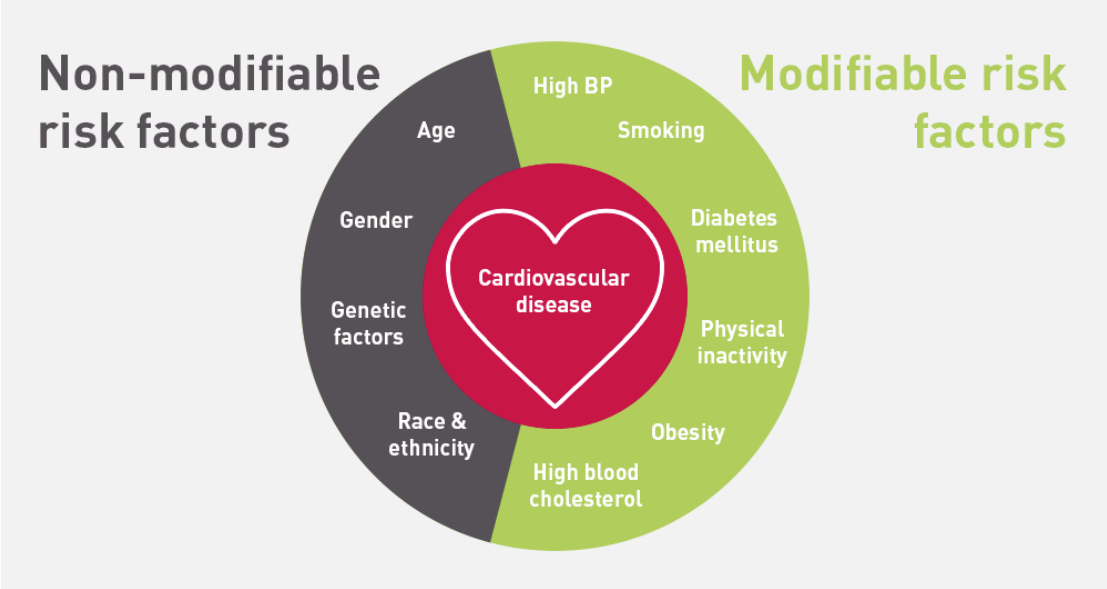


Figure 1.1: Risk Factors[9]

The prevalence of any CVD condition increases with age up to 53.8% of men and 31.1% of women aged 85 and over with much steeper increase in men than in women[4].

Reductions in the prevalence of some risk factors for CVD in the population and improvements in treatment of CVD are main reasons for a decrease in mortality from CVD. Decreased cigarette smoking, lower systolic blood pressure and lower total cholesterol in the general population all contribute to a better cardiovascular profile, although increases in obesity and diabetes counteract some of the benefits[4].

The reduction in risk factors such as high cholesterol, Hypertension and smoking in the last 30 years resulted in more than half of the reduction in CV mortality in the population[1].

1.3 Atherosclerosis

Arterial disease is a common disorder characterized by atherosclerosis of normal arteries, organ transplant, vein grafts, and neointima formation after angioplasty and stenting causing restenosis. There are 3 layers for the arterial wall (i.e. the intima, including the endothelium, the media, and the adventitia) each one has its own role in circulation. It usually takes decades to develop advanced atherosclerotic lesions responsible for clinical symptoms[10]. Figure 1.2 shows the formation of atherosclerosis and its complications overtime.

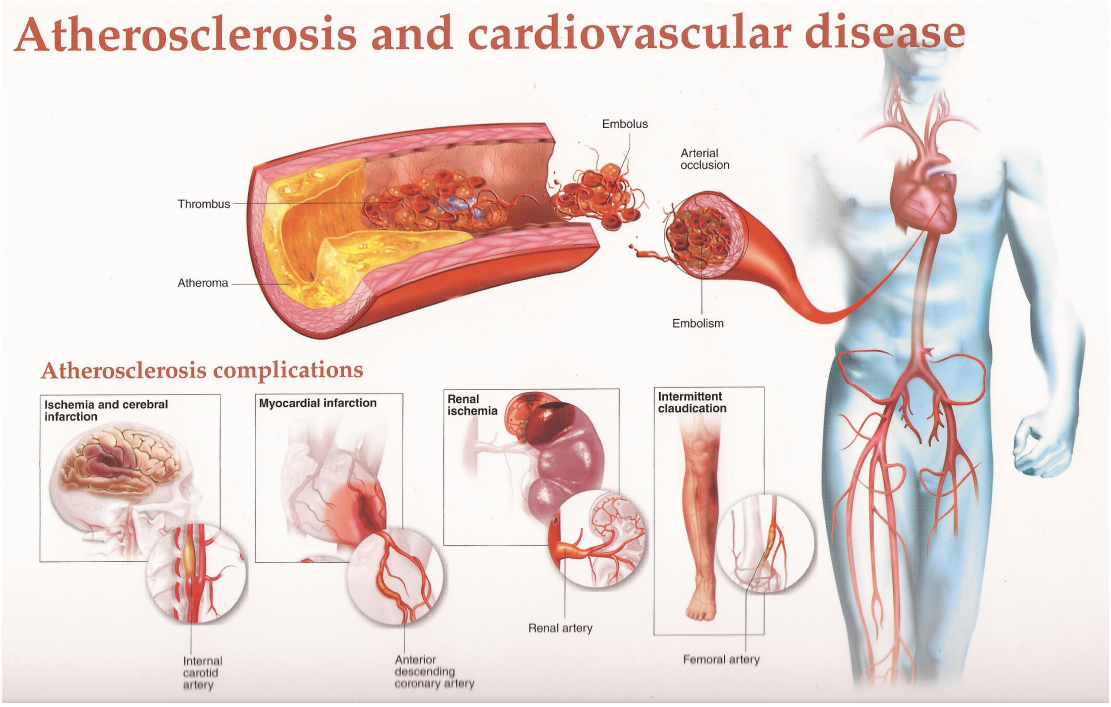


Figure 1.2: Atherosclerosis[11]

In health, the endothelium acts as a physical barrier between the blood constituents and the prothrombotic subendothelial matrix, and releases antithrombotic substances such as prostacyclin and nitric oxide. On a background of endothelial damage, plaque rupture or erosion leads to local exposure of the bloodstream to factors that precipitate thrombosis[12].

Atheroma formation is defined as a fatty deposit on the arterial walls, which can be an effect of all these risk factors. Atherosclerosis is a response to the endothelial cell injury in the form of the plaque formation. Accumulation of the blood lipids is ingested by macrophages forming a foamy appearance. It is followed by smooth muscle cell migration and transformation into fibroblasts. Then a matrix of collagen is formed inside the atheroma and also a fibrous cap is on the top of the plaque which makes it stable. Figure 1.3 shows formation of vulnerable plaques[13].

Total cholesterol comprises three components: LDL cholesterol (low density lipoprotein); VLDL cholesterol (very low density lipoprotein), and HDL cholesterol. The majority of the cholesterol in the blood is carried as LDL cholesterol. It is this that contributes to atherosclerosis. VLDL cholesterol is involved in clearing fat from the bowel after eating. HDL cholesterol is beneficial, as it carries cholesterol away from the arteries back to the liver where it can be excreted[4].

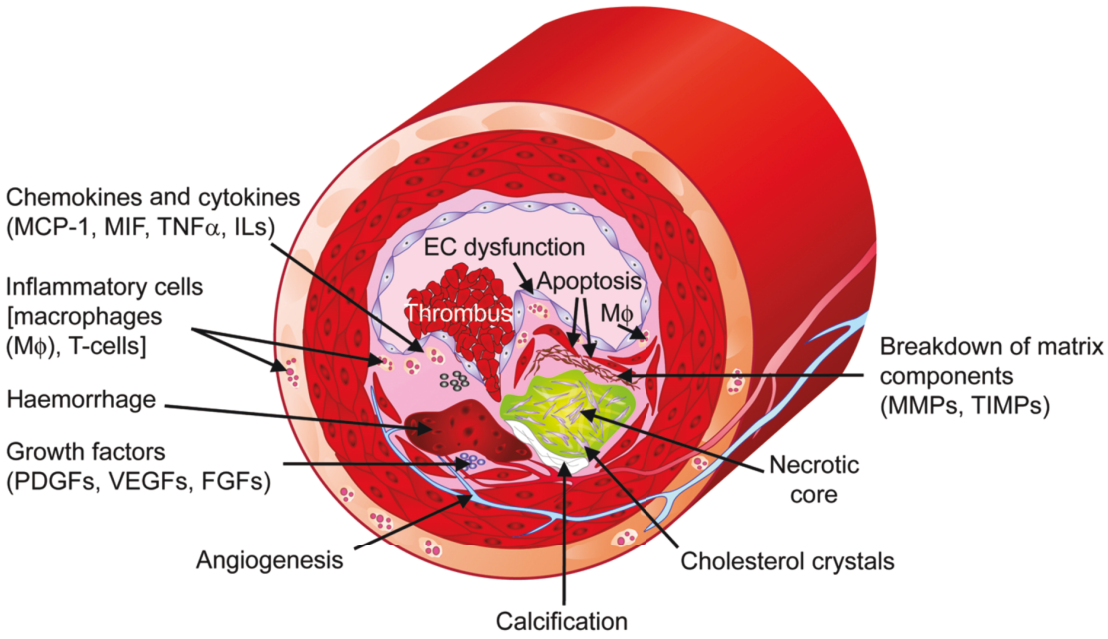


Figure 1.3: Factors contributing to the formation of vulnerable plaques.

MCP-1, monocyte chemotactic protein-1; MIF, migration inhibitory factor; TNFα, tumour necrosis factor-α; ILs, interleukins; MMPs, matrix metalloproteinases; TIMPs, tissue inhibitors of metalloproteinases; PDGFs, platelet-derived growth factors; VEGFs, vascular endothelial growth factors; FGFs, fibroblast growth factors; Mφ, macrophages. Adopted from (https://doi.org/10.1093/eurheartj/eht301)

New evidence has confirmed that the key initiating event in atherogenesis is the retention of low-density lipoprotein (LDL) cholesterol (LDL-C) and other cholesterol-rich apolipoprotein (Apo) B-containing lipoproteins within the arterial wall[14].

Recent advances in basic science have established a fundamental role for low-degree chronic inflammation in mediating all stages of atherosclerosis, from initiation through progression and, ultimately, to the rupture of plaque and ensuing thrombotic complications of atherosclerosis. The cellular and molecular interactions involved during atherogenesis are fundamentally not different from those in chronic inflammatory–fibroproliferative diseases, such as rheumatoid arthritis (RA), glomerulosclerosis, or pulmonary fibrosis[15].

1.4 Epidemiology

Epidemiology involves the study of populations rather than the direct study of individuals which enhances the practice of medicine by increasing the understanding of how diseases arise and how they might be managed both in the individual and in societies as a whole. Epidemiologists promote the health of all populations through etiologic and interventional research supported by innovative methods and the accurate interpretation of research findings[16].

Epidemiologists examine disease in populations rather than in individual organisms (as the clinician would do), or in individual cells (the histologist or microbiologist), or in individual molecules (the geneticist or molecular biologist)[8]. Therefore, this is the study of the origin and causes of diseases in a community. It is the scientific method of investigation problem solving used to get to the root of health problems and outbreaks in a community.

Large population gains result from population level changes in risk factors[4]. Epidemiologists are 'big picture people' (holistic) by nature, in that they seek to understand disease by moving back from the individual molecule, cell, or host organism to see the disease in the population[8].

'You can observe a lot just by watching', Yogi Bera once said. Observational epidemiologists like to watch. They are 'biological accountants' in that they keep track of what they see, and look for patterns and trends in the occurrence of disease which might suggest the cause(s) of particular diseases, and how these might be controlled[8].

Disease surveillance systems provide the data needed to determine the health status of populations. The population is the patient for the epidemiologist and disease surveillance resembles the physical examination[8]. European Society of Cardiology (ESC) aim to map the status of European healthcare systems and will provide key decision makers with better elements than ever before that will inevitably influence allocation of funds for prevention, treatment, education and research[17].

One familiar successful story is related to Aspirin. Understanding exactly how aspirin blocks platelets demonstrated the power of haematology research in translating observations that Aspirin can protect individuals from heart attacks, made by physicians in their practice, to basic science mechanisms ("bedside to bench" research)[18].

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement is a checklist of items that should be addressed in articles reporting on the 3 main study designs of analytical epidemiology: cohort, case-control, and cross-sectional studies[19]. 'Cohort' or prospective studies are usually more expensive and take longer to conduct than do case-control studies[8].

Confounders can cause large problems in observational studies. In an observational study, selection bias occurs when the manner in which study participants are selected for membership in a study group (case versus control or risk cohort versus control cohort) predetermines the study outcome. Informational bias occurs when the way in which the study outcome is measured systematically affects the study results.

Confounding bias occurs when a third factor is associated with both the study factor and the study outcome[8].

Case-control, cohort, and cross-sectional studies, even when given ethics review, are not subject to all of the regulations that facilitate standardized reporting of clinical trials. Nonetheless, when observational studies provide the best evidence available, they influence clinical practice[20].

1.5 The Problem with Traditional Risk Factors

Risk assessment tools or novel risk markers balances an understanding of an individual's absolute risk for CVD and potential treatment benefits against the potential absolute risks for harm from therapy[21].

While there has been much attention to developing different types of CVD risk scores, there is uncertainty about the effects of providing a CVD risk score in clinical practice[22]. Risk factors for atherosclerotic CVD are well known (smoking, dyslipidemia, high blood pressure, diabetes, etc.) [23] and are used by the traditional risk factor–based approach, such as the Framingham risk scores [24] to identify high risk groups. However, although these equations do identify high risk groups, at best only 40% of the heart attacks and strokes that will occur in the next 10 years will be in these groups [25]. The remaining will occur in the low risk group which is very large and about three quarters of the population [25]. Thus, contrary to expectation, the risk factors causing atherosclerotic CVD are not very useful in classifying as high risk the majority of individuals that will develop CVD in the next ten years[26-28].

CV risk is strongly influenced by age (i.e. older people are invariably at high absolute CV risk). In contrast, the absolute risk of younger people, particularly younger women, is invariably low, even in those with a markedly abnormal risk factor profile[29].

A recent study of risk prediction in 1.8 million without CVD concluded that the application of existing CVD risk scores may result in considerable misclassification of high risk status as the Framingham, ASSIGN and QRISK2 risk scores do not predict the presence of high CVD risk well and consistently [25].

Therefore, cardiovascular risk calculated from conventional risk factors (age, gender, raised cholesterol, diabetes, elevated blood pressure, family history, smoking) using the Framingham or PROCAM equations leaves a lot to be desired because such equations are age driven. For example, a 40 year old female who is a heavy smoker, hypercholesterolemic and hypertensive has a low 10 year risk in contrast to a 70 year old male who has no other risk factors and yet has a much higher 10 year risk because of his age.

Risk may also be higher than indicated by risk estimation charts in asymptomatic individuals with preclinical evidence of atherosclerosis, for example plaque on carotid ultrasonography and in those with moderate to severe chronic kidney disease [glomerular filtration rate (GFR) < 60 mL/min/1.73 m2][30]. Patients with documented CVD such as carotid plaque on ultrasound, PAD, Diabetes and severe chronic kidney disease are at very high risk[30].

Current short-term (10-year) risk estimates are likely to substantially underestimate the lifetime cardiovascular risk of younger people (aged under 40 years) with hypertension, because short-term risk assessment is powerfully influenced by age[31].

A particular problem relates to young people with high levels of risk factors; a low absolute risk may conceal a very high relative risk requiring at least intensive lifestyle advice[32].

Another problem relates to older people. In some age categories, the majority of people, especially males, will have estimated 10 year cumulative CV death risks exceeding the 5–10% level, based on age only, even when other CV risk factor levels are relatively low[32].

It is recommended that asymptomatic men over the age of 40 and women over 50 years or post-menopausal should undergo risk factor screening including the lipid profile[33]. Prevention efforts have been highly promoted in recent years and evidence shows that 50% of the reductions seen in CHD mortality relate to changes in risk factors, and 40% to improved treatments[30]. Data from high income countries also indicate that falls in mortality from cardiovascular diseases are the main driver of rising life expectancy at age 60 for both men and women [34]. While women appear to be at lower CVD risk than men, this is misleading as risk is deferred by 10 years rather than avoided[30].

It is well understood that the higher the risk the greater the benefit from preventive efforts[30]. The absolute reduction in Atherosclerotic CVD events is proportional to baseline absolute atherosclerotic CVD risk[35]. The question is how best to identify high risk groups that will contain the majority of cardiovascular events that will occur subsequently.

1.6 Can pre-clinical atherosclerosis detection be useful?

Prevention is defined as a co-ordinated set of actions, either at the population or individual level, aimed at eliminating or minimizing the impact of CV diseases and their related disabilities[32].

There seems to be a window of opportunity between initiation/detection of pre-clinical atherosclerosis and full atherosclerotic cardiovascular event which if identified timely, can improve outcomes by reducing premature events and lead to more positive behaviour and life style changes and if indicated, early medical intervention at the early stages of disease. This silent phase of the disease has not been studied well and is not reflected enough in guidelines.

Chapter 2 Aims and Objectives

2.1 Hypothesis

The presence of pre-clinical atherosclerosis and or undiagnosed Atrial Fibrillation in apparently healthy and asymptomatic individuals could lead to higher risk of developing future events such as heart attack or stroke.

In addition, gender bias in guideline and current recommendations for AAA screening should be addressed. Therefore, this study addressed the following hypotheses:

i. Adults with undiagnosed peripheral or arterial atherosclerosis are at higher risk of developing cardiovascular events in comparison with their counterparts without
ii. There are other risk factors associated with AAA development in females and exclusion from screening based on age and/or gender only is incomplete
iii. The detection rate of AF among apparently healthy and asymptomatic individuals is high enough to justify public screening and or case finding
iv. The prevalence of CKD and its associations with subclinical atherosclerosis as well as traditional risk factors can help in better risk stratification of apparently healthy population

2.2 Study Aim

The aim of this study was to identify contemporary prevalence of preclinical atherosclerotic conditions that enable developing CVD primary prevention strategies by early detection of subclinical atherosclerosis to reduce premature morbidity and

mortality rates. This becomes possible by introduction of primary prevention for apparently healthy but at high risk population. The study consists of a retrospective study of the prevalence of and risk factors for Abdominal Aortic Aneurysm (AAA), asymptomatic Atrial Fibrillation (AF) and Chronic Kidney Disease amongst asymptomatic individuals who voluntarily attended private healthcare screening appointments in the UK and Ireland.

The aim of sub group analysis of AAA study was to identify factors that are independently associated with AAA and to determine the large AAA predictors in a large population cohort including women and younger patients (<65 y/o) with AAA.

In addition, a case-control, prospective study was designed to recruit 1500 participants and follow them up at intervals up to 10 years. The aim of this study was to assess the rate of major cardiovascular events among apparently healthy individuals with and without Carotid Artery Stenosis (CAS) as a marker of subclinical atherosclerosis.

Chapter 3 Global Burden of Cardiovascular Disease and Role of Prevention

3.1 Global Health Challenge

Atherosclerotic cardiovascular disease (CVD), especially coronary heart disease (CHD), remains the leading cause of premature death worldwide[30]. Globally, deaths due to IHD increased by one-sixth, 8.9 million deaths, from 2005 to 2015[36]. WHO reported cardiovascular diseases as the number one cause of death throughout the world. Regrettably, CVD killed 17.5 million people in 2012, which is 3 in every 10 deaths. Of these, 7.4 million people died of ischemic heart disease and 6.7 million from stroke [37]. CVD affects both men and women and of all deaths that occur before the age of 75 in Europe, 42% are due to CVD in women and 38% in men[30]. Figure 3.1 illustrates the global map of CVD related death in 2015.

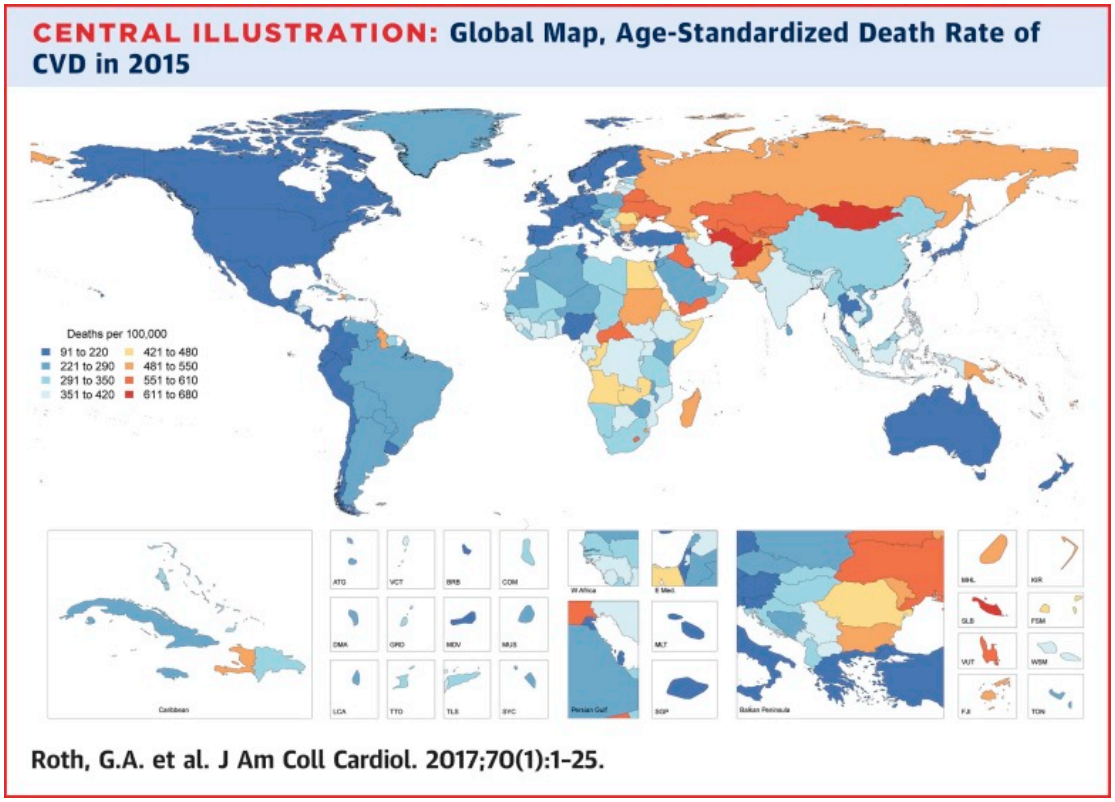


Figure 3.1: CVD Death Rate in 2015[38]

Coronary Heart Disease is the leading cause (43.8%) of deaths attributable to

cardiovascular disease in the US, followed by Stroke (16.8%), Heart Failure (9.0%), High Blood Pressure (9.4%), diseases of the arteries (3.1%), and other cardiovascular diseases (17.9%)[39].

Whilst the total number of deaths from specific causes does not provide a good metric for informing public health priorities, years of life lost (YLL) has been introduced as a measure of premature mortality that takes into account both the frequency of deaths and the age at which death occurs. YLL are calculated from the number of deaths at each age multiplied by a global standard life expectancy for the age at which death occurs [34]. Ischaemic heart disease and stroke were among the top three causes of YLL in 2012 [34]. CVD cost the European Union about €210 billion in 2015, one-half of which was in healthcare costs (~8% of total healthcare expenditure), and the other half in productivity losses and informal care[40].

In 2012, global life expectancy at birth was 68.1 years for men and 72.7 years for women that has increased by six years since 1990 [34]. The incidence of CVD increases sharply with age and given the current longevity seen in the developed countries, the number of patients is expected to increase. Population growth, population ageing, and the increase in risk factors such as obesity and type 2 diabetes mellitus will attenuate the positive trends seen in coronary mortality[41].

Despite gaps in our understanding, there is ample evidence to justify intensive public health and individual preventive efforts[30]. CVD represents a considerable economic burden to society and effective preventive measures are necessary. There is consensus in favour of an approach combining strategies to improve CV health across the

population at large from childhood onward, with specific actions to improve CV health in individuals at increased risk of CVD or with established CVD[1].

Cardiovascular mortality has declined in Europe during the last decades, mostly driven by the decline in coronary death rates. More than half of the reduction in population cardiovascular mortality has been attributed to changes in risk factors levels in the population, cholesterol and blood pressure levels, and smoking[41].

3.2 Primary and Secondary Prevention

Cardiovascular disease prevention is defined as a coordinated set of actions, at the population level or targeted at an individual, that are aimed at eliminating or minimizing the impact of CVDs and their related disabilities[42].

