Prevalence of diagnosed and undiagnosed cardiovascular disease burden in community dwelling 85+ year olds

Fahad Yousaf

Thesis submitted in partial fulfilment of the requirements for the degree of

Doctor of Medicine

Faculty of Medical Sciences

Institute of Ageing and Health

February 2012

ABSTRACT

Objectives: The prevalence of cardiovascular diseases including heart failure (HF), atrial fibrillation (AF) and peripheral vascular disease (PVD) rises sharply among those aged 85 years and over, who now constitute the most rapidly increasing age group worldwide. Majority of this disease burden remains undiagnosed. Most previous community-based studies of left ventricular (LV) dysfunction and HF included only small numbers in this age group. We conducted a community-based study of 85+ year olds using domiciliary echocardiography, electrocardiography and ankle brachial index (ABI) assessments to estimate the prevalence of LV dysfunction, AF and PVD. We cross-referenced our findings to pre-existing HF, AF and PVD diagnoses present in general practice (GP) medical records to estimate the proportion of undiagnosed cardiovascular pathology. We also assessed to diagnostic performance of NT-proBNP to detect underlying LV dysfunction.

Design: Cross-sectional analysis of data from Newcastle 85+ Cohort Study.

Setting: Primary care, North-East England.

Participants: 427 men and women (60.9% women) aged 85+ years and above, from Newcastle 85+ Study.

Measurements: Assessment was conducted in home setting. 2-D and Doppler echocardiography was performed, with LV systolic and diastolic function graded according to American Society of Echocardiography guidelines. A dyspnoea questionnaire was used to assign New York Heart Association (NYHA) functional severity class. ABI measurement and other measures to assess arterial stiffness including pulse wave velocity and pulse wave analysis were carried out by portable sphygmoCor and vicorder devices. Bloods samples were taken for NT-proBNP levels. Previous diagnoses of HF, AF and PVD were abstracted from the GP medical records.

Results: Normal LV function (ejection fraction greater than 55% and normal/mildly impaired diastolic function) was found in just 37.2% of participants. 48.4% had LV systolic dysfunction and 14.4% had isolated diastolic dysfunction. 66.1% people with

underlying LV systolic or diastolic dysfunction, had symptoms of breathlessness (NYHA II or above). Overall 37.4% of participants had undiagnosed symptomatic significant LV dysfunction (29.5% systolic, 7.9% isolated diastolic). 23.8% of participants with pre existing diagnosis of HF, had no echocardiographic evidence of underling systolic or diastolic dysfunction. Markers of arterial stiffness were not significantly associated with LV dysfunction. Diagnostic performance of NT-proBNP to detect underlying symptomatic or asymptomatic dysfunction was not robust. Prevalence of peripheral vascular disease was 22.1%. 19.0% of participants who had no formal GP diagnosis of PVD had definite PVD on the basis of ABI assessment. Prevalence of atrial fibrillation was 25.5% in the entire cohort. Nearly half (53.2%) of these patients had had no existing GP diagnosis of AF. 87.2% participants with AF were CHA2DS2-VASc score 3 or above. Only 15.6% participants with AF were taking warfarin. In remaining 84.4% participants with AF, who were not on warfarin, only 42.4% participants were taking antiplatelet medications.

Conclusions: Systolic and diastolic LV dysfunction was much commoner in 85+ year olds than most previous studies have suggested, affecting around half of a community-dwelling sample; the majority of cases were symptomatic. Despite a national initiative to improve heart failure management within primary care in England, over 80% of very old people with symptomatic significant LV dysfunction remained undetected. Prevalence of AF and PVD is also much common in that rapidly expanding fraction of population, majority of which remains undiagnosed. There is need to establish effective ways to detect this cardiovascular disease burden in very old population.

Index of Contents

Content Pages

Section 1: Introduction and Literature Review

Chapter 1: Ageing

Chapter 2: Heart Failure and 85+ Year Olds

Section 2: Materials and Methods

Section 3: Results 135

Section 4: Final Summary and Discussion

List of Figures

List of Tables

Acknowledgements

I would like to thank Professor Bernard Keavney, Professor Tom Kirkwood and Dr Joanna Collerton for supervising this project and for providing invaluable guidance and support to me throughout, without which this thesis would not have been possible. Dr Antoinette Kenny and Ms Julie Schuster helped me perfect my echocardiography skill and Mr Crispian Oates helped me how to perform CIMT measurements and I would like to thank them for their assistance. I would also like to thank study research nurses for their hard work and their contribution in performing ECGs, collecting blood samples and arranging for my visits. I would also like to thank Andrew Kingston for assisting me perform statistical analyses.

The encouragement, advice and support of my wife and parents throughout my whole career have been invaluable. In the end I would like to thank all of my study participants for their valuable contribution in this study.

Publications

1- High prevalence of undiagnosed cardiac dysfunction in the oldest old: Findings from the Newcastle 85+ Study.
In: Heart: Annual Conference of the British Cardiovascular Society (BCS). 2011, Manchester, UK: BMJ Group.
http://dx.doi.org/10.1136/heartjnl-2011-300198.98

Following two abstracts were presented in "European Heart Failure Congress 2011" Gothenburg -Sweden (21-24 May 2011)

2- Feasibility of domiciliary echocardiography in the oldest old: the Newcastle 85+ study (Poster Session)
European Journal of Heart Failure Supplements (2011) 10 (S1), S33
http://spo.escardio.org/AbstractDetails.aspx?id=95220&eevtid=46

3- High prevalence of undiagnosed cardiac dysfunction in the oldest old: findings from the NEWCASTLE 85+ STUDY (Moderated Poster Session)
European Journal of Heart Failure Supplements (2011) 10 (S1), S162
http://spo.escardio.org/AbstractDetails.aspx?id=95708&eevtid=46

4- Cardiac dysfunction among the community-dwelling very old: cross-sectional findings from the Newcastle 85+ study (This paper is currently with BMJ for peer review)

Section I

Introduction and Literature Review

Chapter 1: Ageing

The world is experiencing a continuing change in the ageing structure of its population, which has never been witnessed in the history of mankind. In almost every country, the proportion of older people is growing faster than any other age group. This overall shift in population structure towards older ages is termed as "ageing of population". Population ageing has many socioeconomic and health implications for societies.

1.1 Measuring Population Ageing

The aging of the population can be described by various indices. The total head count of elderly people is one way of looking at it. The number of older persons has tripled over the last 50 years and is projected to triple again over the next 50 years. According to the figures released by United Nations in 2007, there were just over 200 million persons aged 60 or over throughout the world in 1950, which has increased about three times to 606 million. Over the first half of the current century, the global population 60 or over is projected to expand by more than three times to reach nearly 2 billion in 2050. [1]

The percentage of people of retirement ages (usually 65 years) is often used to describe population ageing and if this exceeds 8-10% a society is considered relatively old. By this standard, the percentage