Primary prevention is defined as prevention of disease through the control of exposure to risk factors. Strategies for primary prevention include population-wide strategies and targeted, high-risk strategies focusing on population sub-groups. For example, careful weight control prevents obesity which in itself is a risk factor for many conditions including heart disease and diabetes.

Secondary prevention is the application of available measures to detect early departures from health and to introduce appropriate treatment and interventions. Screening is a major component of secondary prevention.

Recent guideline suggested that prevention of CVD, either by implementation of lifestyle changes or use of medication, is cost effective in many scenarios, including population-based approaches and actions directed at high-risk individuals[1].

Prevention of disease and the promotion of health are at the heart of population health science. The reasons for this start with our values. Broadly speaking, we would rather not develop disease at all than develop disease and need to be treated for it. Therefore, prevention represents an important corollary focus for population health science and represents a core stratagem of population health. However, prevention is often difficult, strategies for complex chronic diseases are underdeveloped, and prevention efforts face the "prevention paradox"[43].

Since diseases are rare, most individuals who adopt a behaviour designed to lower their risk of disease will not benefit directly, although a few individuals may benefit enormously. For example, any one person's decision to lose weight may only have a small impact on that person's risk of disease in the near future, but if many people each lose a little weight, this may have a substantial impact on the community's obesity-related disorders[44]. Therefore a combination of population and high-risk approaches is usually most effective.

There is a strong evidence base that lipid-lowering and anti-platelet drugs should be used in secondary prevention of CVD and considered for primary prevention of CVD in certain groups of the population[4]. In addition, all patients with PAD should be treated with statins and platelet inhibitors according to guidelines[45].

3.3 Effect of Statin Therapy

Lipoproteins in plasma transport lipids to tissues for energy utilization, lipid deposition, steroid hormone production, and bile acid formation. Lipoproteins consist of esterified and un-esterified cholesterol, TGs, and phospholipids and protein components named apolipoproteins that act as structural components, ligands for cellular receptor binding, and enzyme activators or inhibitors[32].

ApoB-containing lipoproteins retained in the arterial wall provoke a complex process that leads to lipid deposition and the initiation of an atheroma[46] and people with higher concentrations of plasma ApoB-containing lipoproteins will retain more particles and accumulate lipids faster, resulting in more rapid growth and the progression of atherosclerotic plaques[32].

Statins reduce the synthesis of cholesterol in the liver by competitively inhibiting the enzyme HMG-CoA reductase, the rate-limiting step in cholesterol biosynthesis.

Randomised control trials (RCT) have demonstrated that, aggressive risk factor modification can provide effective primary prevention, producing a 40-50% reduction in cardiovascular risk defined as combined events of heart attack and stroke [47, 48]. Patients receiving pravastatin 3 months before carotid endarterectomy showed significantly less inflammation and a higher collagen content in carotid plaques, suggesting plaque stabilization[49]. Results are consistent with pleiotropic, anti-inflammatory effects of statins, which may contribute to the stabilization of plaques[50].

Statins may have benefits other than just lowering your cholesterol. One promising benefit seems to be their anti-inflammatory properties, which help stabilize the lining of blood vessels. In the heart, healthier blood vessel linings would make plaques less likely to rupture, thereby reducing the chance of a heart attack[51].

Patients with non-coronary atherosclerosis (carotid, peripheral, aortic, renal) should receive statin therapy for secondary prevention, irrespective of non-cardiac surgery. Statins also induce coronary plaque stabilization through pleiotropic effects, which may prevent plaque rupture and subsequent myocardial infarction in the perioperative period[52].

Figure 3.2 shows plaque changes overtime observed by intravascular imaging modality of optical coherence tomography (OCT).

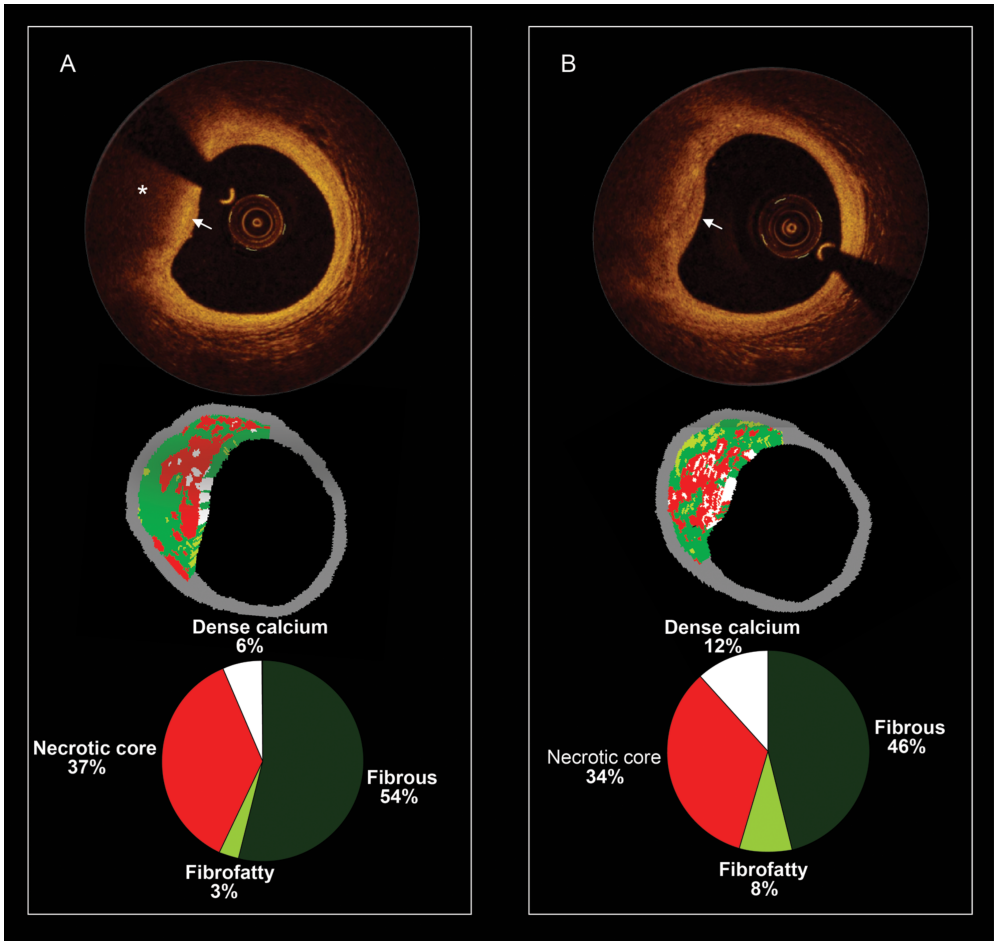


Figure 3.2: Serial and corresponding virtual histology and optical coherence tomography.

(A) The baseline optical coherence tomography frame (top), the corresponding virtual histology frame (mid), and the quantification of the virtual histology tissue types (bottom). The optical coherence tomography frame shows from 8 to 12 o'clock a fibroatheroma which is composed of a fibrous cap (white arrow) and a necrotic core (asterisk). The corresponding virtual histology frames show also a fibroatheroma (necrotic core-rich plaque in red colour). In (B), the patient was reimaged at 1 year and some plaque changes have been observed. In the optical coherence tomography frame, the fibrous cap became thinner (please note that at baseline, the signal rich area overlying the necrotic core was wider). Adopted from (https://doi.org/10.1093/eurheartj/eht301)

In the Cochrane meta-analysis of 14 RCTs of statin therapy in primary prevention, statins were associated with a 28% reduction in fatal and non-fatal CHD events (RR 0.72; 95% CI 0.65-0.79), 22% reduction in fatal and non-fatal stroke (RR 0.78; 95% CI 0.65-0.94) and a 17% reduction in overall mortality (RR 0.83; 95% CI 0.73-0.95) [53]. Men and women, old and young, and people with and without CVD all appear to benefit from LDL cholesterol reduction[2]. In addition, the absolute benefit was found to be higher in those at higher baseline risk. The efficacy of statin therapy in addition

to other risk factor modification therapies indicates the need for accurate identification of high risk individuals.

RCT which included patients with atherosclerotic arterial disease[47, 48] have demonstrated that in addition to reduction in cardiovascular events, aggressive reduction of LDL to 70 mg/dl (1.8 mmol/L) or lower was associated with coronary artery plaque regression [54, 55], and in the METEOR primary prevention trial rosuvastatin delayed the progression of carotid atherosclerosis in individuals with subclinical atherosclerosis and moderately elevated cholesterol levels[56]. Several statin trials have reported a 20% risk reduction in vascular events for each mM of reduction in the LDL cholesterol level in secondary prevention[10].

A review of 17 prospective studies of which 9 were RCT[57] reported changes in plaque morphology as a result of statin therapy. There was increase in plaque echogenicity (9 studies), decrease in lipid core size (9 studies), regression or slower progression of plaques (7 studies) and reduction in TCD microemboli (1 study).

HSE 2011 reported that only 79% of men and 72% of women over 35 with self-reported doctor-diagnosed IHD or stroke were using lipid-lowering drugs[4].

3.4 Antiplatelet therapy

Once thought to be just "dust" particles in blood, platelets were first recognized as a special class of blood cells (actually cell fragments) by an Italian researcher in 1882 (Figure 3.3). Hematology research over the past century has subsequently unraveled what platelets normally do, why they can cause cardiovascular disease under certain

conditions, and how they can be effectively targeted with antiplatelet therapy to prevent and treat heart attacks and stroke[18].

Antiplatelet drugs decrease platelet aggregation and inhibit thrombus formation in the arterial circulation, because in faster-flowing vessels, thrombi are composed mainly of platelets with little fibrin[58].

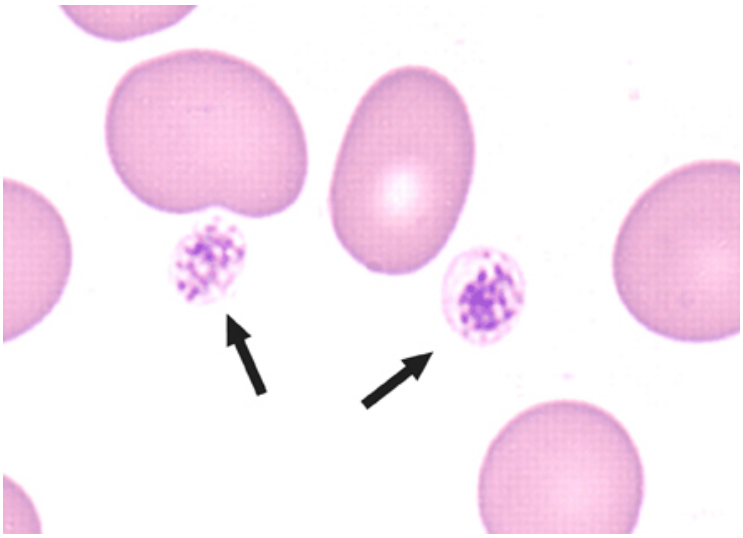


Figure3.3: Platelets with its granular appearances[18]

Thus, basic hematology research to understand how platelets work and how their function can be blocked has transformed our modern approach to the prevention and treatment of cardiovascular disease. Excessive interference with platelet function with any of these antiplatelet agents carries with it the risk of causing the opposite of thrombosis, namely bleeding complications[18]. Antiplatelet therapy is not recommended in individuals free from CVD, due to the increased risk of major bleeding[1, 58] but in known CVD, these agents mostly reduce complications of plaque rupture[13]. Figure 3.4 shows the mechanism of action of different antiplatelet.

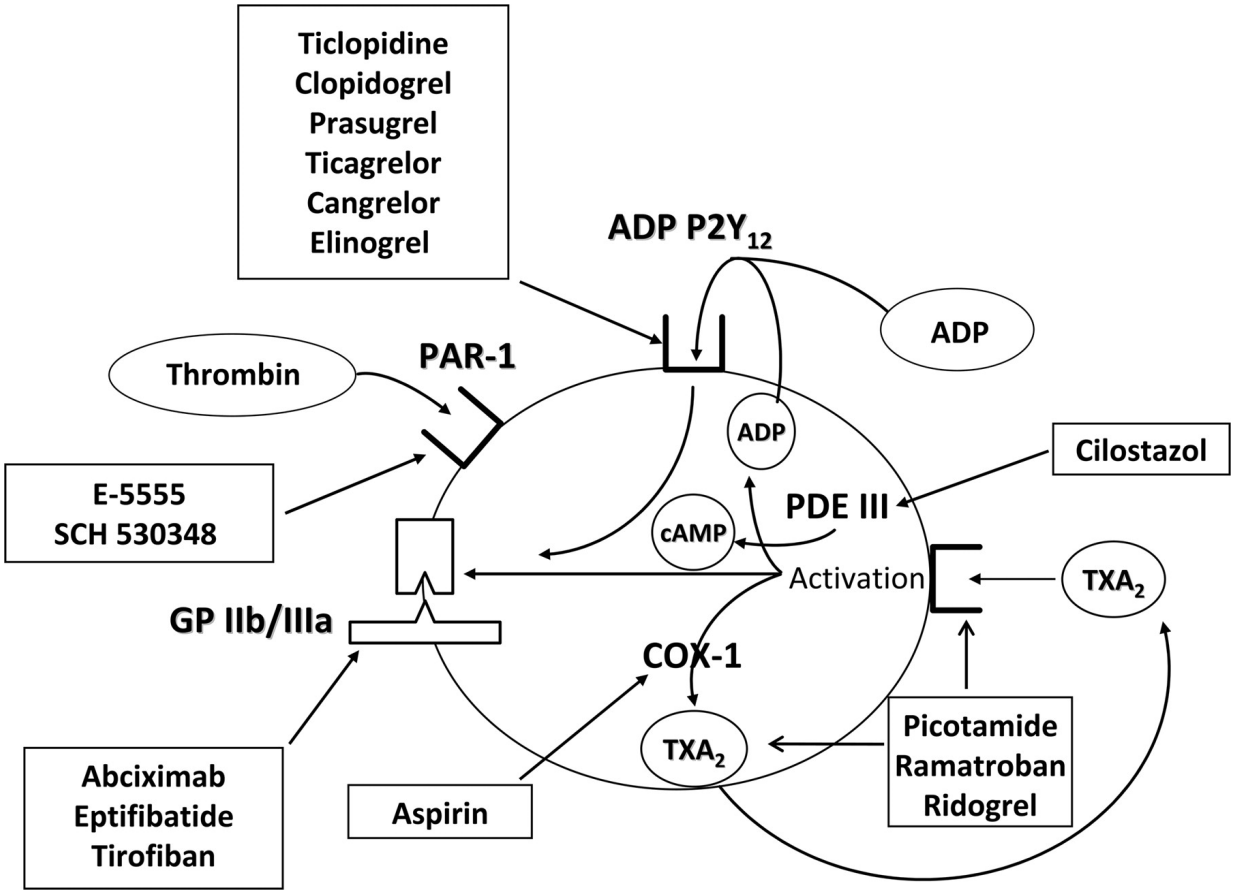


Figure 3.4: Antiplatelet mechanism of action[59]

Platelets are like microscopic circulating band-aids, constantly looking for leaks in the vascular system and then instantaneously plugging these bleeding sites by sticking to the wound (a process called adhesion), becoming activated locally, and then attracting other circulating platelets to build an impermeable clump (a process called aggregation) at the exact point of damage. This protective mechanism, which is a desirable function of platelets, is called hemostasis. But under some conditions platelets can become harmful, causing plugs to form where there is no bleeding and they are not needed. This typically happens in arteries that have become diseased with atherosclerosis, a condition in which deposits of fat or plaque collect and harden in the arteries, blocking the normal flow of blood. Platelets can stick to atherosclerotic plaques in the coronary and brain arteries and obstruct, or occlude, these vessels

causing heart attacks and strokes. This undesirable, pathological process is called thrombosis[18].

Aspirin is effective for CVD secondary prevention by mostly reducing complications of plaque rupture and may not be plaque-stabilizing agents *per se*.[13]. The combination of statin and aspirin are associated with the greatest reduction in mortality among four commonly recommended therapies for secondary prevention (statin, aspirin, beta blocker, angiotensin-converting enzyme inhibitor)[10].

Despite all available evidence supporting the beneficial use of antiplatelet therapy, in England, only 64% of men and 60% of women with diagnosed CVD were using anti-platelet medication[4].

3.5 Antihypertensive Therapy

Hypertension is currently the second most important preventable risk factor for premature death[60]. Recent ESC guideline for HTN suggest that hypertension remains the major preventable cause of cardiovascular disease (CVD) and all-cause death globally and in our continent[61, 62]. During the past four decades, the highest worldwide blood pressure levels have shifted from high-income countries to low-income countries in south Asia and sub-Saharan Africa due to opposite trends, while blood pressure has been persistently high in central and eastern Europe[63].

Blood pressure is normally distributed in the population and there is no natural cut-off point above which 'hypertension' definitively exists and below which it does not. The risk associated with increasing blood pressure is continuous, with each 2 mmHg rise

in systolic blood pressure associated with a 7% increased risk of mortality from ischaemic heart disease and a 10% increased risk of mortality from stroke[31].

Based on office BP, the global prevalence of hypertension was estimated to be 1.13 billion in 2015[63]. The prevalence of hypertension in HSE was 31% of men and 28% of women in 2011. Whilst clinical management of hypertension has improved, the prevalence has remained unchanged since 2003. Between 2003 and 2011, the prevalence of untreated hypertension fell from 20% of men and 16% of women, to 14% of men and 11% of women[4]. Using the 2017 ACC/AHA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults, 45.6% of US adults have hypertension[39].

Hypertension is defined as the presence of persistently raised blood pressure, measuring 140/90mmHg or above[60]. This is based on evidence from multiple RCTs that treatment of patients with these BP values is beneficial[61].

The overall prevalence of hypertension in adults is around $30-45\%$[61]. In England, the prevalence of hypertension among HSE participants with stroke or ischaemic heart disease was 60% of men and 45% of women in 2011. This was around double the prevalence found among those without cardiovascular disease[4].

Elevated BP was the leading global contributor to premature death in 2015, accounting for almost 10 million deaths and over 200 million disability-adjusted life years[63]. Hypertensive patients with documented CVD, including asymptomatic atheromatous disease on imaging, type 1 or type 2 diabetes, very high levels of

individual risk factors (including grade 3 hypertension), or chronic kidney disease (CKD; stages 3 − 5), are automatically considered to be at very high (i.e. ≥10% CVD mortality) or high (i.e. 5 − 10% CVD mortality) 10 year CV risk[61].

3.6 The value of detecting Subclinical Atherosclerosis

Detection of asymptomatic but diseased patients is crucial for an adequate prevention programme. At every level of risk factor exposure, there is substantial variation in the amount of atherosclerosis. This variation in disease is probably due to genetic susceptibility, combinations of different risk factors, and interactions between genetic and environmental factors. Thus measurements of subclinical disease may be useful for improving CVD risk prediction[30].

Early detection of arterial disease in apparently healthy individuals has focused on the peripheral arterial territory and especially on the carotid arteries because they are easily accessible and because atherosclerosis in one arterial territory is often associated with involvement of other territories[64].

Chapter 4 Atherosclerosis Screening

4.1 Screening Guidelines

Screening is the process of identifying healthy people who may have an increased chance of a disease or condition. The screening provider then offers information, further tests and treatment. This is to reduce associated problems or complications[65]. Identification through this process can show that they have the condition screened for.

CV risk assessment or screening can be done opportunistically or systematically. Opportunistic screening means without a pre-defined strategy, but is done when the opportunity arises [e.g. when the individual is consulting his or her general practitioner (GP) for some other reason]. Systematic screening can be done in the general population as part of a screening programme or in targeted subpopulations, such as subjects with a family history of pre-mature CVD or familial hyperlipidaemia[1].

Screening can save lives or improve quality of life through early identification of a condition and reduce the chance of developing a serious condition or its complications[65]. This must be note that Public expectations about screening don't always match what screening programmes can deliver[66] and there are false positive and false negative results in any screening programme[65].

A general concern in screening, including CV risk assessment, is its potential to do harm. False positive results can cause unnecessary concern and medical treatment. Conversely, false negative results may lead to inappropriate reassurance and a lack of

lifestyle changes[1]. Figure 4.1 pictures the role of screening and possible outcomes of a screening programme for the participants.

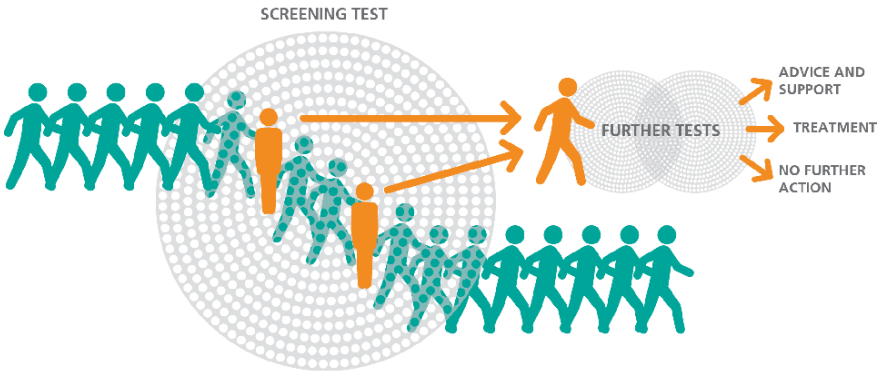


Figure 4.1: Role of Screening

4.2 Carotid artery disease Screening

The 2014 update of the 2007 U.S. Preventive Services Task Force (USPSTF) recommendation statement on screening for carotid artery stenosis recommends against screening for asymptomatic carotid artery stenosis in the general adult population [67]. This recommendation is centred on asymptomatic carotid artery disease producing 60-99% stenosis which has been traditionally considered as a criterion for carotid surgery. Whilst the recommendation against screening to identify those with more than 60% stenosis with the view to offer surgery to non-selected patients is relevant, the statement significantly fails to address asymptomatic carotid stenosis as subclinical atherosclerotic disease which is a marker for all cardiovascular events and could enable one to better target intensive medical therapy.

4.2.1 Asymptomatic Carotid Artery Disease and risk of CVD

Ischaemic heart disease and stroke are the world's biggest killers, accounting for a combined 15 million deaths in 2015 and remained the leading causes of death globally in the last 15 years[68]. Stroke is one of the top four causes of death in England and a leading cause of adult disability[29]. Stroke is the second leading cause of death worldwide[68].

Approximately, There are more than 100,000 strokes in the UK each year that is around one stroke every five minutes[29]. There are around 32,000 stroke-related deaths in England each year. Based on recent press release by Public Health England, deaths related to stroke have declined by 49% in the past 15 years. This has been accredited to a combination of better prevention, earlier treatment and more advanced treatment. NHS Health Check, for those aged 40 to 74 years, can identify early if one is at risk of a stroke[69].

Asymptomatic patients with substantial (e.g. 60–90%) carotid artery narrowing but no recent neurological symptoms are at increased long-term risk of ischaemic stroke, especially in parts of the brain supplied by that artery (the ipsilateral carotid territory)[70].

From 2005 to 2015, the age-adjusted stroke death rate decreased 21.7%, and the actual number of stroke deaths declined 2.3%[39]. Almost two thirds of stroke survivors leave hospital with a disability[29]. Worldwide stroke-related illness, disability and early death is set to double in the next 15 years (by 2035)[71]. The cost of stroke to society is around £26 billion a year[29].

Most strokes are caused by occlusive arterial disease (obstruction in the vessels providing oxygen rich blood), around 15% are due to atrial fibrillation (AF) which is irregular heart rhythm, and a further 15% or more are associated with carotid stenosis. Asymptomatic patients with substantial (eg, 60–90%) carotid artery narrowing but no recent neurological symptoms are at increased long-term risk of ischaemic stroke, especially in parts of the brain supplied by that artery (the ipsilateral carotid territory). Carotid endarterectomy (CEA) can remove the arterial narrowing, but the procedure itself causes some immediate risk of stroke or death[70]. This intervention almost halved the non-perioperative stroke rate over the next 10 years[70].

The latest ACC/AHA guidelines published in November 2013 recommend that non-diabetic individuals without clinical (i.e. asymptomatic) atherosclerotic cardiovascular disease (ASCVD) and an LDL-C of 70-189 mg/dL (1.8-4.9 mmol/L) should be treated aggressively with statins in addition to other risk factor modifications when the 10-year risk of ASCVD is more than 7.5% (average annual risk > 0.75%). [35]. This is because RCTs have demonstrated that in such individuals the reduction in ASCVD risk by statin therapy occurs regardless of risk factor characteristics in both primary and secondary prevention and outweighs potential harm from side effects.

Thus, the high incidence of myocardial infarction and mortality in patients with asymptomatic carotid atherosclerotic plaques as outlined above and by the latest ACC/AHA guidelines (2013) have resulted in a new concept of the value of screening with ultrasound.

4.2.2 Noninvasive Detection of Carotid Artery Atherosclerosis

Ultrasound imaging of the carotid bifurcations is a non-invasive means of assessing subclinical atherosclerosis. Carotid plaques are related to both coronary obstructive disease [72] and the risk of cerebrovascular events[30]. The presence of common femoral plaques is another strong ultrasonic predictor of coronary disease, which is independent of carotid.



Figure 4.2: Carotid Plaque Appearance using ultrasound[73]

It has recently been demonstrated that screening with ultrasound is particularly useful in the absence of risk factors. In one study, 47% of asymptomatic individuals at low 10 year Framingham risk (< 10%) screened with ultrasound had carotid plaques[74]. Such individuals should be reclassified as intermediate (10-20%) or high risk (> 20%) according to plaque number and area present. Figure 3.2 demonstrate an example of carotid artery atherosclerotic plaque identified by ultrasound.

In the CAFES-CAVE study 10,000 asymptomatic, non-diabetic, normotensive individuals with total cholesterol < 5.2 mmol/L had both carotid and both common femoral bifurcations scanned with ultrasound and followed-up for 10 years[75]. In the absence of plaques (90% of the population) the average annual event rate was 0.1%. In the presence of at least one plaque the annual event rate was 5% (mainly myocardial infarction). The annual event rate was 3% if the plaque produced <50% stenosis and 8% in the presence of > 50% stenosis.

Subsequent studies have substantiated these findings and have demonstrated that the presence of carotid plaques, however small, place an individual in a high risk group[72, 76, 77]. In addition, the bigger the plaque as measured by thickness and preferably area, the higher is the risk[72, 77].

High cardiovascular mortality in patients with asymptomatic carotid stenosis greater than 50% was consistently reported in recent publications (2006-2014) in which only some patients were on statins[78-82]. In these publications, the average annual mortality was 5-6%. When causes of death were reported, 67% of deaths were from cardiac ischemic events[83-86].

The above findings indicate that the presence of a carotid plaque, however small places an asymptomatic individual in a high risk group (10 year cardiac event rate > 20% or annual rate of > 2%).

4.3 Abdominal Aortic Aneurysm

An aneurysm is a localized dilation of an artery. Most aneurysms occur in the aorta with diameter ≥30 mm. It has been reported that 90-95 percent of AAAs occur in the infrarenal abdominal aorta. The aetiology and complex pathogenesis of abdominal aortic aneurysm is still not well understood. It has historically been considered to be a manifestation of atherosclerosis[87].

Microscopic investigations of the aneurysm show arteriosclerotic changes; the patients have risk factors in common with those showing obstructive arteriosclerotic lesions; arteriosclerotic changes in other vessels are seen significantly more often in patients with abdominal aortic aneurysm[88].

Abdominal aortic aneurysms usually present none or few symptoms, but they can be associated with life-threatening complications including rupture, thrombosis, and embolization. Surgical repair of the ruptured abdominal aortic aneurysm (rAAA) has a perioperative mortality rate more than 70 percent, resulting in one of the highest surgical mortalities of all vascular emergencies[89], and ruptured AAA is the cause of 1% to 2% of all deaths in the Western world [90, 91]. In contrast, operative mortality in elective surgery of AAAs is reported to be 2% to 6% [92]. Recent studies show that the 30 day mortality after surgery has been improved to 2.4%[93].

The reasons for sex differences in AAA remain unknown but estrogens may play a role in reducing the prevalence of AAA in women[94-96]. In view of the relatively low prevalence, women were excluded from the large trials of screening for AAA [96].The offer of screening to men >65 y/o has been reported to be highly cost-effective[97, 98]. A

population-based study from Finland found that aneurysm diameter was <5.5 cm in 24% of cases of ruptured AAA in women compared with only 5% in men (P<0.01, x^2 test) [99]. Another study concluded that the annual risk of rupture of large AAA (>5 cm in diameter) was 18% (95% CI, 8% to 26%) in women versus 12% (95% CI, 5% to 20%) in men[100].

In the UK Small Aneurysm Trial, the risk of rupture in women was 4-fold that of men [101] and rupture appears to occur at smaller diameters in women[102]. In particular, a threshold of 5.5 cm for intervention would seem too high in women and The Joint Council of the American Association for Vascular Surgery and Society for Vascular Surgery have recommended elective repair at 4.5 to 5 cm in women[103].

The burden of AAA disease has been falling since at least 1991 in NZ and since 1995 in England and Wales. Although survival appears to be improving, most of the reduction is due to lower disease incidence [104, 105], as the mean aortic diameter of the 65-year-old male has reduced over 20 years [105], this can be explained on the basis of the observed reduced exposure to risk factors. Hence, it is important to establish risk factors for AAA to identify at risk population as well as determining the modifiable factors influencing the onset of AAA and its progressive expansion to find the new therapeutic strategies to improve its morbidity and mortality. Important issues to address are the threshold diameter for follow-up, the possible need for rescreening at a more advanced age, and selective screening among smokers[106].

Four RCTs of population screening for abdominal aortic aneurysm (AAA) using ultrasound followed by surgical intervention when AAA maximum diameter reached

5-5.5 cm demonstrated that in men aged 65-80 years old, aneurysm related mortality was reduced by 40% [107-112].

The most recent cost-effectiveness analysis of the NHS AAA screening programme for men in England has estimated the long term incremental cost-effectiveness to be £ 5,758 per life year gained for an AAA prevalence of 1.5% and indicated that the cost-effectiveness ratio would rise above the NICE £20,000 threshold at a prevalence of AAA of less than 0.35% in 65 year old men[113].

However, only one RCT included women and in this study there was no evidence of benefit[107, 114]. In view of the low prevalence of AAA in women, this trial may have been underpowered. Indeed, epidemiological studies have found that the prevalence of AAA in women is nearly a quarter of that found in men[115, 116].

Risk factors reported to be associated with the presence of AAA ≥ 3.0 cm in diameter in men on screening are age, smoking, and history of AAA in first degree relatives, atherosclerosis arterial disease, stroke, hyperlipidaemia and hypertension[114, 115, 117].

Currently, women are not included in AAA screening programs because this is considered as "not indicated or not economically viable"[114]. Very little was found in the literature assessing risk factors associated with AAA in women and patients younger than 65 year old.

Modelling methods can play a role in improving public health decision-making. Modelling has been defined as 'a logical mathematical framework that permits the

integration of facts and values to produce outcomes of interest to decision-makers and clinicians'[118].

The aim of this study is therefore to identify factors that are independently associated with AAA and to determine the large AAA predictors in a large population cohort including women and younger patients (<65 y/o) with AAA. The aim of our study was to determine (a) the prevalence of AAA ≥ 3.0 cm in women screened with ultrasound (b) the risk factors associated with AAA in this population and (c) whether high risk groups can be identified with an AAA prevalence of ≥ 1%.

4.4 Stroke and Atrial Fibrillation:

4.4.1 Introduction

Atrial fibrillation is the most common heart rhythm disturbance and affects up to 800,000 people in the UK. Approximately, 5% of the National Health Service (NHS) expenditure is being spent on stroke [119]. Additionally, stroke causes more than 42,000 deaths in the UK each year. There are approximately 152,000 strokes in the UK each year. Heart disease and associated conditions are a serious issue for the health of the UK population and the economy.

AF Currently affects about 2.7–6.1 million people in the USA[120] and 33 million people worldwide[121], with an annual risk of ischemic stroke estimated to be about 5–7%[122], the cornerstone of management remains interventions for rate control, rhythm control and thrombo-prophylaxis.

Atrial fibrillation is a heart condition that causes an irregular and often abnormally fast heart rate which increases the risk of a stroke by five times [123]. Therefore, Stroke is the most serious complication of AF which is often unrecognized and untreated in patients admitted with acute ischaemic stroke[30]. Stroke risk is significantly reduced with anticoagulation therapy. AF can also lead to heart failure.

Asymptomatic and isolated AF are particularly difficult to diagnose, yet still carry a high risk of stroke[124]. AF is associated with major systemic thromboembolism and about a third of patients with ischemic stroke have been found to have either clinical or subclinical AF[125]. Its association with stroke increases with age and almost one third of all strokes are due to AF[126]. It has been estimated that optimal treatment of AF in the population might reduce the overall incidence of stroke by 10% [119].

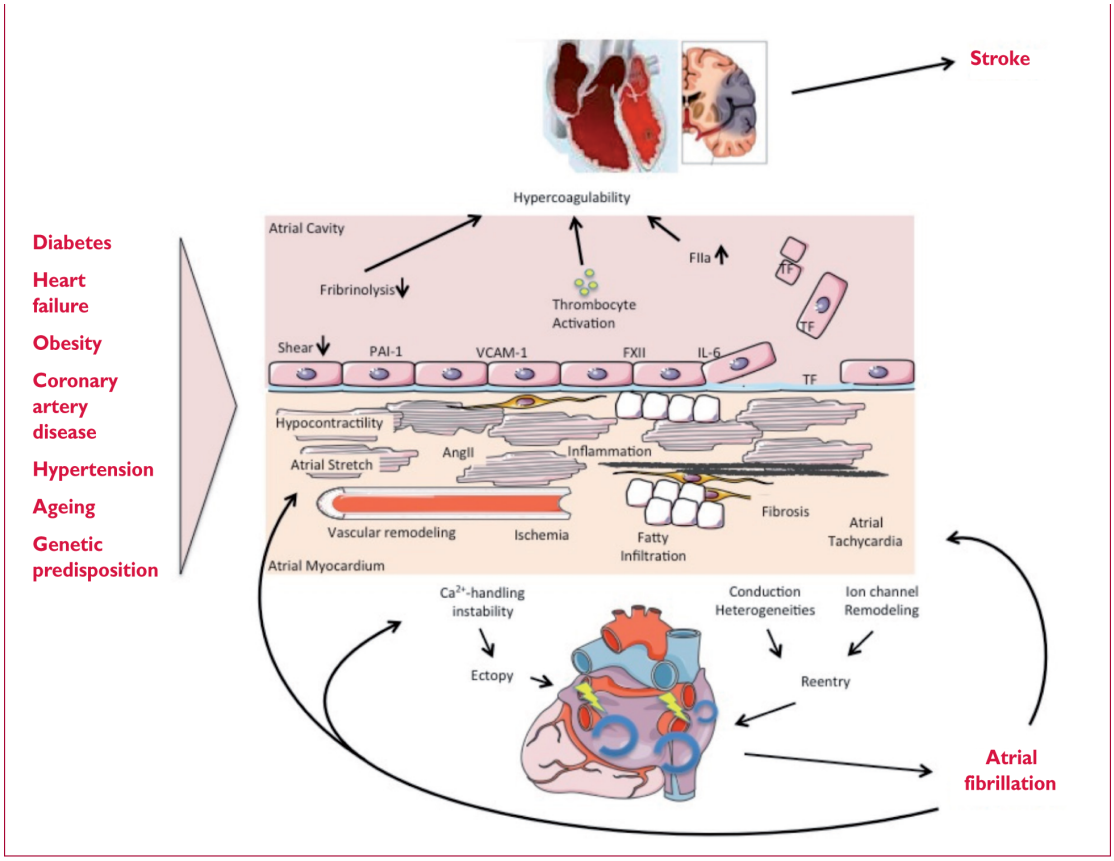
The most obvious symptom of atrial fibrillation is palpitations but it is a very common symptom in those without AF too and one study showed that only 13% of patients with AF reported palpitations, similar to the proportion of participants with no history of AF reporting palpitations [127].

A Recent population-based study showed that AF is more common than previously thought (3.2% of the population aged ≥20 years)[126]. A more recent UK study also detected 4.1% cases of AF in a population of >65 y/o who were invited for primary care screening [124].

According to the WHO, the concept of screening in health care – that is, actively seeking to identify a disease or pre-disease condition in individuals who are presumed and presume themselves to be healthy – is now widely accepted in most of the developed world. Used wisely, it can be a powerful tool in the prevention of disease[128]. Therefore, it is believed that the aim of screening is to promote good health versus the treatment of ill health and screening has become an increasingly recognised tool in improving health in the population.

The direct costs of AF already amount to approximately 1% of total healthcare spending in the UK[129]. Recent studies suggest that community-based screening for AF in more than 65 years old population is cost effective[127, 130]. AF management guideline published by ESC in 2016 advocates use ECG screening in at-risk populations for AF, especially stroke survivors and the elderly[131].

Previously undiagnosed AF was found in 1.4% of those aged >65 years, suggesting a number needed to screen of 70. These findings encourage the further evaluation of systematic AF screening programmes in at-risk populations[132]. Figure 4.1 shows different mechanisms of AF and its relationship with stroke.



AngII = angiotensin II; TF = tissue factor; FXII = factor XII; IL-6 = interleukin 6; PAI-1 = plasminogen activator inhibitor 1; VCAM-1 = vascular cell adhesion molecule 1.

Figure4.1: Major mechanisms causing atrial fibrillation that can be considered when choosing therapy[131].

There are different stroke risk calculators but CHA2DS2-VASc score is still the most widely used scoring system and the 2018 American College of Chest Physicians (ACCP) CHEST guidelines recommend the use of oral anticoagulants, preferably NOACs for patients with a single non-sex CHA2DS2-VASc risk factor (score of ≥ 1 in males, ≥ 2 in females) rather than no anticoagulation or use of single or dual anti-platelet therapy[133]. Figure 4.2 shows the contributing factors in calculation of CHA2DS2-VASc score.

Risk Factors	Scores
Congestive heart failure/Left ventricular dysfunction	1
Hypertension	1
Age ≥75Yrs	2
Diabetes mellitus	1
Stroke/TIA	2
Vascular disease (prior myocardial infarction, peripheral artery disease	1
Age 65 to 74 years	1
Sex category (female)	1

Figure 4.2: Individual components of the CHA2DS2-VASc risk factors[134].

4.4.2 AF Screening

Recent data suggest that the resulting societal burden of the largely preventable strokes in unrecognized AF could be substantially reduced by screening programs to detect incidental AF and initiating appropriate thrombo-prophylaxis with oral anticoagulants (OAC)[130].

Some studies suggest that simple pulse check may provide similar results to that of an ECG [135]. However, pulse palpation screening is believed to have low specifity since a more recent population-based study using limb-lead ECGs detected many cases of ectopy, twice as many times as AF[124] which can cause irregular heart rhythm too when checked by pulse. This is well known that both ectopy and AF commonly present as an abnormal irregular pulse.

It is suggested that a systematic screening programme using limb-lead ECGs could increase the detection rate of AF by around a third [124]. These newly identified patients

may benefit from anticoagulation treatment and, in turn, prevent stroke from occurring. This underlines the impact of screening in the community for AF, particularly given the strong association of AF with stroke, and the social, financial and personal burden that stroke carries.

Another study conducted in Sydney showed that using pulse palpation, almost a quarter of AF cases was not identified, and only 73% of newly identified AF cases were detected. In addition, over 70% of cases with false positive pulse diagnosis, had just multiple atrial or ventricular ectopic beats or sinus arrhythmia noted on the ECG[127].

4.5 Chronic Kidney Disease

Chronic kidney disease (CKD) is a progressive reduction in the kidneys' ability to filter blood. People with CKD have greatly increased mortality risk in comparison to the non-CKD population[136], with cardiovascular disease being the cause of death in almost half of all cases[137]. Even mild-to-moderate CKD is associated with adverse clinical outcomes[136]. CKD also impacts negatively on patients' quality of life (QoL) and places a heavy economic burden on healthcare systems[138]. It is not known whether a pathological process underlies CKD or if it is simply part of aging[139].

Risk assessment with a calculator is not required in patients who are at high risk of cardiovascular disease. High-risk patients include those with established cardiovascular disease, chronic kidney disease (eGFR <60 mL/minute/1.73 m^2),

albuminuria, familial hypercholesterolaemia, and those who are over 40 years of age with diabetes mellitus[5].

Glomerular filtration rate (GFR) is considered to be the best indicator of kidney function[140]. GFR is usually estimated from serum creatinine levels and adjusted for age, sex and ethnicity using the Modification of Diet in Renal Disease formula (MDRD) and/or Cockroft-Gault (C-G). However, these formulas are known to underestimate GFR[141, 142], leading to over diagnosis, particularly in low-risk individuals[141].

4.5.1 CKD Stages

There are 5 stages of CKD defined by GFR (ml/min/173 m^2), as shown in Table 4.1. This classification is based on GFR levels over a 3-month period. Single GFR determinations are apt to overestimate prevalence[138].

Table 4-1: Stages and description of CKD

CKD stage	GFR (ml/min/173 m^2)	Description
1	≥90	Normal or increased GFR, but with other evidence of kidney damage
2	60–89	Slight decrease in GFR, with other evidence of kidney damage
3A	45–59	Moderate decrease in GFR, with or without other evidence of kidney damage
3B	30-44	
4	15–29	Severe decrease in GFR, with or without other evidence of kidney damage

5	<15	Established renal failure

Clinically significant CKD (Stages 3-5)[143] is relatively common and the incidence is probably rising[138]. Three major studies[139, 144, 145] have estimated prevalence in England. The results are summarised in Table 4.2.

Table 4-2: Estimates of incidence of CKD (%) in England in three major studies[139, 144, 145].

Study	Denominator	Population	Male	Female	All
HSE[144]	16+	6,000+	6%	7%	
NEOERICA[145]	18+	130,226	5.8%	10.6%	8.5%
QICKD[139]	Whole population	930,997	3.5%	7.3%	5.4%

The picture is similar in other countries, with prevalence rates of, for example, 5.84% in the Netherlands[146], 8% in Northern Ireland,13 11.2% in Australia and 8.04% in the US[147]. It is more common in females than males[145, 148]. Since it is not known whether a pathological process underlies CKD, there is currently no explanation for the greater prevalence in females[139].

4.5.2 CKD and Atherosclerosis

CKD is closely associated with arterial thickening[149], leading to increased risk of cardiovascular events. The risk rises in inverse proportion to GFR[138] and is independent of known cardiovascular risk factors such as hypertension, smoking and hypercholesterolemia[136]. In England, CKD is associated with thousands of extra cases of stroke and myocardial infarction every year[138]. It leads to longer hospital stays;

even for patients who go into hospital for treatments unrelated to CKD, the average stay is 35% longer than for patients without CKD[138]. Furthermore, methicillin-resistant Staphylococcus aureus (MRSA) is more common in the CKD population, especially those receiving hemodialysis[138]. CKD is also associated with significant reductions in QoL[138].

4.6 Rationale for Current Study

The effects of known risk factors can vary enormously from one population to another, and there is still substantial uncertainty as to how important these are in different settings and as to how their importance is changing with time. By understanding the medical, social and ethical factors that affect community health, solutions to public health problems could be developed.

In addition, many cardiovascular events including stroke could be avoided if people with subclinical/asymptomatic Carotid artery stenosis were identified and treated appropriately with antithrombotic, anti-hypertensive and lipid-lowering drugs as well as encouraging them to stop smoking. Some younger patients with tight carotid stenosis, who are well treated medically, can avoid future stroke by appropriate carotid intervention.

Studies suggested that that the implemented abdominal aortic screening programme of 65-year-old men in some countries, offers an opportunity to find individuals with carotid artery atherosclerosis who may benefit from best medical treatment[150, 151].

Recent guidelines stated that future RCTs will be needed to determine the optimal treatment strategy to provide the greatest reduction in atherosclerotic cardiovascular disease events with best margin of safety[35].

Having access to a large dataset for a range of cardiovascular screening tests provided by Life Line Screening, enable us to reliably study risk factors responsible for different cardiovascular conditions.

The main interest of this study was centred on early detection of serious four cardiovascular atherosclerotic conditions including Abdominal Aortic Aneurysm, Atrial Fibrillation, Chronic Kidney Disease and Carotid Artery disease among asymptomatic, apparently healthy population.

In addition, we identified a cohort of people with asymptomatic CAS and a matching cohort with no CAS, drawn from those attending Life Line Screening appointments in the UK and Ireland to conduct a prospective study to assess the number of cardiovascular events in the cohort and compare.

Chapter 5 Methods and Statistical Analysis

5.1 Data Collection

There are two sets of data that were analysed for this study. The main dataset were collected via a private, CQC registered screening company operating in the UK and Republic of Ireland called Life Line Screening UK Ltd. The smaller dataset was collected by research team prospectively. Details of screening method and protocols followed for different examinations and data collection are provided in the following paragraphs.

5.2 Retrospective Study

Participants of different ages were screened privately in the UK and Ireland. Screened individuals generally included men and women >50 years of age. Patients were screened between August 2008 and Dec 2014.

Before screening, patients completed consent along with a comprehensive health questionnaire on their demographic information and risk factors for cardiovascular disease. The self-reported variables included demographics and biometric information such as age, gender, race/ethnicity, marital status, height, and weight. Information on family history of AAA, coronary artery disease, stroke, peripheral vascular disease, and smoking was also collected.

Detailed risk factors and comorbidities such as coronary artery disease, cerebrovascular disease (previous transient ischemic attack or stroke), hypertension, hypercholesterolemia, and diabetes were gathered.

Patients were considered to have hypertension, hypercholesterolemia, or diabetes if they had been given these diagnoses by a physician or were treated for these conditions. Known cardiovascular disease was defined as having had a prior myocardial infarction, a history of percutaneous or surgical coronary revascularization. A family history of AAA was defined as a first degree relative who carried a diagnosis of AAA.

5.2.1 Ultrasound test for AAA

Duplex ultrasonography of the abdominal aorta after a 4-hour fasting period was performed by portable ultrasound scanner. B-mode grey-scale images of the aorta were obtained in longitudinal and transverse orientations with the patient in the supine position. Measurements were obtained at the area of largest diameter in the supra-celiac, supra-renal, and infra-renal aorta, as well as the distal common iliac arteries. An infra-renal aortic diameter of 3.0 cm or larger was defined as an AAA for both men and women, and aneurysms were further divided into those measuring 3 to 4.99 cm (small to medium size) or ≥5 cm (Large size). All abnormal studies were confirmed by a second technologist, and all studies were reviewed afterwards. Patients were divided to groups based on their age (≥65 and <65) and the size of their AAA. Figure 5.1 shows an example of AAA identified by abdominal ultrasound.

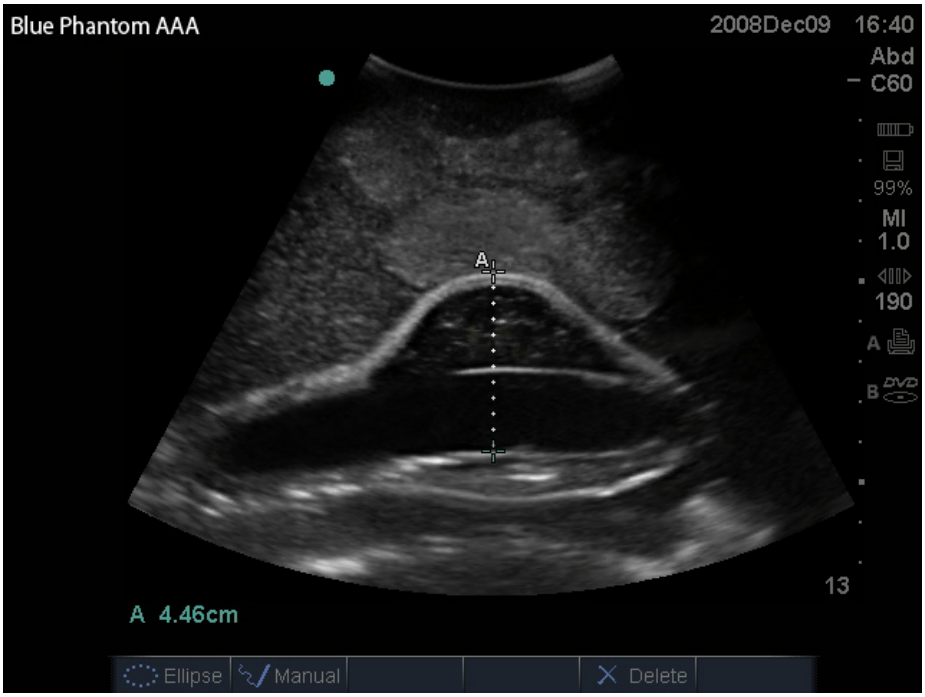


Figure: 5.1: AAA detected by ultrasound[152]

5.2.2 Ultrasound test for Carotid artery disease

Bilateral Carotid arteries were scanned in supine position with head slightly turned to the opposite site. Portable ultrasound was used by qualified sonographers to first scan transverse and longitudinal in B-Mode from the proximal Common Carotid Artery (CCA) to the distal Internal Carotid Artery (ICA) and External Carotid Artery (ECA) and then back to the base of the CCA.

Any plaque formation observed throughout the common, external and internal carotid arteries, were recorded. Plaque must be observed in both scan planes in order to confirm a positive finding.

In the next step, color flow and Doppler throughout the ECA for identification only and then Doppler the ICA proximal, mid, and distal.

In the presence of plaque, the Doppler sample placed in the area of greatest stenosis or immediately thereafter. This will give you the highest Peak Systolic Velocity (PSV) and End Diastolic Velocity (EDV). Pulsed wave was set at 56 degrees and parallel to the posterior wall with at least 3 clean waveforms.

Normal result was defined as the absence of atherosclerotic plaque in common and internal carotid arteries. In the presence of atherosclerotic plaque (thickness > 2 mm), narrowings were divided into 3 stenotic categories according to the recorded Peak Systolic Velocity as <50% (PSV <125 cm/s), 50-70% (PSV of 125-230 cm/s) and >70% (PSV > 230 cm/s).

5.2.3 Community ECG recording

Standard 10-second limb-lead ECG (6 leads including I, II, III, aVL, aVR and aVF) were recorded on the screening day by applying 4 limb leads to both arms and both legs when participants were lying supine on a bed. Those with exisitng pacemaker or known, self-reported AF were excluded. ECGs were subsequently reviewd by a consultant cardiologist to indicate the presence or absence of AF. Limb-lead ECG was preferred to 12-lead ECG for ease, simplicity and better privacy in the community settings, while also maintaining the ability to provide information for AF detection. When participants were diagnosed with AF, a copy of the ECG along with their report was posted to them advising participants to visit their GP for follow up and appropriate course of action.

5.2.4 Kidney Function Test

Between January and May 2012, Finger-stick blood test was performed using the Nova StatSensor™ Creatinine Meter (Nova Biomedical). Creatinine and estimated GFR (eGFR) were assessed using C-G and abbreviated MDRD formulas. Results were ready at point of care and provided to participants with information sheath. Participants were categorised as normal with eGFR of more than 90 and 60-90 were considered within normal range or mild CKD. eGFR of 30-59 was classed as Moderate CKD and those with eGFR less than <30 as severe CKD.

5.2.5 ABPI measurement

Ankle-Brachial Pressure Index (ABPI), a measure of peripheral arterial disease (PAD), was calculated using a handheld continuous wave Multi Duplex II bi-directional Doppler with an 8-MHz Doppler probe (Huntleigh Healthcare Ltd., Cardiff. UK) and standard 12 or 14 cm pressure cuff and an analogue sphygmomanometer. Participants were asked to lie supine as flat as possible and keep the foot and leg still. Systolic brachial pressure (SBP) was measured bilaterally and the highest pressure reading was recorded as a brachial pressure reference. Distal Tibias systolic pressures were measured bilaterally and the highest reading was used to calculate ABI using the standard formula (SPTP/SBP ratio) for each side. ABI ≤ 0.9 or > 1.4 was considered abnormal.

5.3 Prospective Study

Study consists of an observational, prospective study of the risk factors for CAS and stroke amongst apparently healthy population. Study population was chosen from participants who voluntarily attended cardiovascular screening appointments provided

by Life Line Screening. They were tested for the following conditions: AF; CAS (with Duplex scanning); Abdominal Aortic Aneurysm (with aortic ultrasound); Peripheral Vascular Disease (with ankle-brachial pressure index). They were provided with a written report and advised to consult their GP to discuss abnormal results. The company recorded all such anonymised data in a research database.

Participants were invited to take part in the study by sending an invitation letter Appendix 1) and provided with an information sheet (Appendix 2) explaining the study and the level of involvement required. They were also provided with a consent form (Appendix 3) to make an informed choice and if agreed, were included in the study.

Invitations were sent to 1250 randomly selected participants who have at least moderate or worse carotid artery disease or Atrial Fibrillation as case group. There were 3750 invitations sent to participants who had screening and were found to have sinus rhythm on ECG with no prior history of AF and no evidence of visible carotid artery atherosclerotic disease by ultrasound study.

5.3.1 Response Rate

There were 456 participants who responded to the invitation and provided valid consent for research team to have access to their data collected by Life Line Screening, complete a detailed questionnaire (Appendix 4) and to respond to regular follow-ups. The response rate was just under ten percent with 456 case and control. The response rate was just under ten percent.

Participants were asked to provide information on: prior disease; current medications (i.e. anti-hypertensive, lipid-lowering and anti-platelet therapies); exercise; alcohol intake; smoking history; relevant family medical history; and physical measurements (including height, weight, waist circumference, blood pressure).

5.3.2 Pre-registration Evaluation

There is no pre-registration evaluation required for this study which consists of a prospective analysis on a cohort of apparently healthy participants from Life Line Screening customers. The control group was drawn from a population that was similar to the exposed group in all respects other than their carotid disease. The data collected for the control group was the same and were obtained in the same way as those on the exposed group.

Participants were followed to enable us record changes in their lifestyle and/or medication as well as potential events such as Stroke, Heart Attack or death. Data were gathered every 18 month via a health questionnaire.

5.3.3 Inclusion Criteria

Participants who underwent self-selected, private screening program held by Life Line Screening, adult participants mainly over the age of 40 were included.

Participants required to fill in appropriate health questionnaire and signed relevant consent part of their questionnaire. Observation cohort included participants with significant carotid artery disease (>50% stenosis) detected by duplex ultrasound

versus control cohort of participants without CAS detected by Duplex ultrasound.

5.3.4 Exclusion Criteria

Those who are unable to give informed consent and participants under 20 years old were excluded. In addition, participants who filled in the health questionnaire incompletely were not included.

5.3.5 Withdrawal

Withdrawal was allowed for a few of those who originally agreed to join the study in case they changed their minds. Some such patients may still be willing for information about their health to be collected according to the trial protocol but may prefer not to be contacted directly. Others may wish to withdraw entirely. In either case, if, after agreeing to join, the patient subsequently changes his or her mind, (s)he is free to do so without this adversely affecting his/her medical care.

5.3.6 Assessment and Follow-up

The initial follow up was post-screening by completing detailed health questionnaire form, which was returned to the co-ordination office via enclosed pre-paid envelope for return to the research office.

For long-term follow up, participants were contacted by an electronic letter originating from the research center, asking if they remained well. Reminders were sent for 3 times before telephone attempts were made by research team.

If the participant did not reply, a similar letter was sent to any friends or relatives whose contact details were given when the patient joined the study. If the patient is too disabled to complete the questionnaire, someone else (eg, the patient's carer) could complete it with answers provided by the patient, or could complete it based on their own assessment of the patient. In the cases where the patient and the contacts they gave do not provide the annual information, the patient was removed from the study.

For the purpose on this PhD project and in interest of time to submit thesis, it was decided to write up the project based on the first set of follow up data collected. These data were collected after 18 months follow up from the recruitment date and a significant number of participants were lost in the follow up. At least 3 attempts were made for those who did not respond including contact with NOK based on data provided by the participants when entered study. The whole study populations were sent follow up questionnaire (Appendix 5) but there were 217 participants who responded consisting of 27 participants with CAS and 190 healthy individuals.

5.4 Study Flow Chart

Below diagram (figure 5.2) shows two parts of this research including prospective observational study as well as retrospective data analysis.

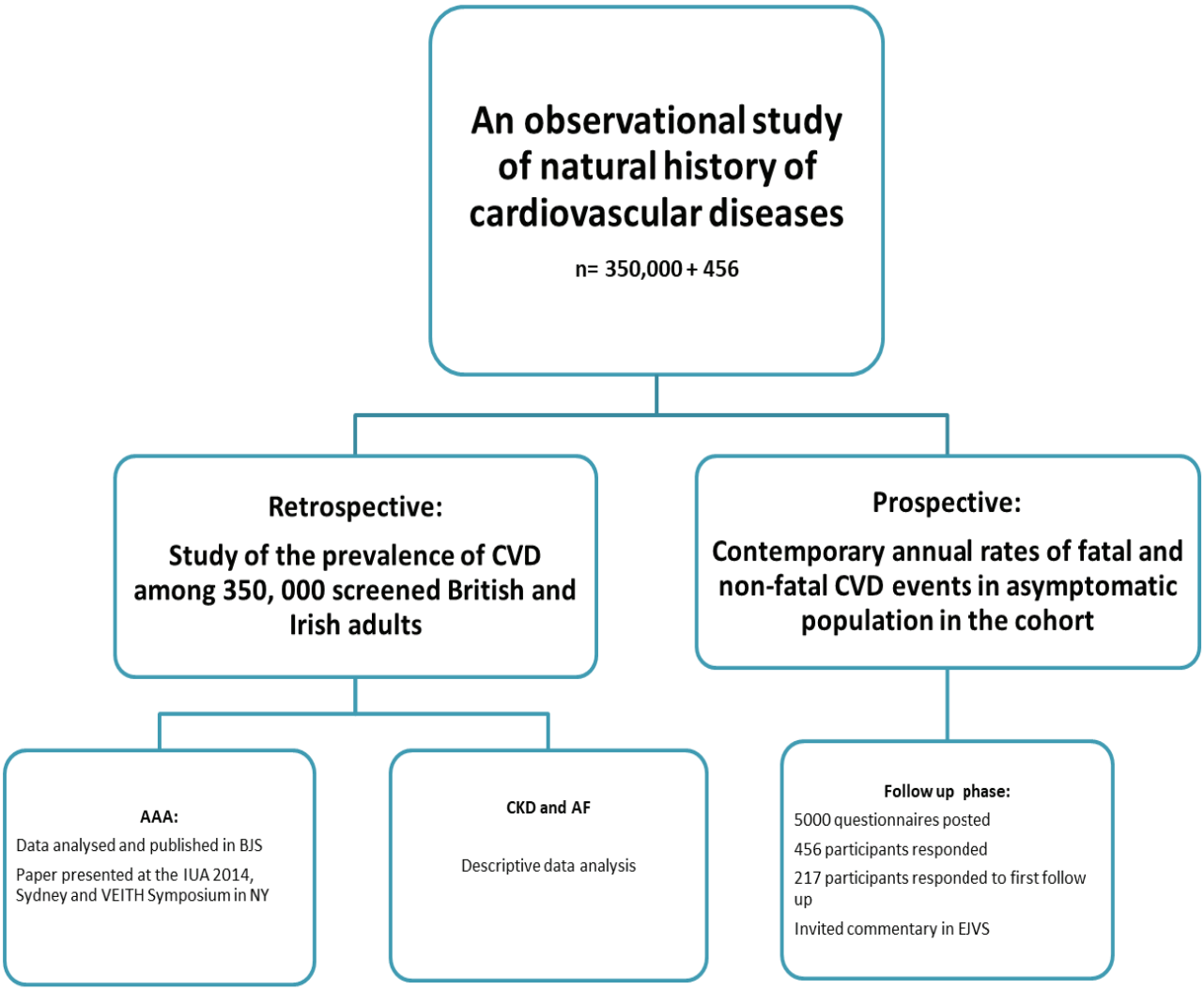


Figure 5.2: Study Flow Chart

5.5 Data Analysis:

All study design, data analysis and interpretation was conducted independently by Vascular Department at Hammersmith Hospital London and Imperial College Statistical Advisory Service. The median and interquartile range was used to summarise BMI in the two age groups. The Mann-Whitney test was used to see whether there is any evidence of a difference in BMI between the two age groups (<65 versus ≥65 years old). The Chi-square test was used to compare the two age groups against other categorical variables such as sex and cardiovascular disease.

Logistic regression was used to look at factors associated with having a large aneurysm. The factors used were age group, sex, race, diabetes, cardiovascular disease, high blood pressure, high cholesterol, exercise, ever smoker, family history of cardiovascular disease, family AAA and BMI. Stata version 10 was used for analysis.

In addition, the prevalence of AAA was determined for each 5 year age group for the whole population of 50,000 women studied. Subsequently, the mean (± SD) diameter of the AAA present was determined. The percentage of AAA with a maximum diameter ≥ 3.0 cm was calculated.

Because the prevalence of AAA was very low in women younger than 66 and close to 1.0% in those over 85, subsequent analysis was confined to those in the age group 66-85 (n=25,710) with 72 AAA (overall prevalence of 0.28%). The association between potential risk factors and prevalence of AAA in this group was determined using univariate analysis and odds ratios.

After recoding continuous variables which were not normally distributed the significant risk factors were included in a multivariate linear logistic regression analysis in two models with AAA as the dependent variable. Model 1 was based on history and comorbid conditions recorded prior to any clinical examination. Model 2 included the significant risk factors (independent predictors) from Model 1 with AF, ABI and carotid stenosis obtained from clinical examination ECG and carotid duplex examination. After identification of the independent predictors of AAA, the predicted probability estimate for AAA was calculated for every individual in each model and

used to construct ROC curves. The area under the curve (AUC) was measured for each model.

Using 0.5% probability of AAA as a cut off point the number of women having an estimated probability greater than 0.5% was determined. The actual prevalence of AAA was calculated in this group for each model. All analyses were performed using IBM, SPSS statistical package, version 20.

For AF subgroup analysis, the prevalence of AF was determined for each 5-year age group for the whole population of 74,394 participants studied. Because the prevalence of AF was lower in particpants younger than 65 and their CHADSVASC2 were likely to be low too, subsequent analyses were confined to those in the age group > 65 years. Risk factors with high percentage of missing values were removed such as race and AAA. Therefore, samples with no missing values were included and analysed.

A binary variable was used in order to represent smoking. A person is considered as a smoker only if he has been smoking for more than a year with more than 2 cigarettes per day. Carotid and PAD variables were modified to encode the more severe level of each pathology (comparing right and left severity levels). Colinearity was checked by means of correlation.

For quantitative study with clear numerical interpretation, Mann-Whitney test and t-test was used for the statistical analysis. The median and interquartile range will be used to summarise continuous variables such as age. Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study including the follow-up period.

5.6 Ethical Approval

There are 2 separate ethical approval sought for these studies. The first ethical approval with Study Title of "An observational study of natural history of cardiovascular diseases" was obtained with ICREC reference of ICREC_13_6_2.

The above study was approved by HoD on 10th October 2013 and by the Joint Research Compliance Office on the 11th October 2013.

Under the Imperial College Research Ethics Committee process, a study that has been reviewed by the Joint Research Compliance Office and Head of Division/Department (or Principal), where no significant ethical issues have been identified in the protocol or ethics application, can be approved without requiring it to go to full committee.

In addition, second ethical approval obtained for Study Title of "A retrospective UK & Ireland study of the prevalence of cardiovascular disease among 350, 00 screened British and Irish adults" with ICREC reference number of ICREC_14_3_7.

The above study was approved by Head of Department on 11th April 2014 and by the Joint Research Compliance Office on the 18th June 2014.

Under the Imperial College Research Ethics Committee process, a study that has been reviewed by the Joint Research Compliance Office and Head of Division/Department (or Principal), where no significant ethical issues have been identified in the protocol or ethics application, can be approved without requiring it to go to full committee.

Chapter 6 Results

6.1 Sub Group Analysis

There are 4 sub group analysis of data for different conditions that where of interest. These results are summarised below for individual conditions.

6.2 Results of Epidemiological study and risk analysis in men and women of different ages with Abdominal Aortic Aneurysm (AAA):

The Database is comprised of adult participant records across the UK and Ireland including both urban and rural population. Approximately, 60% of the cohort were female and the overall prevalence of AAA in the cohort was just above 1.0% (2049/ 199,490). A total of 2049 patients from the UK and Ireland population with AAA were identified as part of this screening program and were studied for the purpose of this study. Where data related to certain variables was not available, these records were not included in the count. There are 84.04% (1517) men and 15.96% (288) women with AAA and 244 patients did not indicate their gender in the questionnaire. 311 (15.2%) of subjects are younger than 65 years whilst 1634 (79.8%) including women are 65 years or more. Excluding females and men aged less than 65, 59.25% (1214) remain in the cohort.

Majority of this population (89.70%) are white. Diabetes was reported in 9.52% (195) of the cohort. There are 484 (23.62%) with known cardiovascular diseases. The prevalence of hypertension is 33.63% (689) and 740 (36.3%) have high cholesterol. The total number of smokers is 1,123 (54.81%) among the population. Less than half of patients (43.97%) reported having regular exercise. There are 786 patients with family history of CVD (38.36%). History of AAA in the first degree relatives were

reported in11.08% of patients (121/1047). The median BMI is 26.99 and the interquartile range goes from 24.68 to 29.55.

As shown in Table 6.1, there are 38/280 (13.57%) females who are under 65 years old while 242/280 (86.43%) of females are 65 years or above. There are 8 patients with incomplete age records. The difference between the two groups is 72.9% (-0.729). The 95% confidence interval for the difference goes from -0.785 to -0.672. There is strong evidence of a difference between the two groups ($p<0.0001$). There are also differences in diabetes ($p<0.0001$), cardiovascular disease ($p<0.0001$), cholesterol ($p=0.01$), smoking ($p<0.0001$) and family history of AAA ($p<0.0001$). Table 6.1 shows demographics and baseline characteristic information of females with AAA detected regardless of their age group via community screening programme in the UK and Ireland.

Table 6-1: Females Demographic Information

Variable	Frequency	Percentage
Age		
≥ 65 y/o	242	86.43%
<65 y/o	38	13.57%
Unlisted	8	
AAA Size		
≥5cm	25	8.68%
< 5cm	263	91.32%
Unlisted	0	
Diabetes		
Yes	15	5.21%
No	223	94.79%
Unlisted	50	
Cardiovascular Disease		
Yes	56	19.44%
No	222	80.56%
Unlisted	10	
Hypertension		

Yes	105	36.46%
No	116	63.54%
Unlisted	67	
Hyperlipidaemia		
Yes	115	39.93%
No	145	60.07%
Unlisted	28	
Exercise		
Yes	122	42.36%
No	120	57.64%
Unlisted	46	
Smoking		
Yes	149	51.74%
No	87	48.26%
Unlisted	52	
Family history: CVD		
Yes	118	40.97%
No	134	59.03%
Unlisted	36	
Family history: AAA		
Yes	17	5.90%
No	140	94.10%
Unlisted	131	

Results of demographic information of different age groups are shown in table 6.2. The prevalence of smoking was higher in the younger age group than the remainder of the patients (75% vs 66%) and reached statistical significance ($P < 0.005$). Whilst the history of CVD was reported in 11% of younger patients with AAA (<65 y/o), the prevalence was significantly higher (26%, $P<0.0001$) in the older age group (≥65 y/o) with AAA.

Table 6-2: Demographic information and risk factors of the patients with AAA based on age and gender

Risk Factors	< 65 y/o (311)	≥ 65 y/o (1634)	Unlisted	P-value
Gender			244	
♂	85.61% (226)	83.38% (1,214)		0.367
♀	14.39% (38)	16.62% (242)		
AAA Size				
Large		12.84% (209)	117	0.632

Small	11.84% (36) 88.16% (268)	87.16% (1419)		
Race White	95.93%(283)	94.08% (1,463)	102	0.206
Genetic	12.57%(24)	10.75% (92)	938	0.469
Diabetes	11.03% (30)	11.46% (158)	306	0.839
CVD	11.88% (36)	26.97% (427)	59	<0.0001
CVD in Family	38.38% (109)	44.52% (634)	246	0.057
HTN	38.02%(100)	42.72% (549)	408	0.159
HLP	38.81% (111)	39.25% (588)	185	0.889
Exercise	50.56%(135)	53.07% (727)	337	0.453
Ever Smoked	75.38%(196)	66.59% (877)	381	0.005
BMI (Median)	28.05 (95% CI: 27.4-28.6)	26.85 (95%CI: 26.5-27)		<0.0001

Logistic regression was performed to predict large AAA and univariate results are presented in Table 6.3. There is evidence of an association between sex and aneurysm size. Females are 39% less likely to have large aneurysms. There is evidence of an association between cardiovascular disease and aneurysm size and subjects with cardiovascular disease are 38% more likely to have large aneurysms. Additionally, subjects with positive smoking history are 59% more likely to develop large aneurysms.

Table 6-3: Regression Model Predicting Large (≥ 5cm) AAA, Univariate results

Factors		OR (95% CI)	p
Sex	Male	1*	
	Female	0.608 (0.390 – 0.948)	0.028
Age	>65	1*	
	≤65	1.096 (0.752-1.599)	0.632

Race	White	1*	
	Other	1.053 (0.590 – 1.877)	0.860
DM	No	1*	
	Yes	0.003 (0.637 – 1.578)	0.990
CVD	No	1*	
	Yes	1.381 (1.028 – 1.856)	0.032
HTN	No	1*	
	Yes	1.143 (0.848 – 1.541)	0.377
HLP	No	1*	
	Yes	0.817 (0.610 – 1.094)	0.176
Exercise	No	1*	
	Yes	1.130 (0.846 – 1.508)	0.407
Ever Smoked	No	1*	
	Yes	1.591 (1.139 – 2.221)	0.006
CVD in Family	No	1*	
	Yes	1.026 (0.774 – 1.360)	0.855
AAA in Family	No	1*	
	Yes	0.936 (0.519 – 1.687)	0.827
BMI		1.014 (0.974 – 1.055)	0.493

*Redundant term

The factors used for the multiple logistic regression model were gender, smoking, CVD and high cholesterol. Age group was not included in the multiple logistic regression model since it was not significant in the univariate results (P=0.632). Multivariate analysis indicates that large aneurysm is associated with male gender, having cardiovascular disease, smoking history and not having high cholesterol (see table 6.4).

Table 6-4: Predicting Large (≥ 5cm) AAA, Multivariate results

Factors	OR (95% CI)	P
Sex_(Female)	1.542 (0.694 – 3.427)	0.287

Ever smoker	2.649 (1.591 – 4.409)	<0.0001
Sex*Ever smoker	0.306 (0.107 – 0.869)	0.026
CVD	2.421 (1.208 – 4.853)	0.013
CVD*Ever smoker	0.389 (0.173 – 0.875)	0.022
High Cholesterol	0.650 (0.46 – 0.918)	0.014

There is evidence of an interaction between gender and smoking. The odds ratio of having a large aneurysm for male smokers is 2.649 and its effect is 3 times less for females (OR=0.811).

Although the risk factors that predict large AAA are not qualitatively different from factors that predict smaller aneurysms, we found that, among patients with AAA, higher age, male gender, history of cardiovascular disease, smoking history (active and/or past) are more strongly associated with large AAA than with small and medium AAAs.

6.3 Prevalence of AAA in Republic of Ireland

Part of the community screening was conducted in the Republic of Ireland with the same screening followed for participants. There were 25,730 participants over the age of 50 years old who took part in the private screening for AAA and 217 were found to have the condition (overall prevalence of 0.84%). Table 6.5 shows the age related prevalence of the condition among both genders. It was a unique set of data which highlighted the prevalence of AAA in the country enabling comparison with the UK results.

Table 6-5: AAA Prevalence in Republic of Ireland

	Male			Female		
Age	Screened	AAA	**P%**	Screened	AAA	**P%**
50-59	3382	12	0.35%	5866	1	0.02%
60-69	3900	71	1.82%	7035	19	0.27%
70-79	1794	71	3.96%	3053	18	0.59%
80+	279	15	5.38%	421	10	2.38%
Total	**9355**	**169**	**1.81%**	**16375**	**48**	**0.29%**

Graph 6.1 pictures the age related prevalence among both genders which shows similar rate of increase by age and significant difference between age groups.

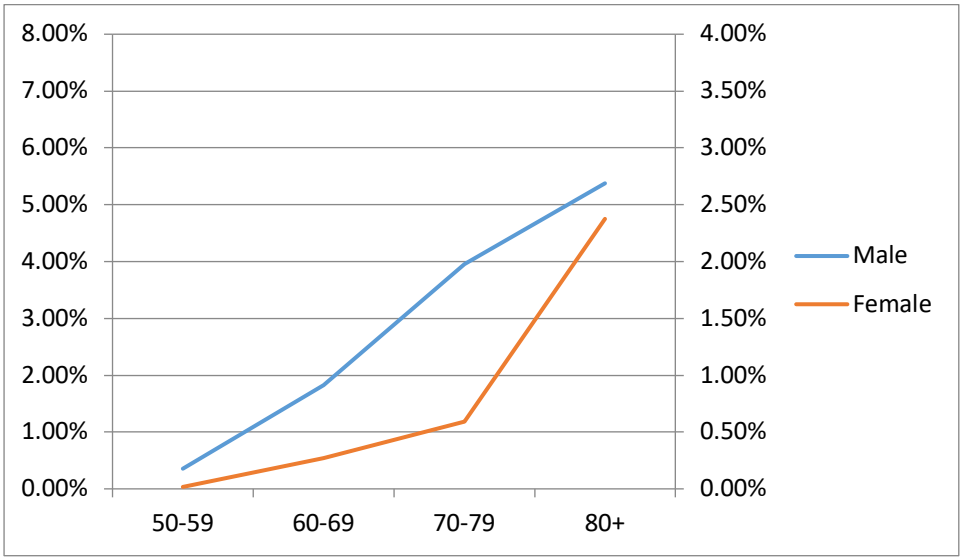


Figure 6.1: Point prevalence of AAA among both genders

In addition, table 6.6 shows the point prevalence comparison with UK data for AAA which interestingly shows higher prevalence of the condition for every age group and gender in the Republic of Ireland.

Table 6-6: UK and Ireland Prevalence of AAA

Ireland	Male	Female	**UK**	Male	Female
50-59	0.35%	0.02%	50-59	0.49%	0.04%
60-69	1.82%	0.27%	60-69	1.15%	0.12%
70-79	3.96%	0.59%	70-79	2.01%	0.04%
80+	5.38%	2.38%	80+	4.78%	1.17%

6.4 Published Article: Risk factors associated with increased prevalence of abdominal aortic aneurysm in women:

This subgroup analysis was aimed at identifying a practical method of selecting women aged 66 to 85 for AAA screening which resulted in the publication of below article in the British Journal of Surgery.

The prevalence of AAA in different age groups of the 50,000 women screened is shown in Table 6.7. The results show that the presence of an AAA below the age of 66 is rare. The prevalence of AAA increases with age from 0.20% in the 66-70 age group to 0.52% in the 81-85% age group. The prevalence of AAA over the age of 85 is 0.91%.

Table 6-7: Prevalence of abdominal aortic aneurysms ≥ 3 cm in diameter in different age groups in 50000 consecutive women screened with ultrasound

Age	Number Screened	AAA Present
<51	2544	0
51-55	4936	1 (0.02%)
56-60	6752	1 (0.01%)
61-65	10267	5 (0.05%)
66-70	11236	22 (0.20%)
71-75	8141	19 (0.23%)
76-80	4439	24 (0.54%)
81-85	1354	7 (0.52%)
>85	331	3 (0.91%)
Total	**50000**	**82**

A total of 82 AAA with an internal diameter ≥3.0 cm were detected with mean (± SD) maximum diameter of 3.82 ± 0.85 cm and range 3.0-6.3 cm. Of these 12 (14%) had a maximum diameter of 5.0 cm or greater.

In the age group of 66-85 there were 72 (0.26%) AAA in 27,170 women. The association between each risk factor and prevalence of AAA is shown in Table 6.8 using univariate analysis. Age, history of stroke/TIA, hypertension, history of smoking, presence of atrial fibrillation (AF), ankle-brachial index less than 0.9, and carotid bifurcation atherosclerosis were associated with increased prevalence of AAA. The strongest risk factor was the presence of internal carotid stenosis > 50%, followed by ABI < 0.9 and smoking. Interestingly, diabetes and ABI > 1.4 (data not shown) which is associated with incompressible arteries were not associated with AAA.

Table 6-8: Association of risk factors with prevalence of AAA in 25,710 women screened in the age group 66-85

	No AAA	AAA	Odds Ratio	P
Age (years)				
66-70	11214	22 (0·20)	1·00 (reference)	
71-76	8122	19 (0·23)	1·19 (0·64, 2·20)	0·575
76-80	4415	24 (0·54)	2·77 (1·55, 4·95)	0·001
81-85	1347	7 (0·52)	2·65 (1·13, 6·21)	0·025
Recoded according to prevalence				
<76	19336	41 (0·21)	1·00 (reference)	
76-85	5762	31 (0·54)	2·54 (1·59, 4·05)	<0·001
History of MI or myocardial ischaemia				
No	24592	71 (0·29)	1·00 (reference)	
Yes	507	1 (0·20)	0·68 (0·95, 4·95)	0·705
History of stroke or TIA				
No	23791	60 (0·25)	1·00 (reference)	
Yes	1307	12 (0·91)	3·64 (1·95, 6·78)	<0·001
Hypertension and/or antihypertensive medication				
No	20112	44 (0·22)	1·00 (reference)	
Yes	4986	28 (0·56)	2·57 (1·60, 4·13)	<0·001
Hyperlipidaemia and/or anti hyperlipidaemia medication				
No	16768	42 (0·25)	1·00 (reference)	
Yes	8330	30 (0·36)	1·44 (0·90, 2·30)	0·127
Diabetes				
No	22778	70 (0·31)	1·00 (reference)	
Yes	2320	2 (0·09)	0·28 (0·07, 1·14)	0·058
Smoking (pack-years)				
0	24135	63 (0·26)	1·00 (reference)	
1-9	285	2 (0·70)	2·69 (0·65, 11·04)	0·170
10-19	295	2 (0·67)	2·60 (0·63, 10·63)	0·185
20-39	246	2 (0·81)	3·11 (0·75, 12·80)	0·115
≥40	137	3 (2·14)	8·40 (2·60, 27·04)	<0·001

Recoded according to prevalence				
0	24135	63 (0·26)	1·00 (reference)	
1-39	826	6 (0·72)	2·78 (1·20, 6·44)	0·077
≥40	137	3 (2·14)	8·40 (2·60, 27·04)	<0·001
Family history of CAD				
No	18416	52 (0·28)	1·00 (reference)	
Yes	6682	20 (0·30)	1·06 (0·63, 1·77)	0·825
Family history of stroke/TIA				
No	16880	54 (0·32)	1·00 (reference)	
Yes	8215	18 (0·22)	0·68 (0·40, 1·68)	0·162
Family history of AAA				
No	23652	64 (0·27)	1·00 (reference)	
Yes	1446	8 (0·55)	2·04 (0·98, 4·27)	0·052
Atrial fibrillation				
No	24872	68 (0·27)	1·00 (reference)	
Yes	226	4 (1·74)	6·47 (2·34, 17·90)	<0·001
ABPI				
Both limbs≥0·9	24331	61 (0·25)	1·00 (reference)	
One limb<0·9	471	5 (1·05)	4·23 (1·69, 10·59)	0·002
Both limbs<0·9	296	6 (2·59)	8·08 (3·47, 18·85)	<0·001
Recoded				
Both limbs≥0·9	24331	61 (0·25)	1·00 (reference)	
At least 1 limb<0·9	767	11 (1·41)	5·72 (3·00, 10·91)	<0·001
Carotid bifurcation plaques and internal carotid stenosis				
Both normal or one with<50%	14351	11 (0·08)	1·00 (reference)	
Bilateral plaques both<50%	10261	49 (0·48)	6·23 (3·24, 12·00)	<0·001
At least one with≥50%	486	12 (2·41)	32·21 (14·14, 73·37)	<0·001
Recoded				
Both normal or<50% stenosis	24612	60 (0·24)	1·00 (reference)	
At least one with≥50% stenosis	486	12 (2·41)	10·13 (5·41, 18·95)	<0·001

In a multivariate linear logistic regression analysis using the significant risk factors based on the history (Model 1) (Table 4.7), age ≥ 76 , history of stroke/TIA, hypertension and number of pack years were independent predictors of AAA. This model had an ROC area under the curve of 0.711 (95% CI 0.649 to 0.772). This model could identify 2,235 women who had 22 AAA (prevalence 0.98%).

Table 6-9: Results of multivariable linear logistic regression

Model 1

	Odds Ratio	P
Age (≥ 76 or < 76 years)	2·43 (1·51, 3·91)	<0·001
History of stroke/TIA (yes versus no)	3·03 (1·61, 5·69)	0·001
Hypertension (yes versus no)	2·25 (1·39, 3·64)	0·001
Smoking (≥40 versus 1–39 pack-years)	2·92 (1·78, 4·80)	<0·001

By adding ABI, AF and carotid stenosis (Model 2) (Table 4.8) the prediction improved to an ROC area under the curve of 0.771 (95% CI 0.710 to 0.832). This model could identify 3,031 women who had 39 AAA (prevalence 1.29%). The presence of internal carotid stenosis ≥50% found in 486 women was associated with an AAA prevalence of 2.41% and is in itself an indication for screening for AAA.

Table 6-10: Results of multivariable linear logistic regression

Model 2

	Odds Ratio	P
Age (≥ 76 or < 76 years)	2·08 (1·38, 3·14)	<0·001
History of stroke/TIA (yes versus no)	2·25 (1·28, 3·95)	0·005
Hypertension (yes versus no)	2·46 (1·64, 3·68)	<0·001
Smoking (≥10 or <10 pack-years)	5·09 (2·83, 9·14)	<0·001
Family history of AAA (yes versus no)	1·93 (1·02, 3·66)	0·043
Atrial fibrillation (yes versus no)	3·48 (1·35, 8·97)	0·010
ABPI (<0·9 in at least 1 leg)	2.59 (1.44, 4.66)	0·002
Internal carotid stenosis (at least 1 with≥50%)	5.88 (3.36, 10.27)	<0·001

6.4 AF Results

For the purpose of AF study, a random subgroup of 74,394 participants were assessed and table 6.11 shows the age related prevalence of AF among the population. There were 750 cases of newly identified AF among the cohort with overall prevalence of 1.01% (750/74,394).

Table 6-11: Prevalence of newly diagnosed AF in different age groups in a cohort of 74394 consecutive participants screened with ECG

	No. of participants screened	AF present
Age		
<45	1683	2 (0.11%)
45-54	10931	21 (0.19%)
55-64	25235	99 (0.39%)
65-74	27305	299 (1.09%)
75-84	8618	278 (3.22%)
>85	622	51 (8.19%)
Total	**74394**	**750 (1.00%)**

Figure 6.2 shows that AF is significantly prevalent in population aged more than 55 years compared to people aged less than 45. The regression coefficients increase when age is greater than 65 years where the P-value is highly significant.

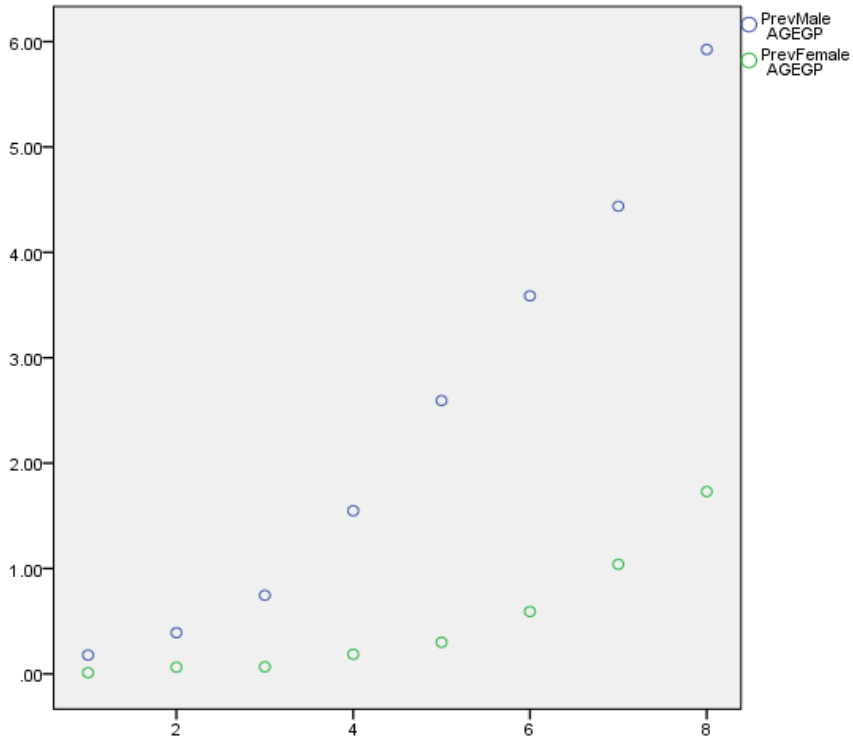


Figure 6.2: Age related prevalence of AF in both genders

Figure 6.3 shows the Plot of odds of developing AF against age for both genders, indicating a gradual increase by age which is more prominent among males reaching as high odds as more than 20% among those over 85 years of age.

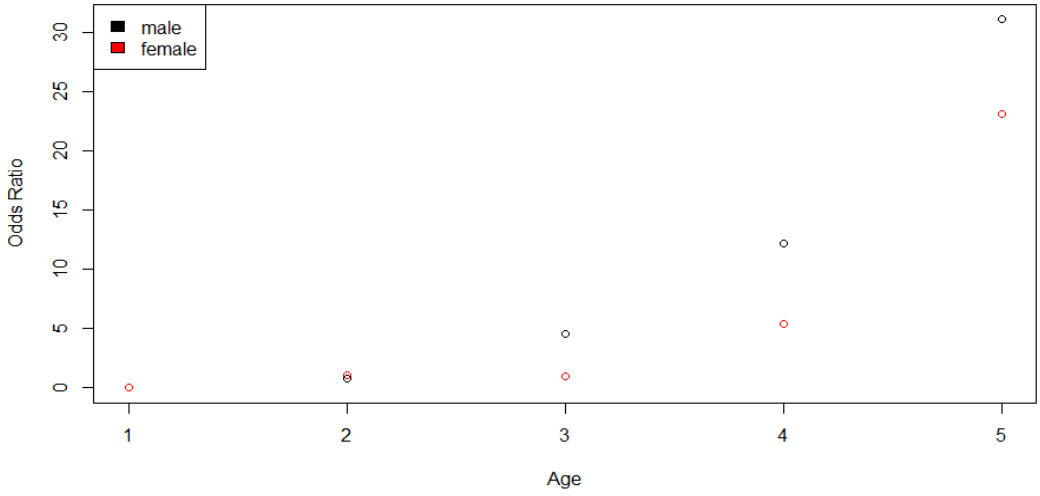


Figure 6.3: Plot of AF prevalence against age for both genders

A first multivariable logistic regression on R version 3.3.2 was made including all the kept risk factors. Most significant factors are age (above 74), gender, carotid artery disease and DM. Backward stepwise logistic regression was realised. The final model included age, sex, Diabetes, history of stroke/TIA, hypertension, high cholestrol, carotid aretry disease and PAD with p-values between 0.02 and <0.001.

A Model was defined based on history and co-morbid conditions recorded as independent predictors in addition to ABPI and carotid stenosis from continus Doppler and carotid duplex imaging. After identification of the independent predictors of AF, the predicted probability estimate for AF was calculated for every individual in the model and used to construct receiver operating characteristic (ROC) curves. The area under the curve (AUC) was measured for the model (Fig 6.4). Using 0.5 per cent probability of AF as the cut-off, the number of participants having an estimated probability greater than 0.5 per cent was determined. The actual prevalence of AF was calculated in this group for the model.

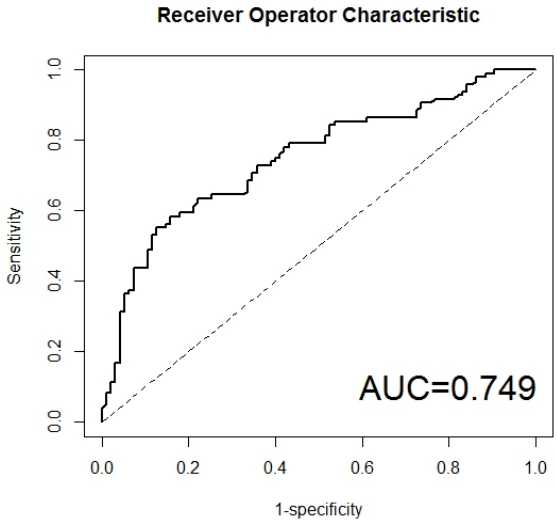


Figure 6.4: logistic regression classification accuracy

For the purpose of this study, the prevalence of AF and in accordance to CHA2DS2-VASc score, it was decided to analyse data related to those over the age of 65 as they are at higher risk of stroke with high likyhood of requiring anticoagulation for stroke prevention. Therefore, there were 29,489 participants in this subgroup. Table 6.12 shows baseline characteristics as well as associate risk factors.

Table 6-12: Association of risk factors with prevalence of AF in 29,489 participants screened in the age group older than 65.

Risk Factor	No AF	AF	OR (95% CI)	P
Age				
<65	32039	97(0.30%)	1	
≥65	29018	471(1.59%)	5.3 (4.3, 6.6)	**< 0·0001**
Sex				
Male	31817	521(2.57%)	1	
Female	42577	229(0.86%)	3.01 (2.4, 3.6)	**< 0·0001**
History of Diabetes				
Absent	69140	629(0.90%)	1	
Present	5254	121(2.30%)	2.05 (1.5, 2.6)	<0.0001
History of stroke and/or TIA				
Absent	72195	667 (0.92%)	1	
Present	2199	83(3.77%)	3.03 (2.2, 4.0)	<0.0001
HTN				
Absent	48581	356(0.73%)	1	
Present	25813	394(1.52%)	1.67 (1.4, 2.0)	<0.0001
History of CAD				
Absent	70893	645(0.90%)	1	
Present	3501	105(2.99%)	0.98 (0.80, 1.2)	0.87
Smoking				
Absent	21218	323(0.97%)	1	
Present	8148	153(1.39%)	1.2 (1.0, 1.5)	0.03
Carotid artery disease				
Both normal or <50% stenosis	33379	137(0.4%)	1	
At least one with mild disease	38559	563(1.43%)	3.55 (2.9, 4.2)	<.0001
Severe disease	837	8(0.94%)		
Ankle-Brachial index (ABI)				
Both limbs >0.09	69602	631(0.89%)	1	

At least One	3209	77 (2.34%)	2.64 (2.1, 3.3)	<.0001
<0.09				

6.5 Chronic Kidney Disease Results

Data related to the first 2995 individuals who had CKD test were used for this subgroup analysis. Where individual variables for a patient were not available, they have not been included in the calculations for that variable. The mean age of the population was 63.3 (±9.98) and the mean age of patients with CKD was 68.3 (±10.06) years, whilst it was 62.8 (±11.66) in participants with eGFR≥ 60 (P=0.002). 43.3% (1183) of attendees were male. Demographic characteristics and risk factors among the population are shown in Table 6.13. The average BMI was 28.5 kg/m2. Diabetes mellitus was present in 6.7% (196), hypertension in 34.9% (939), and hyperlipidemia in 36.2% (970).

Table 6-13: **Study population: demographic characteristics and risk factors**

Characteristics	
Age Range (Mean ± Std Dev)	21 – 94 (63.3 ± 9.98) years
95% CI for Age	63.94 – 64.65
Males (%)	1183 (43.33%)
Risk Factors	**% (Number)**
Active Smoker	15.03% (411/2733)
Ever Smoker	29.43% (827/2810)
Diabetes Mellitus	6.7% (196/2898)
Hypertension	34.9% (939/2683)
Hyperlipidaemia	36.2% (970/2677)

Ischaemic Heart Disease	5.0% (137/2874)
Stroke/TIA	2.9% (84/2813)
Atrial Fibrillation	7.8% (218/2770)
Peripheral Arterial Disease	2.7% (71/2615)
Abdominal Aortic Aneurysm	1.7% (45/2545)

8.9% of participants had eGFR less than 60 (Stage 3+ CKD) (266/2984): 10.4% (161/1547) in women and 7.1% (84/1183) in men. The mean age in the descriptive analysis of risk factors and cardiovascular disorders are shown in Tables 6.4 according to eGFR results.

The point prevalence of cardiovascular risk factors and cardiovascular disease was higher in the Stage 3+ group than the remainder of the population for every category. Figure 6.5 shows the prevalence of participants with eGFR <60.

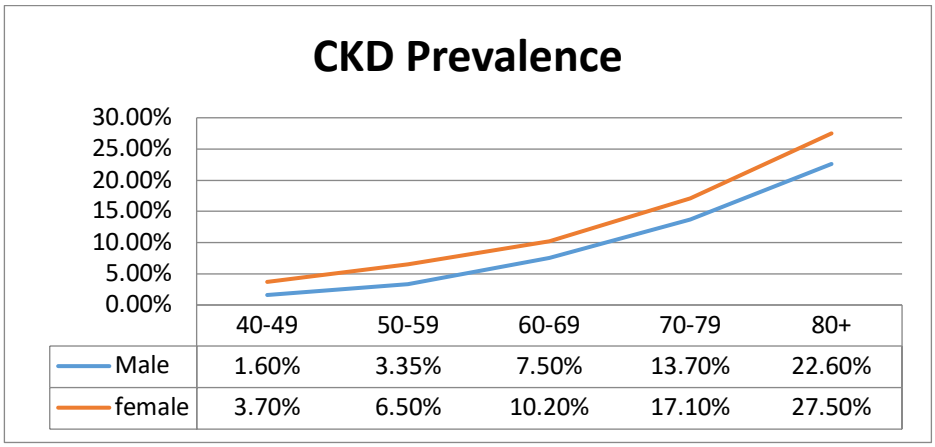


Figure 6.5: Age related prevalence of CKD among both genders

The difference reached statistical significance (P < 0.05) in female group (P<0.001), high blood pressure (P<0.001), hypercholesterolemia (P= 0.04), ever smoker (P= 0.01), heart disease (P< 0.001), stroke/TIA (P= 0.01) and in participants with carotid artery disease (P< 0.0001).

Table 6-14: Prevalence of risk factors and CVD according to eGFR

	eGFR ≥ 60	**eGFR ≤ 60**	**Odds ratio**	**P**
	2718 (91.1%)	**266 (8.9%)**		
Female	1384 (55.9%)	161 (65.7%)	1.50 (1.14, 1.99)	0.001
Hypertension	830 (34%)	106 (45.2%)	1.60 (1.22, 2.10)	0.001
Hypercholesterolemia	869 (35.6%)	98 (42.4%)	1.39 (1.01, 1.74)	0.04
Diabetes	173 (6.5%)	22 (8.5%)		0.2
Ever smoker	746 (26.5%)	81 (33.7%)	1.40 (1.06, 1.86)	0.01
CAD	115 (4.4%)	21 (8.3%)	1.97 (1.18, 3.15)	0.001
Stroke/TIA	70 (2.7%)	14 (5.6%)	2.13 (1.31, 2.19)	0.0001
Carotid artery disease	990 (37.2%)	130 (50.1%)	1.69 (1.31, 2.19)	0.0001
ABPI < 0.9	29 (1.0%)	5 (2.3%)		0.2
AAA	40 (1.7%)	5 (2.3%)		0.5
Atrial Fibrillation	195 (7.7%)	20 (8.5%)		0.6

6.6 Prospective Study Results

Table 6.15 shows baseline characteristics of the cohort of 456 participants at baseline. Around two third (63.8%) of participants were female. The mean age of the cohort was 65.8 with standard deviation of 8.6. It was noticeable that whilst around 40% reported smoking history of at least 100 cigarettes in lifetime, there was only 21 (4.61%) of participants remained current and active smoker suggesting that vast majority quitted smoking.

Table 6-15: Baseline characteristics of recruited population

Variable	Frequency	Percentage
Sex		
Male	165	36.18%
Female	291	63.82%
Atrial Fibrillation		
Yes	33	7.24%
No	423	92.76%
Unlisted		
Diabetes		
Yes	33	7.24%
No	423	92.76%
Unlisted		
Heart Attack		
Yes	15	3.29%
No	441	96.71%
Unlisted		
Stroke		
Yes	7	1.54%
No	449	98.46%
Unlisted		
Hypertension		
Yes	158	34.65%
No	298	65.35%
Unlisted		
Hyperlipidaemia		
Yes	166	36.40%
No	290	63.60%
Unlisted		
Exercise		
Yes	349	97.49%
No	9	2.51%
Unlisted	98	
Smoking at least 100		
Yes	194	42.54%
No	260	47.46%
Unlisted	2	
Peripheral Arterial Disease		
Yes	13	2.85%
No	443	97.15%
Unlisted		

As shown in table 6.17 and table 6.18, the vast majority of participants were from white ethnicity and more than 80% reported their overall health as excellent or at least good.

Table 6-16: Ethnicity of participants

Ethnicity

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	White	425	93.2	94.7	94.7
	Others	24	5.3	5.3	100.0
	Total	449	98.5	100.0	
Missing	System	7	1.5		
Total		456	100.0		

Table 6-17: Reported overall health status

Overall Health

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	EXELLENT	78	17.1	17.2	17.2
	GOOD	297	65.1	65.4	82.6
	FAIR	70	15.4	15.4	98.0
	POOR	9	2.0	2.0	100.0
	Total	454	99.6	100.0	
Missing	System	2	.4		
Total		456	100.0		

Baseline demographic shows that two third of the cohort were females and prevalence of previous MI or Stroke were very low among the cohort. Since there were only 217 participants responding to the first follow up, it was decided to study this cohort only for further analysis. Below P-P Plot (Figure 3.1) shows normal distribution of age so T-Test was suitable to be used for statistical analysis.



Figure 6.6: P-Plot shows normal age distribution

There were 190 participants in the control group and 27 participants as case group who were newly found to have carotid artery disease by screening. Table 6.19 shows gender distribution among these groups and there was no statistically significant gender difference between case and control group with Fisher's Exact Test (P= 0.1). However, we can see a trend toward higher prevalence of carotid artery disease among male population not reaching statistical significance. This is in line with previous findings with suggests CVD is more prevalent in men than in women; this is particularly true in older age-groups. Male sex is well-documented as a risk-factor for cardiovascular disease. This may be due to non-modifiable differences between the sexes, such as hormonal influence[4].

Table 6-18: Gender distribution in case and control group

			Sex		
			FEMALE	MALE	Total
CAS	CONTROL	Count	129	61	190
		% within CAS	67.9%	32.1%	100.0%
		% within Sex	89.6%	83.6%	87.6%
		% of Total	59.4%	28.1%	87.6%
	CASE	Count	15	12	27
		% within CAS	55.6%	44.4%	100.0%
		% within Sex	10.4%	16.4%	12.4%
		% of Total	6.9%	5.5%	12.4%
Total		Count	144	73	217
		% within CAS	66.4%	33.6%	100.0%
		% within Sex	100.0%	100.0%	100.0%
		% of Total	66.4%	33.6%	100.0%

Risk factors and characteristics related to follow up population and their risk factors are shown in the table 6.20.

Table 6-19: Baseline data related to case and control group

Risk Factor	**No Carotid disease**	**Carotid disease**	**P**
Sex			
Male	61	12 (16.4%)	
Female	129	15 (10.4%)	0·1
Heart Attack			
No	189	24 (21.2%)	
Yes	1	3 (75%)	0.006
Angina			
No	185	26 (12.3%)	
Yes	5	1 (16.6%)	0.5
History of Diabetes			
Absent	181	24 (11.7%)	
Present	9	3 (25%)	0.1

History of stroke			
Absent	190	26(12%)	
Present	0	1 (100%)	0.1
History of TIA			
Absent	187	23 (10.9%)	
Present	3	4 (57.1%)	0.005
HTN			
Absent	132	11 (7.7%)	
Present	58	16 (21.6%)	0.004
Hyperlipidaemia			
Absent	122	10 (7.6%)	
Present	68	17(20%)	0.007
Smoking history (at least 100)			
No	124	9 (6.8%)	
Yes	66	18 (21.4%)	0.002
AF			
No	175	26 (12.9%)	
Yes	15	1 (6.2%)	0.3
Ankle-Brachial index (ABI)			
Both limbs >0.09	187	23 (10.9%)	
One <0.09	3	4 (57.1%)	0.005

Data shows that, from past medical history alone, history of previous heart attack and TIA but not stroke, history of high blood pressure, high cholesterol and smoking were significantly different between case and control groups. This is in line with current knowledge of traditional risk factor's impact. In addition, ABI was shown to be significantly associated with asymptomatic carotid atherosclerosis. This further highlights that identification of atherosclerotic disease in one vascular bed indicates the increased likelihood of concurrent disease in other vascular beds.

Table 6.21 shows the prevalence of cholesterol lowering medication amongst the case and control cohort. This is striking that a significant percentage (37%) of patients with known carotid artery disease were not on preventative cholesterol lowering therapy

which is recommended by most guidelines. This may suggest that based on their risk calculators, the traditional risk estimate incorrectly place them in the lower risk category whereas with non-invasive ultrasound, they were found to have evidence of atherosclerosis and therefore, being placed in the high and very high risk group for which primary prevention is indicated.

Table 6-20: Use of cholesterol lowering mediation among the cohort

			cholesterol		
			NO	YES	Total
CAD	CONTROL	Count	122	68	190
		% within CAD	64.2%	35.8%	100.0%
		% within cholesterol	92.4%	80.0%	87.6%
		% of Total	56.2%	31.3%	87.6%
	CASE	Count	10	17	27
		% within CAD	37.0%	63.0%	100.0%
		% within cholesterol	7.6%	20.0%	12.4%
		% of Total	4.6%	7.8%	12.4%
Total		Count	132	85	217
		% within CAD	60.8%	39.2%	100.0%
		% within cholesterol	100.0%	100.0%	100.0%
		% of Total	60.8%	39.2%	100.0%

In addition, table 6.22 shows the prevalence of aspirin use as the main stream antiplatelet among the population and over 50% of those with known carotid artery disease did not report use of Aspirin.

Table 6-21: Prevalence of Aspirin use amongst the cohort

			Aspirin		
			NO	YES	Total
CAD	CONTROL	Count	169	21	190
		% within CAS	88.9%	11.1%	100.0%
		% within aspirin	91.8%	63.6%	87.6%
		% of Total	77.9%	9.7%	87.6%
	CASE	Count	15	12	27
		% within CAS	55.6%	44.4%	100.0%
		% within aspirin	8.2%	36.4%	12.4%
		% of Total	6.9%	5.5%	12.4%
Total		Count	184	33	217
		% within CAS	84.8%	15.2%	100.0%
		% within aspirin	100.0%	100.0%	100.0%
		% of Total	84.8%	15.2%	100.0%

Table 6.23 shows that there was no statistically significant gender difference between case and control groups with Fisher's Exact Test (P= 0.1). However, the mean age of case group (M = 72.7, SD = 6.0) was higher than control group (M = 65.0, SD = 7.3) with significant P value of 0.001. This could partially be responsible for the increased rate of cardiovascular events secondary to age as a major risk factor.

Table 6-22: Gender distribution

			Sex		
			FEMALE	MALE	Total
CAS	CONTROL	Count	129	61	190
		% within CAS	67.9%	32.1%	100.0%
		% within Sex	89.6%	83.6%	87.6%
		% of Total	59.4%	28.1%	87.6%
	CASE	Count	15	12	27
		% within CAS	55.6%	44.4%	100.0%
		% within Sex	10.4%	16.4%	12.4%
		% of Total	6.9%	5.5%	12.4%

Total	Count	144	73	217
	% within CAS	66.4%	33.6%	100.0%
	% within Sex	100.0%	100.0%	100.0%
	% of Total	66.4%	33.6%	100.0%

After first follow up at 18 months since recruitment, there were 14 events recorded, in 13 participants, including 2 hospitalisation due to angina, 1 stroke, 5 TIAs, 3 cases of coronary revascularisation with PCI and 3 non-coronary arterial surgery (Endarterectomy and peripheral arterial angioplasty). Table 6.24 shows the distribution of the events which was statistically significant with much higher prevalence (21.4% vs 3.6%) among case group (P= 0.002).

Table 6-23: Prevalence of observed events amongst both groups

			CAS		
			CONTROL	CASE	Total
OBSERVED EVENT	NO	Count	183	21	204
		% within EVENT	89.7%	10.3%	100.0%
		% of Total	84.3%	9.7%	94.0%
	YES	Count	7	6	13
		% within EVENT	53.8%	46.2%	100.0%
		% of Total	3.2%	2.8%	6.0%
Total		Count	190	27	217
		% within EVENT	87.6%	12.4%	100.0%
		% of Total	87.6%	12.4%	100.0%

There is no statistically significant difference in gender distribution between those with event and those without as shown in Table 3.10 (P = 0.1). In addition, mean age of those with observed event was 66.7 (SD = 9) compared to 65.9 (SD = 7.5) in the control group, as shown in table 6.25, which is not statically significant (P = 0.7).

Table 6-24: Gender distribution of participants with observed event and those without

			Sex		
			FEMALE	MALE	Total
EVENT	NO	Count	138	66	204
		% within EVENT	67.6%	32.4%	100.0%
		% within Sex	95.8%	90.4%	94.0%
		% of Total	63.6%	30.4%	94.0%
	YES	Count	6	7	13
		% within EVENT	46.2%	53.8%	100.0%
		% within Sex	4.2%	9.6%	6.0%
		% of Total	2.8%	3.2%	6.0%
Total		Count	144	73	217
		% within EVENT	66.4%	33.6%	100.0%
		% within Sex	100.0%	100.0%	100.0%
		% of Total	66.4%	33.6%	100.0%

It was surprising that overall health was rated as good or excellent by 11 participants out of 13 who suffered an event. In addition, there were 6 females and 7 males among the group with only one participant from ethnic minority. Around 9 participants (69.2%) reported smoking at least 100 cigarettes in their lifetime and 4 (30.8%) were current smoker.

Table 6-25: Mean age of event group vs those free of event

	EVENT							
	NO				YES			
	FEMALE		MALE		FEMALE		MALE	
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
Age	65	7	67	8	71	6	63	10

Table 6.27 shows data related to the event group compared to those who had no events, highlighting the risk characteristic differences among these groups.

Table 6-26: Follow up data comparing participants with CV event with those free of CV event

Risk Factor	No CV Event	CV Event	OR (95% CI)	P
Sex				
Male	66	7 (9.59%)		
Female	138	6 (4.17%)		0·1
Heart Attack				
No	200	13 (6.1%)	1	
Yes	4	0 (0%)	3.3 (0.3,30.6)	0.7
Angina				
No	199	12 (5.7%)	1	
Yes	5	1 (16.7%)	0.3 (0.03,2.7)	0.3
History of Diabetes				
Absent	193	12 (5.8%)	1	
Present	11	1 (8.3%)	1.4 (0.1,12.2)	0.5
History of stroke				
Absent	203	13 (6%)	1	
Present	1	0 (0%)		0.9
History of TIA				
Absent	198	12 (5.7%)	1	
Present	6	1 (14.3%)	2.7 (0.3,24.7)	0.3
HTN				
Absent	137	6 (4.2%)	1	
Present	67	7 (9.5%)	2.3 (0.7,7.3)	0.1
Hyperlipidaemia				
Absent	126	6 (5.5%)	1	
Present	78	7 (8.2%)	1.8 (0.6,5.8)	0.2
Current Smoker				
No	104	6 (5.6%)	1	
Yes	4	4 (100%)	17.3v(3.4,86.8)	0.002
Smoking history (at least 100)				
No	129	4 (3%)	1	
Yes	75	9 (10.7%)	3.8 (1.1,13)	0.02
AF				
No	188	13 (6.5%)	1	
Yes	16	0 (0%)		0.3
Carotid plaques and internal carotid stenosis (%)				

Both normal or <50% stenosis	183	7 (3.7%)	1	
At least one with >50% stenosis	21	6 (22.2%)	7.4 (2.2,24.3)	0.002
Ankle-Brachial index (ABI)				
Both limbs >0.09	199	11 (5.2%)	1	
One <0.09	5	2 (28.6%)	7.2 (1.2,41.5)	0.05

These results very strikingly show that smoking history and the presence of asymptomatic Carotid artery disease as well as peripheral arterial disease were predictors of cardiovascular event in the studied population.

In addition, tables 6.28 and 6.29 show and compare the prevalence of exercise and alcohol consumption among the population with cardiovascular event and those free of event.

Table 6-27: Exercise Frequency

			Exercise frequency			
			NUL	1-3	4>	Total
EVENT	NO	Count	3	38	163	204
		% within EVENT	1.5%	18.6%	79.9%	100.0%
		% within Exercise frequency	75.0%	97.4%	93.7%	94.0%
		% of Total	1.4%	17.5%	75.1%	94.0%
	YES	Count	1	1	11	13
		% within EVENT	7.7%	7.7%	84.6%	100.0%
		% within Exercise frequency	25.0%	2.6%	6.3%	6.0%
		% of Total	.5%	.5%	5.1%	6.0%
Total		Count	4	39	174	217
		% within EVENT	1.8%	18.0%	80.2%	100.0%
		% within Exercise frequency	100.0%	100.0%	100.0%	100.0%
		% of Total	1.8%	18.0%	80.2%	100.0%

Table 6-28: Alcohol consumption

			how much/lager, sider, beer			
			Less than 1	1-3	>4	Total
EVENT	NO	Count	104	28	12	144
		% within EVENT	72.2%	19.4%	8.3%	100.0%
		% within how much/lager, sider, beer	92.9%	96.6%	85.7%	92.9%
		% of Total	67.1%	18.1%	7.7%	92.9%
	YES	Count	8	1	2	11
		% within EVENT	72.7%	9.1%	18.2%	100.0%
		% within how much/lager, sider, beer	7.1%	3.4%	14.3%	7.1%
		% of Total	5.2%	.6%	1.3%	7.1%
Total		Count	112	29	14	155
		% within EVENT	72.3%	18.7%	9.0%	100.0%
		% within how much/lager, sider, beer	100.0%	100.0%	100.0%	100.0%
		% of Total	72.3%	18.7%	9.0%	100.0%

Chapter 7 Discussion and Concluding Remarks

7.1 Overview

Since the introduction of landmark Framingham risk score based on traditional cardiovascular risk factors, medicine witnessed great improvements in the mortality and morbidity reduction of cardiovascular disease. However, there is still much room for further improvement and rightly, policy makers are focusing on prevention.

In addition, this is well known that effect of risk factors are not similar in individuals and lack of risk factors does not guarantee no cardiovascular disease. Therefore, more individualised approach is needed to look for early signs of disease such as subclinical atherosclerosis which could be considered as end product of all interacting risk factors (both known and unknown risk factors).

This approach may introduce more individualised risk estimate and better encourage one to change behaviour and take personal responsibility and ownership of their health and wellbeing. Moreover, early preventative steps could be taken to minimise the risk of future events and comorbidities.

7.2 Abdominal Aortic Aneurysm screening for high risk individuals

While this study supports aforementioned research in the field, it also describes factors not previously described. AAA has historically been considered to be a manifestation of atherosclerosis[87]. It has been shown that abdominal aortic aneurysm and atherosclerosis share many risk factors such as age, smoking, hypertension, and hypercholesterolemia[153, 154]. Smoking, particularly current smoking is a very strong

risk factor for AAA[95, 117, 153-159] in both genders. The association of AAA with smoking was reported to be stronger for AAA of 3.0 to 3.9 cm and weaker for AAA of 4.0 cm or larger[96]. However, the results of this study indicate that smokers are more likely to develop large AAA. Prevalence of smoking was significantly higher (P= 0.005) in the subjects younger than 65 years old with AAA compared to AAA patients in the older group. This indicated that smoking might trigger the onset of disease at an earlier stage in life. Whilst over 50% of the cohort reported history of smoking in their life, smoking prevalence in the female cohort was slightly lower than overall smoking prevalence.

The present findings seem to be consistent with other research, which found that high blood pressure (HTN) is an independent risk factor for AAA [95, 117, 153, 154], and defined HTN as the only atherosclerotic risk factor that has been consistently associated with AAA. HTN was one of the most prevalent comorbidities and its prevalence was higher in women with AAA.

However, it is not known whether hypertension is involved in the pathogenesis of aneurysms directly or indirectly[115]. Other studies further indicate the relation between hypertension and AAA[87, 94, 96, 115, 157].

High serum total cholesterol and low HDL cholesterol were shown to be significantly associated with the risk of developing an AAA[91, 153, 160, 161]. In the present study whilst over one third of the cohort reported having high cholesterol, it is somewhat surprising that it is showed a negative correlation between developing large AAA and high cholesterol. This could be explained by corrective actions taken by patients

including risk factor modifications and medical management for high cholesterol following identification of the condition, which could have had protective effect on AAA growth.

Prior studies have noted higher prevalence of cardiovascular disease among AAA patients compared with subjects without an aneurysm[96, 115, 117, 153]. Findings of the current study further support the idea and also highlight the fact that people with history of cardiovascular disease are more likely to develop large AAA.

Surprisingly, patients with history of smoking and cardiovascular disease were found to have less risk of developing large AAA as opposed to their counterparts without history of cardiovascular disease. Some individuals may have been aware of the high risk of cardiovascular diseases and changed their living habits accordingly, and this may influence its association with large AAA. On the other hand, it may highlight the selection bias within the population as those with AAA and CVD would have been less able to attend community screening and therefore, might be under represented.

Familial history of AAA was firstly reported in 1977 by Clifton[162]. It was reported by only 5.1% incidence in AAA patients[153], by increased prevalence of AAA in first degree relatives of patients with AAA ranging from 6% to 29% among male relatives and 0% to 11% among female relatives. Observing overall 11.08% family history of AAA in first degree relatives indicates that genetic susceptibility may play a key role in their pathogenesis[87, 162-164] and is consistent with those of other studies which suggest that aging brothers of patients with known AAA have the highest risk for developing the disease. The prevalence of AAA history in the first degree relatives of

younger group, 12.57% (24/191), was higher than that in older group, 10.75% (92/856). However, the observed difference between <65 year old patients and ≥65 ones in this study was not significant (P=0.469). Therefore, considering a predictive value for early diagnosis of AAA at younger ages in first-degree relatives of AAA patients must be interpreted with caution.

Modelling studies have indicated that screening for AAA in women could be cost-effective because the rupture rate appears to be much higher in women than in men[165]. One possible explanation may be that at equal measurements, an aneurysm in a female may actually be proportionally larger than in a male[166]. It is also conceivable that aneurysms in females may be subjected to an accelerated expansion rate compare to males[167]. Recently, Wanhainen et al, utilizing a Markov simulation model, determined that the cost-effectiveness ratio of screening women, in terms of cost per life year gained was equivalent to that of men, with the lower prevalence of AAA in women being offset by the increased rupture risk concluding that women should be included in future AAA screening studies[168].

One of the issues that emerges from these findings is that limiting AAA screening to men aged 65 and over is perhaps neglecting the needs of the female population and therefore, a legitimate reason for reconsidering current recommendations. This should be noted that although women are inherently less likely than men to develop an AAA, those who develop an AAA experience poorer outcome than men.

It is interesting to note that only 59.25% (1214) of this population based cohort fall within current AAA screening recommendations (Males ≥65 y/o). This finding has

important implications for developing a conservative screening selection threshold for those who have one or more element of a broader range of risk factors including smoking, cardiovascular disease history and family history of AAA as well as age and gender. In understanding the risks associated with large AAA at different ages in both genders, this information can be used to develop targeted screening aimed at population at increased risk and prevents AAA deaths in men and women.

Further studies on the current topic looking at the denominators assessing AAA prevalence among different categories are recommended. The Database may be subject to some biases including selection bias.

It is hoped that this results will provide a robust foundation for contemporary prevalence and cost analysis in future studies and in the discussion of strategies for early detection and disease management; as well as providing valuable information when it comes to tackling questions as to the cost-effectiveness and viability of extending AAA screening to at risk women and younger men.

7.3 Introducing AAA Screening Model for Females

Whilst the AAA mortality has not declined globally[169], studies suggest that since 1996, the burden of AAA has been decreasing in the US, UK and Australia[169, 170]. A steady reduction in mortality (from 40 4 to 25 7 per 100 000 population over 50 years) was noticed with the changes being more marked for men than for women[170]. It appears that the rate of decline in female AAA mortality is less than the rate of decline in male AAA mortality[169]. The reasons for sex differences in AAA remain

unknown but oestrogens may play a role in reducing the prevalence of AAA in women[94-96].

The offer of screening men older than 65 is currently well-established and has been reported to be cost-effective[97, 98]. Women were excluded from several large trials of screening for AAA [96] due to the low prevalence of the condition. However, smoking, the principal risk factor for AAA, has been increasing in women and the future incidence of AAA in female smokers is unknown[171]. England and Wales Death Registrations report shows that 40% of AAA related mortality happened in females in 2013 accounting for more than 2000 deaths in females older than 55. In a UK trial, the risk of rupture in women was 4-fold that of men[101] occurring at smaller diameters[102].

It has been shown that abdominal aortic aneurysm and atherosclerosis share many risk factors such as age, smoking, hypertension, and hypercholesterolaemia[153, 154]. Several studies have noted higher prevalence of cardiovascular disease among AAA patients compared with subjects without an aneurysm[96, 115, 117, 153]. The results of our study further support these findings and also highlight the fact that women with history of cardiovascular disease are more likely to develop AAA.

It is believed that reaching population prevalence of 1% would make AAA screening program cost effective[97]. This study shows that in women aged 66-85 a prevalence of AAA greater than 1.0% is found in the presence of a history of heavy smoking (≥40 pack-years) (prevalence of 2.14), ABI > 0.90 (prevalence 1.41%) and carotid artery

stenosis >50% (prevalence 2.41%). Thus, the presence of any of the above could be considered as an indication to screen for AAA cost effectively.

Smoking is a very strong risk factor for AAA[95, 117, 153-159] in both genders. Our findings on hypertension are consistent with other research, which found that high blood pressure is an independent risk factor for AAA [95, 117, 153, 154]. High serum total cholesterol and low HDL cholesterol were also shown to be significantly associated with increased risk of developing an AAA[91, 153, 160, 161]. However, in our population of 27,170 women they were not.

Family history of AAA was first reported as a risk factor in 1977 by Clifton[162, 172]. This observation that higher prevalence of AAA in first degree relatives of females with AAA, indicates that genetic susceptibility plays a key role in pathogenesis and is consistent with those of other studies[87, 162-164]. In our population, family history of AAA was of borderline significance (P = 0.052).

Linear logistic models 1 and 2 (Table 3) indicate both the potential of identifying high prevalence groups using risk factors, but also the weakness of these risk factors in identifying groups that contain the majority of the AAA present in the population studied. Model 1 is based on risk factors prior to any screening. A probability cut-off point of 0.5 identifies 2,235 women with 22 AAA (i.e. only 30% of the AAA in the population studied) with a prevalence of 0.98%. A lower cut-off point of 0.3 identified a larger group of 10,830 women with 57 AAA (i.e. 79% of the AAA in the population studied) with a prevalence of 0.53%. When atrial fibrillation ABI and carotid stenosis were added (Model 2), a cut-off point of 0.5 could identify 3,701

women with 58 AAA (i.e. 71% of the AAA in the population studied) with a prevalence of 1.57%.

A carotid scan in itself is not a practical test for screening for AAA. It is more expensive and more time consuming than an abdominal scan. However, for patients who present with a carotid stenosis (symptomatic or asymptomatic), knowledge that a prevalence of 2.4% of AAA has been reported may make one consider asking for an abdominal aortic scan added to their next carotid scan as and when scheduled.

Another message originating from this report is that AAA is rare in women below the age of 60 (Table 1) and screening for AAA can be omitted in this age group.

Therefore, the most obvious finding to emerge from this study is that currently recommended national screening programme based on age and gender only, could results in under detection of this fatal condition among females and hence, contributing to the worsening of the gender-based inequity in health which has become a subject of growing interest among researchers.

Health inequities are deeply embedded within populations. Groups with power, prestige, and resources have better health than those who do not have such status[173]. These inequalities are not idiosyncratic "differences" across groups, but arise as a result of the distribution of resources in a way that privileges those with more status. Therefore, inequalities in health refer to differences generated by social and political structures, and can be undone[43].

When considering initiatives—both those aimed at shifting the curve of population health as well as those aimed at high-risk groups—ideally, we want population health interventions that are both efficient and equitable. In many ways, however, these two goals—equity and efficiency—are often at odds with each other; that is, there is a trade-off when maximizing one potentially results in a cost for the other[174].

In line with WHO action plan, it is hoped that findings of this study will inform evidence based AAA screening programme for those at high risk which could improve gender equity in health and address women's rights to health as one of the most direct and potent ways to reduce health inequities and ensure effective use of health resources.

For example, in the case of AAA screening, this is a current national program for male population over the age of 65 years old which could be extended to the selected female cohort with risk factors identified by current study. This is hoped that results of published paper raised from this study will better inform decision making by policy makers around appropriateness and cost effectiveness of AAA screening in selected female cohort.

The findings of our report should stimulate further studies towards the development of a screening selection plan for women over 65. However, whether such screening will be associated with benefit can only be determined by RCTs and cost-benefit studies. The importance of RCT cannot be overemphasised because of the higher operative risk and cardiovascular risk in women with the risk factors that are used for their selection. The presence of such risks may render screening in women unviable.

7.4 AF Screening Discussion

Recent data suggests an estimated 170 individuals needed to be screened to detect one additional AF case compared with no screening[175]. Current study suggest the number needed to screen of 63 for those aged over 65 years old in order to detect one AF case. Studies showed that screening can identify 1.4% of the population ≥65 years with previously undiagnosed AF. Many of those identified would be eligible for, and benefit from OAC to prevent stroke. Given this incidence, community AF screening strategies in at risk older age groups could potentially reduce the overall health burden associated with AF[132]. This study conforms previous findings and showed that screening can identify 1.59% of ≥65 years in the cohort had new diagnosis of AF detected by screening.

Systematic reviews of multiple studies including large number of participants showed the incidence of previously undiagnosed AF was 1.0% (14 studies, n=67,772) increasing to 1.4% (8 studies, n=18,189) among participants ≥65 years[132]. Those ≥65 years with newly diagnosed AF should be considered for anticoagulation for stroke prevention even in the absence of any other risk factors (based on CHA2DS2-VASc score of ≥1).

More recent published UK study using single lead ECGs recorded in 1805 patients (703 female and 1102 male), mean (SD) age 74.9 (7.1) years showed that 92 patients (5.1%) were found to have AF. Median CHA2DS2-VASc score was 4 (2-7) and median HAS-BLED score was 2 (1-5).[176]

Age is an important risk factor for AF and therefore, the CHA2DS2-VASc score assigned a score of 2 for age ≥ 75 years and 1 for ages 65–74 years. This study

conforms these findings and shows that prevalence of AF increases significantly with increased age which subsequently leads into higher risk of stroke.

Studies showed that DM independently increases the risk of stroke in patients with AF by 1.7 fold which is in keeping with our results showing 1.5-2.6 times greater risk of developing AF.

Hypertension is the most prevalent risk factor for new-onset atrial fibrillation. Controlled or uncontrolled hypertension and history of hypertension scores a point in the CHA2DS2VASc score. In one study, the observed absolute stroke risk from hypertension alone as a risk factor in non-anticoagulated patients with atrial fibrillation was about 1.5–3.0% per year[177].

Previous stroke or transient ischemic attack (TIA) is perhaps the strongest independent risk factor for stroke in patients with AF[178]. Studies have shown that this risk is increased by 2.5-fold following a previous stroke of TIA[179]. This study showed that participants with previous history of AF/Stroke have 3 times greater risk of developing AF.

Peripheral arterial disease (PAD) is observed to increase the risk of incident AF in elderly patients with risk increasing with progressively lower ankle-brachial pressure index (ABPI)[178].

Another important practical implication of the is study is that AF screening could result in identification of a noticeable number of undiagnosed cases who may benefit

from stroke prevention by anticoagulation as well as better management of their condition to avoid late cardiac complications and remodelling.

This was reflected in the guideline published by European Society of Cardiology published in 2016, 3 years after the initiation of the current study, encouraging the further evaluation of systematic AF screening programmes in at-risk populations such as those ages 65 and older.

7.5 CKD Screening Discussion

This study showed a very strong correlation between CKD and both traditional risk factors as well as subclinical and clinical atherosclerosis. Therefore, including eGFR measurement in risk calculation could better inform risk management as these conditions typically tend to cluster. This simple but very important additional information could be more routinely utilised to risk stratify at risk population and may save NHS and DOH a noticeable amount of budget. The present findings are consistent with previous research, such as the HSE, NEOERICA and QICKD studies.

The Health Survey for England (HSE) 2010 report[144] was a population-based study of the prevalence of CKD in England using MDRD to estimate GFR. It was nationally representative with respect to ethnic and socioeconomic factors. It found that 6% of men and 7% of women (aged ≥16 years) had stage 3–5 CKD, based on eGFR levels.

The New Opportunities for Early Renal Intervention by Computerised Assessment (NEOERICA) project[145] examined primary care records for Kent, Manchester and Surrey over a five-year period ending in 2003. It was not nationally representative

with respect to ethnic and socioeconomic factors. eGFR was calculated from the MDRD equation using calibrated creatinine levels. The study estimated the prevalence of stage 3–5 CKD in the UK adult population at 8.5% (10.6% for females and 5.8% for males).

The Quality Improvement in CKD (QICKD) study[139] used patient records from 129 general practices in England, with an age and sex distribution similar to the national average. The prevalence of stage 3–5 CKD was estimated at 5.41% of the entire (not adult-only) population (7.34% in females and 3.48% in males). The criterion for stage 3–5 CKD diagnosis was two consecutive eGFR of <60, at least three months apart. In this study, 97% of the CKD population were recorded as being at stage 3 of the disease.

As with the above studies, in the present study prevalence of CKD is higher in females (10.4% vs. 7.1%) and increases with age. However, the overall prevalence of CKD is slightly higher among this self-selected population. One possible explanation may be that the population may have had a higher mean age (63.3 y/o).

While this study supports earlier research in the field, it also brings to light aspects of CKD not previously described, highlighting the fact that people with history of asymptomatic cardiovascular disease such as Carotid artery disease are more likely to develop CKD. In particular, there is strong evidence that subjects with asymptomatic carotid artery disease are at up to two times greater risk of developing CKD (OR: 1.69, CL=1.3-2.1). Having an established history of heart disease and stroke also puts individuals at greatly increased risk of CKD (OR: 1.9 and OR: 2.1 respectively).

While the prevalence of diabetes was higher in patients with CKD (8.5% vs. 6.5%), this difference did not show statistical difference, which is primarily due to the limited size of the sample population. It is possible that some diabetic individuals may have been tested for the condition as part of their diabetic care, and so decided not to select and pay for the CKD test on the screening day.

CKD is relatively common and exacts a heavy toll in terms of mortality, morbidity, QoL and healthcare resources[138]. This study has demonstrated that a limited screening programme, using standard methods and targeted at a high-risk population – those with known risk factors such as diabetes, hypercholesterolemia and smoking, and/or those with a history of cardiovascular disease – can bring previously unsuspected cases to light.

While earlier diagnosis is intuitively beneficial, in the case of CKD there is also a need for raising disease awareness and better disease management strategies, which should result eventually in improved QoL. QoL has mostly been studied in end-stage renal disease (ESRD), but there is evidence that it is also significantly affected in patients with CKD stages 3 and 4[138]. A further potential benefit is reduced economic burden on healthcare systems, especially if progress to ESRD can be prevented or delayed, reducing the need for dialysis and transplants.

Guidelines recommend that an eGFR result of less than 60ml/min/1.73m2 in a person not previously tested should be confirmed by repeating the test within two weeks. Therefore, further studies on the current topic looking at larger populations and with repeated eGFR measurements to confirm sustained kidney damage are recommended.

CKD is responsible for significant mortality and morbidity, independent of known risk factors for cardiovascular disease. It is associated with a high prevalence of cardiovascular risk factors and ageing. In particular, PAD and history of stroke or heart disease double the risk. Being a smoker (or past smoker), female, and having hypercholesterolemia, hypertension or carotid artery disease also put individuals at increased risk of CKD.

Understanding the current prevalence of cardiovascular risk factors associated with CKD may help inform the development of new strategies for early detection and disease management, which could prevent premature deaths in men and women, improve patient QoL, and offer significant savings to healthcare systems.

7.6 Prospective Carotid Artery Stenosis Study

Studies showed that Successful CEA for asymptomatic patients younger than 75 years of age reduces 10-year stroke risks and 50% of this reduction is in disabling or fatal strokes[70]. Identifying and starting primary prevention for those falsely classified as low risk using traditional risk calculators is even more important and crucial in the mission to reduce premature coronary artery disease and stroke.

The findings of these study which showed higher prevalence of cardiovascular events observed among those with asymptomatic carotid artery disease and peripheral arterial disease further confirms previous findings.

These findings highlights the value of ultrasound as a non-invasive and inexpensive tool to identify cases early and manage the atherosclerotic process at early stages where individual and healthcare system has the most benefit to achieve. More importantly, evidence based preventative measures could be taken in order to minimise the cardiovascular mortality and morbidity.

This small prospective study suggest that valuable information regarding the presence of subclinical atherosclerosis in peripheral beds such as Carotid artery and distal limb could improve the predictability of cardiovascular events. These could be achieved with Duplex ultrasound which is a rapidly developing, simple and non-invasive tool that is easily reproducible and accessible.

The findings of the current study is in line with other publications suggesting that assessment of carotid or femoral plaque burden with ultrasound has also been demonstrated to be predictive of CV events, comparable to CAC[180, 181].

This was reflected in ESC guideline published in 2019 suggesting Non-invasive imaging techniques can detect the presence, estimate the extent, and evaluate the clinical consequences of atherosclerotic vascular damage. Reclassification of risk score value in people identified as being at moderate CV risk by using markers such as CAC score >100 Agatston units, ankle–brachial index (ABI) <0.9 or >1.40, carotid–femoral pulse wave velocity >10 m/s, or the presence of plaques at carotid or femoral ultrasonography is now included in new 2019 guidelines[32].

7.7 Concluding remarks

This study highlights the value of proactive approach in the primary prevention of cardiovascular disease which would enable use of inexpensive and non-invasive modalities such as community ECG and carotid ultrasound in identification of apparently healthy but at risk population early enough; when lifestyle changes and simple medical interventions are most effective. Moreover, it yield a high value in reducing significant morbidities such as stroke and heart attack with potential substantial cost savings for the healthcare system.

Conditions screened as part of this study were serious one with potential of high morbidity and resultant poor quality of life. At the same time, interventions used to detect early signs of developing these conditions are fairly simple and highly cost effective.

In addition, same level of equipment and expertise used for AAA screening could be utilized to include carotid artery disease screening for added benefit. As for Atrial fibrillation, PAD and CKD, screening for selected subgroups could be added to current NHS health check program currently conducted in the community via GP surgeries since current study showed such program is both possible and practical with very good detection rate achieved via a well conducted community program.

This research has raised many questions which require further investigations. It is recommended that further research be undertaken to validate screening role and its cost effectiveness at selected population base. It would be interesting to further assess the changes in the health behavior of those identified with atherosclerosis overtime

and in a long term study to evaluate its correlation with CAD progression and future events.

Moreover, long term prognosis of the patients with and without subclinical atherosclerosis can be followed to investigate whether or not it can predict the higher mortality and morbidity rate more accurately than current risk score calculators.

Associations between current health states and current behaviour need careful interpretation, as current health may reflect past, rather than present behaviour. Similarly, current behaviour may be influenced by advice or treatment for particular health conditions[4].

Considerably more work will need to be done to determine the role of early intervention such as lifestyle modifications, pharmacotherapy and in some cases invasive interventions of the cohort with subclinical condition. Therefore, large population based studies could provide more definitive evidence.

7.7 Potential Impact

In order to convince policy-makers to take action on non-communicable diseases, and to persuade the general public that such action is justified, evidence is needed. Findings of the current study has the potential to act as such and in particular, data related to AAA screening in women has been shared with relevant think tank for consideration.

In addition, part of this projects hypothesis was validated during the course of the PhD and has been reflect in recent major international clinical guidelines.

7.8 Limitations

The large sample size is a key strength of this study. However, since participants were self-referred to screening, the database was subject to selection bias, so the sample in this study was not representative. Nonetheless, valid assessment of exposure-disease relationships may be widely generalizable and does not require participants to be representative of the population at large[182].

Screening was an expense for participants and they travelled to screening sites so seriously ill participants may have been unlikely to travel to screening centres. Incomplete records were also a potential source of bias; some participants underwent only part of screening tests and therefore did not fully complete the questionnaire.

A limitation of this study is the potential of selection bias of 1% response rate and 80% attendance of those responding who may have done so because of family history or relatives with cardiovascular problems.

However, the prevalence of major risk factors of this cohort is comparable with published prevalence from population based studies. In our population aged 66-85 history if MI was present in 2.01%, which is similar to the 2.05% self-reported heart attack among females in a Canadian study [183] and lower than the 3.5% coronary heart disease prevalence reported by the National Cardiovascular Intelligence Network [184].

The observed prevalence of hypercholesterolaemia of 33% is also similar to that of US Heart Disease and Stroke Statistics recently published by American Heart Association showing overall prevalence of 32% history of high cholesterol among women[185]. The prevalence of hypertension of 20% was lower than in population based studies showing 28.5% prevalence among women in the last few years[186]. A history of stroke/TIA of 5.2% reported by our population is in line with WHO estimates on UK stroke prevalence among women (50 per 1000 population aged 65-74 and 79 per 1000 population in 75-84 years old[187]. Nevertheless, our data should be a stimulus for further studies rather than a definitive extrapolation to the general population.

Another limitation of the study is that the sample has been obtained from the whole of UK and Ireland and no conclusions can be made about variations in cardiovascular risk factors or related socioeconomic factors in different regions.

The prospective part of the current study was underpowered for this endpoint because of limited recruitment of participants over the age of 70 and low CVD event rates. In addition, there were a significant drop out as nearly half of the participants did not respond to follow up questionnaire. Moreover, the observational nature of study dictate that results should be interpreted with caution as not all correlations would necessarily indicate causality.

The small sample size and case group requires very long term follow up to improve the study power. However, first follow up data are analysed for the purpose of fulfilling this time limited PhD project.

Therefore, the short follow up of recruited participants underpowered the results despite striking statistically significant differences even after 18 months. It is hoped that further follow up of the cohort, may further show separation of lines between case and control group.

7.9 Future Work

It is hoped that this project will form a strong case for consideration of a large trial looking at the annual rate of MACE in participants with asymptomatic carotid artery disease and evaluate the role of primary prevention in these cohort. In addition, a registry of population with subclinical atherosclerosis such as peripheral arterial disease and carotid artery disease would better inform their future risk of fatal and non-fatal cardiovascular events and therefore optimal management and therapy.

Additionally, the current recruited cohort, although small, will continue to have ongoing regular follow up by the vascular department at Hammersmith Hospital.

Chapter 8 References

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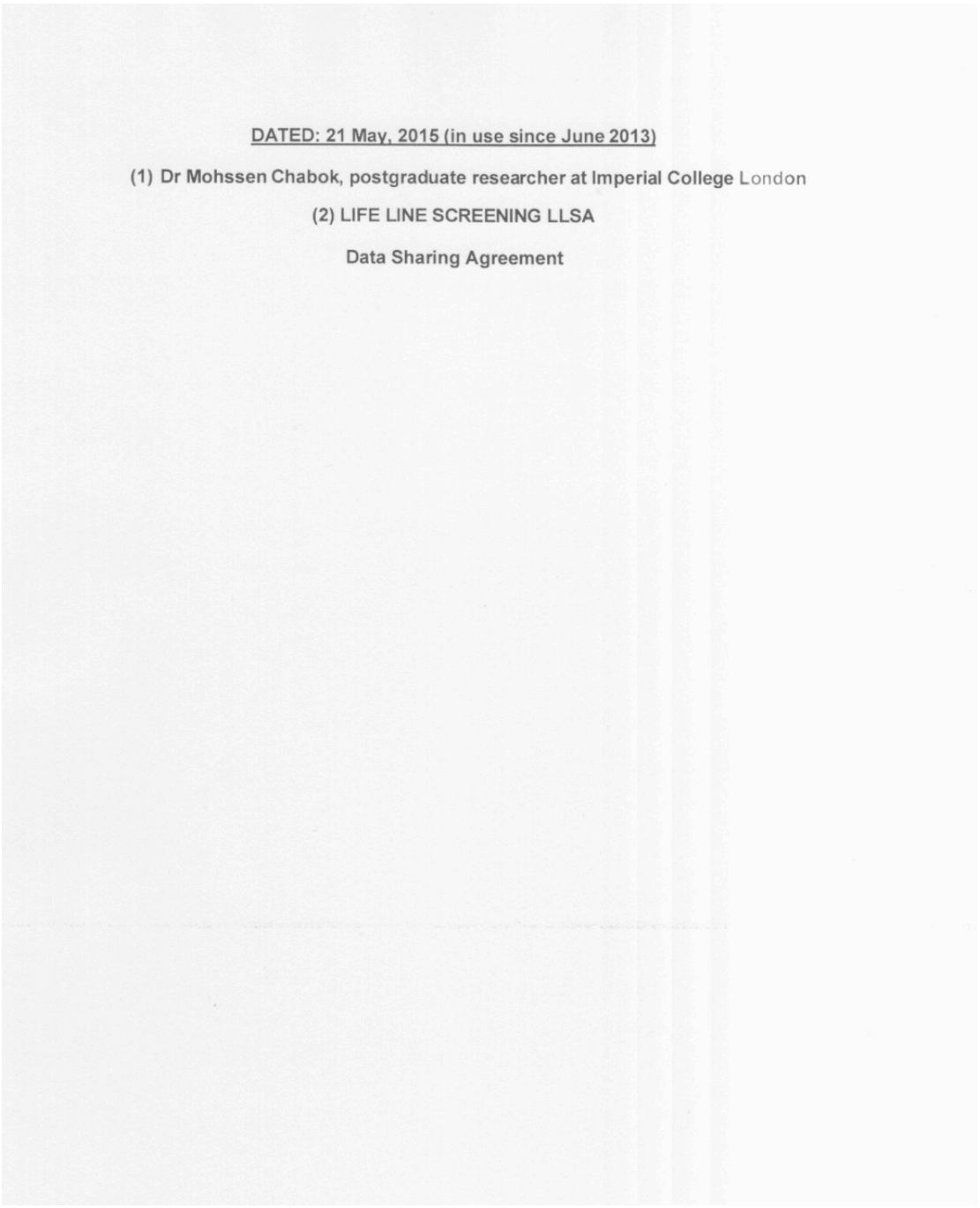
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Chapter 9 Appendices

Appendix 1: Data Sharing Agreement



DATED: 21 May, 2015 (in use since June 2013)

(1) Dr Mohssen Chabok, postgraduate researcher at Imperial College London

(2) LIFE LINE SCREENING LLSA

Data Sharing Agreement

THIS DATA SHARING AGREEMENT updated 21 May, 2015 is made **BETWEEN**:

(1) **Dr Mohssen Chabok, postgraduate researcher at Imperial College London** whose administrative offices are at Vascular Lab, Hammersmith Hospital, Ducane Road, London W12 0HS ("the Recipient"); and

(2) **LIFE LINE SCREENING LLSA** whose registered office/principal place of business is at 901 South MoPac Expressway, Bldg II Suite 130, Austin, TX 78746 ("the Company").

WHEREAS:-

(A) The Company has collected and owns certain data sets derived from participants attending appointments to be screened for various cardiovascular conditions ("Data") described in Appendix A;

(B) The Data is to be used by Recipient in the research described in the Appendix B ("the Research") and Company is willing to supply the Recipient with the Data.

IT IS AGREED as follows:

1 Subject to Recipient's compliance with the terms and conditions hereof, the Company shall use its reasonable efforts to collect, compile, and provide the Data requested in accordance with Recipient's request.

2. The Data remains the property of the Company. There is no transfer or licence or implied transfer or licence of rights in the Data from the Company to the Recipient including any intellectual property rights. This Agreement does not restrict the rights of the Company to distribute the Data to other institutions or to publish any of its proprietary documents relating to the Data.

3 The Recipient will retain the Data in a secure location on its premises and will not permit the Data or any part of it to come into the possession or control of any other organisation or any individual other than those researchers who are involved in the Research described in Appendix B. The Recipient will not transfer the Data in whole or in part to third parties without the relevant third party entering into a separate data transfer agreement which shall contain terms no less onerous than those contained in this Agreement.

4. The Recipient will use the Data only to carry out the Research described in Appendix B to this Agreement, and only for Research that has appropriate ethical approval (if applicable). The Recipient will not use the Data or any parts thereof for any commercial purpose.

5. The Recipient will use reasonable endeavours to ensure that the Data in its possession, or under the control of the Recipient shall as soon as possible be returned or destroyed upon (i) the reasonable request of the Company; or (ii) on termination of this Agreement which shall be effective on completion of the Research; or (iii) in the event that the Recipient is in breach of any of the conditions of this Agreement; or (iv) withdrawal of consent of the relevant participant. If the Recipient is required to destroy

the Data then it will confirm in writing to the Company that the Data has been destroyed.

6. The Recipient will keep the Company informed of the results of the Research. All results, data, work, reports, writings and ideas in any form that are created, developed, written, conceived or made by the Recipient as a result of or in connection with the Research or the performance of its obligations under this Data Sharing Agreement (hereafter the "Results") shall be the property of the Recipient. The Recipient hereby grants to the Company, subject to the prior written consent of the funder of the Research, a royalty-free, indefinite, non-transferable, non-exclusive, right and licence to use the Results for the sole purpose of internal research and development.

7. The Recipient acknowledges that the Data may contain some details that constitute personal information and shall ensure that such information is not disclosed and treated in accordance with the Data Protection Act 1998.

8. In addition to its obligations under Clause 7 hereinabove, the Recipient will keep the Data confidential and will not try to identify the relevant participants. Further, and for the purposes of this Agreement, "Confidential Information" shall mean the Data and any information in whatever form relating to the business, products, affairs or finances of the Company or the Recipient that is for the time being confidential to that party. Each Party shall keep confidential all Confidential Information of the other Party and shall not disclose any such Confidential Information, unless expressly permitted by this Agreement or as may be required by law or pursuant to an order made by a court or other authority of competent jurisdiction.

9. The Recipient may receive a request under the Freedom of Information Act 2000 that would require it to disclose information which, under this Agreement, is the Company's Confidential Information. To help protect the Company's Confidential Information, if the Recipient receives a request under the Act, it will notify the Company and will consult with the Company. The Recipient is required to respond to a request under the Act within twenty (20) working days. Accordingly, the Company agrees to respond to the Recipient within five (5) working days after receiving the Recipient's notice if that notice requests the Company to provide information to assist the Recipient to determine whether or not an exemption in the Freedom of Information Act applies to the information requested under that Act.

10. The Company recognizes the necessity of preserving the spirit of free and open inquiry in connection with clinical investigations. The Company agrees that researchers of the Recipient who were engaged in the Research reserve the right to present and publish the Results of the Research at symposia, national or regional professional meetings, in professional journals, or through other means of their own choosing, subject always to the obligations of confidentiality under Clause 8 hereinabove. Such presentations and publications will be co-authored where appropriate by researchers of the Recipient, Imperial College and the Company.

11. For the avoidance of doubt, nothing in this Agreement shall constitute or create an agency, partnership, joint venture or employment or worker relationship between the parties.

12. Each party shall at all times act in good faith towards the other and undertakes not to do anything that would or may bring the other into disrepute or damage its reputation. For the avoidance of doubt, the Data provided hereunder imposes no obligation, express or implied, for the Recipient to purchase, recommend or otherwise support the services and/or products of the Company. The Recipient agrees that the Data provided hereunder do not constitute an inducement to supply or recommend any services and/or products of the Company. Further, the Company will not use the name of the Recipient nor of any of its employees, students, agents or appointees in any press release or product advertising, or for any other commercial purpose, without the prior written consent of the Recipient. For the avoidance of doubt, the Recipient's logo shall not be used in any Company advertising or advertising of any services and/or products of the Company.

13. The Company accepts no liability in connection with the Recipient's use of the Data. The Company does not represent that (i) the Data is of satisfactory quality or fit for any particular purpose; or (ii) use of the Data is free from infringement of third party rights, including intellectual property rights. To the extent permissible by law the Recipient will indemnify and hold the Company harmless for any damages howsoever arising from Recipient's use of the Data.

14. The Company reserves the right to end this agreement at any point and for any reason. The Company will be reasonable and act in good faith in such an occurrence.

AS WITNESS the hands of authorised signatories for the parties on the date first mentioned above.

SIGNED for and on behalf of **DR MOHSSEN CHABOK,** **Imperial College London**	**SIGNED** for and on behalf of **LIFE LINE SCREENING America:**
Name: Mohssen Chabok	Name: Jim Waters
Position: PGt Researcher ICL	Position: Executive Vice-President
Date: 21/05/2015	Date: 21 May, 2015

APPENDIX A

Description of Data

Life Line Screening UK will provide Dr Chabok at Imperial College London with anonymized customer data detailing the results of various cardiovascular screening tests (including aortic diameter, carotid artery stenosis, ankle brachial pressure index and tests for atrial fibrillation). Additionally, customer demographics and other background data (including medical history, use of certain prescription medications and family history) will be made available.

Data are currently available for around 400,000 UK. Such data will be provided in an agreed electronic format to allow analysis by Imperial College London.

APPENDIX B

Description of Research

To explore the point prevalence (by age and gender) of abdominal aortic aneurysms (AAA), significant carotid artery stenosis (CAS), and other screened conditions in those people who have attended Life Line screening.

Additionally, detailed background information provided (including: the use of lipid lowering therapy, blood pressure lowering drugs and anti-platelet agents; smoking status; height and weight; family history and co-morbidities) should allow determination of correlates for AAA, CAS, peripheral vascular disease and atrial fibrillation.

Appendix 2: Ethical Approval for Retrospective Study

Imperial College London

Imperial College Research Ethics Committee

Imperial College London
Room 5L10D, 5th Floor, Lab Block
Charing Cross Hospital
Fulham Palace Road
London
W6 8RF

Tel: +44 (0)203 331 0206 Fax: +44 (0) 203 311 0203

researchethicscommittee@imperial.ac.uk

Mohssen Chabok
Vascular Surgery Department
Hammersmith Hospital
London
W12 0HS

18th June 2014

Dear Mohssen,

Study Title: A retrospective UK & Ireland study of the prevalence of cardiovascular disease among 350, 00 screened British and Irish adults.

ICREC reference: ICREC_14_3_7

The above study was approved by your Head of Department on 11th April 2014 and by the Joint Research Compliance Office on the 18th June 2014.

Under the Imperial College Research Ethics Committee process, a study that has been reviewed by the Joint Research Compliance Office and Head of Division/Department (or Principal), where no significant ethical issues have been identified in the protocol or ethics application, can be approved without requiring it to go to full committee.

Documents
The documents reviewed were:

- ICREC Application form
- Protocol (V1.1 04/06/14)
- Sponsorship and Insurance Form

Yours sincerely,

Gary Roper,
Head of Regulatory Compliance,
Imperial College London

Appendix 3: Ethical Approval for Prospective Study

Imperial College London

Imperial College Research Ethics Committee

Imperial College London
Room 5L10D, 5th Floor, Lab Block
Charing Cross Hospital
Fulham Palace Road
London
W6 8RF

Tel: +44 (0)203 331 0206 Fax: +44 (0) 203 311 0203

researchethicscommittee@imperial.ac.uk

Mohssen Chabok
Vascular Surgery Department
Hammersmith Hospital
Du Cane Road
London
W12 0HS

11th October 2013

Dear Mohssen,

Study Title: An observational study of natural history of cardiovascular diseases..

ICREC reference: ICREC_13_6_2

The above study was approved by your HoD on 10th October 2013 and by the Joint Research Compliance Office on the 11th October 2013.

Under the Imperial College Research Ethics Committee process, a study that has been reviewed by the Joint Research Compliance Office and Head of Division/Department (or Principal), where no significant ethical issues have been identified in the protocol or ethics application, can be approved without requiring it to go to full committee.

Documents
The documents reviewed were:

- ICREC Application form
- Protocol (V1 26/07/13)
- Participant Health Questionnaire
- Participant info sheet (V1 26/07/13)
- Participant letter (V1 03/09/13)
- Consent form (V1 03/09/13)
- Participant annual follow-up questionnaire (V1 03/09/13)
- Participant annual follow-up letter (V1 03/09/13)
- Alternative follow-up letter (V1 03/09/13)
- Friends/ relatives contact info (V1 03/09/13)
- Sponsorship form

Yours sincerely,

Gary Roper,
Head of Regulatory Compliance,
Imperial College London

Appendix 4: Invitation letter

An observational study of natural history of cardiovascular diseases

[PARTICIPANT NAME]
[PARTICIPANT ADDRESS, LINE 1]
[PARTICIPANT ADDRESS, LINE 2]
[PARTICIPANT ADDRESS, LINE 3]
[DATE]

Dr Mohssen Chabok
Dept of Surgery and Cancer
Hammersmith Hospital,
Imperial College London, N12 0HS

Dear [PARTICIPANT],

Life Line Screening UK Ltd is working with the Imperial College London University on a study to explore what risk factors contribute to cardiovascular events such as heart attack and stroke and to assess the contemporary annual risk of cardiovascular events in people without symptom. We would like to know if you would be willing to take part in this study. The study will involve answering a health questionnaire which can be completed in your own time and submitted by post. Then you will be contacted annually for up to 5 years to find out whether you have been well since your last contact. Each task should take you no longer than 20-30 minutes to complete.

If you are interested in taking part, please find enclosed an information sheet, a consent form and the health questionnaire. Should you have any questions, please contact the study coordination centre at the Imperial College London University and we will provide you with further information about the study before you decide. This study has gained ethical approval and it meets all of the necessary research standards.

Please complete the health questionnaire and the consent form and send it back in the prepaid enclosed envelope. If you cannot complete this form yourself, perhaps a friend, relative or carer can help.

Yours Sincerely

Dr Mohssen Chabok
Chief Investigator

Appendix 5: Participant Information Sheet

Participant Information Sheet

Date: 11.04.2014, Version: 1.2

Study title: An observational study of the natural history of cardiovascular diseases

Principle Investigator: Dr M Chabok

Invitation to take part

You are being invited to take part in a research study. Before you decide to partake it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish.

This information sheet explains the purpose of this study and what will happen if you take part. Please contact us if there is anything that is not clear or if you would like more information.

Introduction

Cardiovascular disease (CVD) affects the lives of millions of people and is one of the largest causes of death and disability in this country. Stroke is one of the top three causes of death in England and is a leading cause of adult disability. Within the UK, over 100,000 strokes occur annually and over 300,000 people are living with moderate or severe disability due to stroke. Stroke costs about £7 billion a year. Most strokes are caused by occlusive arterial disease (obstruction in the vessels providing oxygen rich blood), around 15% are due to atrial fibrillation (AF) which is an irregular heart rhythm, and a further 15% or more are associated with carotid artery stenosis (CAS), narrowing of the vessels supplying blood to the brain. Many strokes could be avoided if people with AF and CAS were identified and treated appropriately with the relevant drugs as well as encouraging them to stop smoking. Some younger patients with tight carotid stenosis, who are well treated medically, can avoid future stroke by appropriate carotid intervention.

What is the purpose of the study?

The purpose of the study is to estimate the contemporary prevalence of cardiovascular diseases in the UK and to describe the incidence and prevalence of stroke, mini stroke (TIA), Heart Attack (MI), deaths and intervention repairs for carotid and occlusive arterial disease in a large population. This study will also allow us to obtain reliable information on the age- and sex-specific relevance of tobacco and alcohol consumption, obesity, diabetes and blood pressure as risk factors for different cardiovascular diseases. By following a large

group of participants for 5 years, we will be able to estimate the annual risk of stroke and other CVD events associated with asymptomatic carotid artery stenosis and atrial fibrillation.

Why have I been chosen?

You have been chosen because you have already decided to take part in a cardiovascular screening programme conducted by Life Line Screening and did not have apparent signs of cardiovascular diseases prior to your screening.

Do I have to take part?

Your participation is voluntary. It is up to you whether or not you take part. You do not need to decide immediately. If you wish you may take this information away with you and decide at a later date. If you do decide to take part you will be given this information to keep and will be asked to give us your consent to participate. You are free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive.

What will happen to me if I do take part?

You will be asked to sign a consent form and you will also be asked for your contact details. Your screening results and medical history details will be anonymously included in our research database for analysis. We will follow up for up to 5 years via annual interviews and/or health questionnaires to monitor your health and wellbeing. We will enclose a questionnaire with a prepaid envelope for return to the research office. We will ask you to provide a report of your medical history (including disclosure of all medication you are taking) should you agree to participate. When completing the first questionnaire, you will be asked to provide contact details of your GP, and of one or two friends or relatives (with their agreement), any of whom could be contacted if we lose contact with you. The number of people that need to be recruited for this epidemiological case-control study is 5,200. The researcher will let you know how many participants have been recruited so far.

What do I have to do?

There are no specific requirements for this study and all you need to do is to allow us to include your screening data into our research database and complete a questionnaire annually or alternatively take part in

an annual interview with our research nurse. The time required for completing the form or the interview is about 20-30 minutes. In addition, we seek your agreement to allow your health to be monitored through centrally held medical and other health related records. Such information will be used in an anonymised form by researchers to help improve the prevention, diagnosis and treatment of a wide range of illnesses (including heart disease, strokes and aneurysms).

What are the possible risks and benefits of taking part?

There are little potential risks if you were to participate. We cannot promise the study will help you but the information we get from this study may help improve the early diagnosis of people at high risk of heart disease and stroke. The findings from this study will be reported and published so that a better understanding of cardiovascular disease will be achieved. It will also help us to develop well informed and useful educational materials for people who are thinking about taking these screening tests in the future.

What happens when the research study stops?

When the study stops we will analyse the results. There will be no affect on your care or access to treatment as a result of this study.

What if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the Investigator: **Dr M Chabok, Department of Surgery, Imperial College London, Hammersmith Hospital, W12 0HS, Tel: 0208 383 1541**

The normal National Health Service complaint procedure is also available to you. If you are not satisfied with the response, you may contact the Imperial AHSC Joint Research Compliance Office.

Will my taking part in this study be kept confidential?

If you join the study, all information that is collected about you during the course of the study will be kept strictly confidential. All of your personal information will be held by Imperial College London/Life Line Screening in strict confidence in accordance with the Data Protection Act 1998, and no identifiable

information about participants would be available to anyone outside of Imperial College London/Life Line Screening.

What will happen to the results of the research study?

The results will be published in fulfilment of a PhD degree. The research is registered on clinicaltrials.gov which is a free, public register and if you wish, you can access the results and details of the study. In addition, you will not be identified in any report or publication.

Who has reviewed the study?

All research in the NHS and research institutions are looked at by an independent group, named the Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given the favourable opinion by Imperial College Research Ethics Committee (ICREC-13-6-2, Oct 2013).

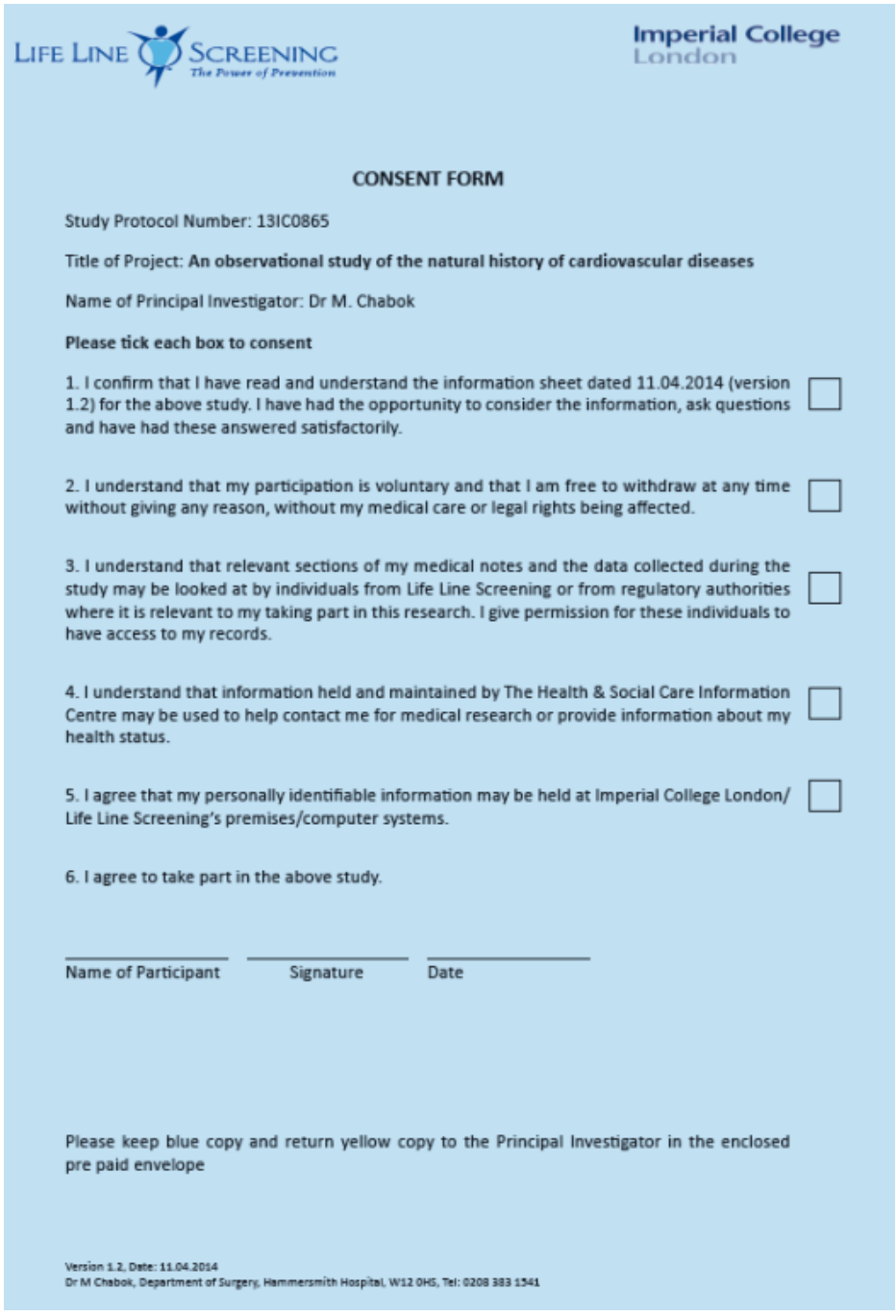
Contact for further information

For questions about your responsibilities or rights as a participant, please contact:

1) Dr M Aslam, Department of Vascular Surgery, Hammersmith Hospital, Tel: 0208 383 1541

2) Dr M Chabok, Department of Surgery and Cancer, Imperial College London, N12 0HS, Tel: 0208 383 1541

Appendix 6: Consent Form



LIFE LINE SCREENING
The Power of Prevention

Imperial College London

CONSENT FORM

Study Protocol Number: 13IC0865

Title of Project: **An observational study of the natural history of cardiovascular diseases**

Name of Principal Investigator: Dr M. Chabok

Please tick each box to consent

1. I confirm that I have read and understand the information sheet dated 11.04.2014 (version 1.2) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and the data collected during the study may be looked at by individuals from Life Line Screening or from regulatory authorities where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I understand that information held and maintained by The Health & Social Care Information Centre may be used to help contact me for medical research or provide information about my health status. ☐

5. I agree that my personally identifiable information may be held at Imperial College London/ Life Line Screening's premises/computer systems. ☐

6. I agree to take part in the above study.

_____ _____ _____

Name of Participant Signature Date

Please keep blue copy and return yellow copy to the Principal Investigator in the enclosed pre paid envelope

Version 1.2, Date: 11.04.2014
Dr M Chabok, Department of Surgery, Hammersmith Hospital, W12 0HS, Tel: 0208 383 1541

Appendix 7: Participants Health Questionnaire

LIFE LINE SCREENING The Power of Prevention

Imperial College London

Participant Health Questionnaire:

An observational study of natural history of cardiovascular

Please be reassured that all of your answers will be treated with absolute confidentiality.

Your Name (please **PRINT**)	
Your **NHS** Number:	
Address (please **PRINT**), if different from that on the letter	
tel & email, if known	

General Questions About You			
1. Please indicate your	**Sex:** ☐ Female ☐ Male	**Date of Birth:** DD/MM/YYYY	**Age:** yrs
2. What is your ethnic group? ☐ White ☐ Mixed ☐ Asian/Asian British ☐ Black /Black British ☐ Chinese ☐ Other			
3. In general, how would you rate your overall health? ☐ Excellent ☐ Good ☐ Fair ☐ Poor			
4. Do you have private healthcare? ☐ Yes, always ☐ Yes, most of the time ☐ Yes, sometimes ☐ No, never			
Lifestyle: Exercise			
5. In a typical week, on how many days did you walk or have physical activities for 10 minutes or more? ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7			
6. How would you describe the intensity of your physical activities? ☐ Light ☐ Moderate ☐ Vigorous			
7. How many times in the last 4 weeks did you do exercises such as swimming, cycling, keep fit? ☐ Once in the last 4 weeks ☐ 2-3 times in the last 4 weeks ☐ 2-3 times a week ☐ 4-5 times a week ☐ Every day			
8. Each time you did exercises such as swimming, cycling, keep fit, about how long did you spend doing them? ☐ 0-15 minutes ☐ 15-30 minutes ☐ 30-60 minutes ☐ 1-1 ½ hours ☐ 1 ½-2 hours ☐ 2-3 hours ☐ Over 3 hours			
Lifestyle: Tobacco			
9. In your lifetime, have you smoked a total of at least 100 times? ☐ Yes ☐ No (Please go to the next section)			
10. Do you smoke tobacco now? ☐ Yes ☐ No			
11. What type of tobacco did/do you mainly smoke? ☐ Manufactured cigarette ☐ Hand-rolled cigarette ☐ Cigars or pipes ☐ None			
12. About how many cigarettes do you smoke/used to smoke on average each day? ☐ less than 5 ☐ 5-9 ☐ 10-14 ☐ 15-19 ☐ 20-24 ☐ 25 or more			
13. How old were you when you first started smoking on most days? Years old			
14. How old were you when you last smoked cigarettes on most days? Years old			
15. Have you tried to give up smoking? ☐ Yes, tried but was not able to stop or stopped for less than 6 months ☐ Yes, tried and stopped for at least 6 months ☐ No			
16. Why did you stop or reduce smoking? (you can select more than one answer) ☐ Illness or ill health ☐ Doctor's advice ☐ Health precaution ☐ Financial reasons ☐ None			
17. Does anyone in your household smoke? ☐ Yes, one member ☐ Yes, more than one member ☐ No			

Version 1.0, Date: 3.09.2013
Dr M Chabok, Department of Surgery and Cancer, Hammersmith Hospital, N12 0HS, Tel: 02083831541

LIFE LINE SCREENING *The Power of Prevention*

Imperial College London

Lifestyle: Alcohol

18. About how often do you drink alcohol? ☐ Daily or almost Daily ☐ 3-4 times a week ☐ 1-2 times a week ☐ 1-3 times a month ☐ Special occasions only ☐ None (Please go to the next section)

19. About how much wine, beer or spirits do you drink on average each week?

Wine (glasses per week)		**Lager/Cider/Beer** (pints per week)		**Spirits** (lots per week)	
☐ none	☐ less than 1	☐ none	☐ less than 1	☐ none	☐ less than 1
☐ 1-3	☐ 4-6	☐ 1-3	☐ 4-6	☐ 1-3	☐ 4-6
☐ 7-10	☐ 11-15	☐ 7-10	☐ 11-15	☐ 7-10	☐ 11-15
☐ 16-20	☐ 21+	☐ 16-20	☐ 21+	☐ 16-20	☐ 21+

20. If you used to drink, why did you stop/reduce drinking alcohol?

☐ Illness or ill health ☐ Doctor's advice ☐ Health precaution ☐ Financial reasons ☐ None

Your Medical History

21. Have you EVER had your blood cholesterol checked? ☐ Yes ☐ No ☐ Not sure

22. Have you had your blood pressure taken in the last 5 years? ☐ Yes ☐ No ☐ Not sure

23. Has a doctor ever told you that you have had any of the following conditions? If yes, what was your age when it was first diagnosed? (you can select more than one answer)

☐ Heart attack ----- years old	☐ Stroke ----- years old	☐ Diabetes ----- years old
☐ Angina ----- years old	☐ TIA or mini stroke ----- years old	☐ High blood pressure ----- years old
☐ Irregular heart rhythm(AF)---- years old	☐ Narrowed leg arteries ----- years old	☐ High blood cholesterol ----- years old

24. Do you regularly take any of the following? (You can select more than one answer)

Medications		Vitamins		Supplements	
☐ Cholesterol lowering medication		☐ Folic acid or folate (Vit B9)		☐ Fish oil (including cod liver oil)	
☐ Blood pressure medication		☐ Multivitamines+/- minerals		☐ Glucosamine	☐ Calcium
☐ Aspirin	☐ Clopidogrel	☐ Vitamin A	☐ Vitamin B	☐ Zinc	☐ Iron
☐ Warfarin	☐ Insulin	☐ Vitamin C	☐ Vitamin D	☐ Selenium	
☐ Gliclazide	☐ Metformin	☐ Vitamin E		☐ None	
☐ None		☐ None			

Your Family History

25. Have/did any of your family members ever suffer from below conditions? (You can select more than one answer)

Your father	Your mother	Your brothers or sisters
☐ Heart disease	☐ Heart disease	☐ Heart disease
☐ Stroke	☐ Stroke	☐ Stroke
☐ High blood pressure	☐ High blood pressure	☐ High blood pressure
☐ Diabetes	☐ Diabetes	☐ Diabetes
☐ High cholesterol	☐ High cholesterol	☐ High cholesterol
☐ Peripheral vascular disease	☐ Peripheral vascular disease	☐ Peripheral vascular disease
☐ None ☐ Do not know	☐ None ☐ Do not know	☐ None ☐ Do not know

Please tick a box to say who filled out this form

☐ Participant ☐ Carer ☐ Friend/relative ☐ Other

Signature:

Your Name (please **PRINT**): Today's date: DD/MM/YYYY

Please check that you have answered every question, and signed and dated the form.

Version 1.0, Date: 3.09.2013

Dr M Chabok, Department of Surgery and Cancer, Hammersmith Hospital, N12 0HS, Tel: 02083831541

Appendix 8: Participants Annual Follow-up Questionnaire

LIFE LINE SCREENING The Power of Prevention

Imperial College London

Participant annual follow-up questionnaire

An observational study of natural history of cardiovascular

We hope you have been well since attending your health screening when you first joined the study, but if not then please tell us.

1. Since you were last contacted, have you had any of the below events?

	No	Yes	If YES, please give the date and name of the hospital you attended.	
			Day / Month / Year	Hospital
Heart attack (MI)			/ /	
Admission to hospital with angina			/ /	
Stroke			/ /	
TIA or 'mini stroke			/ /	
Coronary artery surgery (CABG or "cabbage")			/ /	
Coronary angioplasty (a "stent" or"balloon")			/ /	
Other arterial surgery			/ /	

2. If you have had a stroke, how are you now? (Tick ONE box)

☐ No symptoms from the stroke	Anything else you would like to tell us?
☐ Minor problems, but I can carry out everything I usually do	
☐ A few problems from the stroke, but I can manage without help	
☐ Problems from the stroke, I now need help with things	
☐ Because of the stroke I now need help with most things	

3. If you have had a stroke, which side of your body was affected?

☐ Left ☐ Right ☐ Neither side ☐ Both sides ☐ Don't know

4. Which medications do you take regularly? Please **PRINT** the names and doses of all prescription medications you take regularly (ie, on most days), or state **NOT KNOWN**

Version 1.0, Date: 3.09.2013

Dr M Chabok, Department of Surgery and Cancer, Hammersmith Hospital, N12 0HS, Tel: 02083831541

Thank you very much. Do you have any comments, further information or questions?

Address (please **PRINT**), if different from that on the letter	
tel & email, if known	

Please tick a box to say who filled out this form

☐ Participant ☐ Carer ☐ Friend/relative ☐ Other

Signature:

Your Name (please **PRINT**):

Today's date: / /
Format Day /Month/Year

Please check that you have answered every question, and signed and dated the form.
Please put this form in the prepaid envelope provided (no stamp is needed) to:
Dept of vascular surgery, B block, Hammersmith Hospital, Imperial College London, N12 0NN

Appendix 9: Participants Annual Follow-up Letter

Participant annual follow-up letter

An observational study of natural history of cardiovascular diseases

[PARTICIPANT NAME] [PARTICIPANT ADDRESS, LINE 1] [PARTICIPANT ADDRESS, LINE 2] [PARTICIPANT ADDRESS, LINE 3] [DATE]	Dr Mohssen Chabok Dept of Surgery and Cancer Hammersmith Hospital, Imperial College London, N12 0HS

Dear [PARTICIPANT],

Following your vascular screening conducted by Life Line Screening, you agreed to take part in a national prospective study assessing the contemporary annual risk of stroke, mini-stroke and other Cardio Vascular Disease events in people without symptom. I am now writing to find out how you have been since last year.

I need to know if you have had any kind of stroke or heart attack since then and, if so, whether it still affects you. I hope that you will continue to be part of this study, and I would like to write to you again one year from now.

I would be very grateful if you could set aside some time to answer these questions. It should not take more than 20-30 minutes. Please complete the short form and kindly send it back to the above address. If you cannot complete this form yourself, perhaps a friend, relative or carer can help.

Yours Sincerely

Dr. Mohssen Chabok
Chief Investigator

PS: Further information about this study is available on https://clinicaltrials.gov/.

Appendix 10: Publications

Chabok, M, A Nicolaides, M Aslam, M Farahmandfar, K Humphries, N Z Kermani, J Coltart, and N Standfield. 'Risk Factors Associated with Increased Prevalence of Abdominal Aortic Aneurysm in Women'. British Journal of Surgery 103, no. 9 (1 August 2016): 1132–38. https://doi.org/10.1002/bjs.10179.

Giannoukas, A. D., M. Chabok, K. Spanos, and A. Nicolaides. 'Screening for Asymptomatic Carotid Plaques with Ultrasound'. European Journal of Vascular and Endovascular Surgery 52, no. 3 (1 September 2016): 309–12. https://doi.org/10.1016/j.ejvs.2016.04.013.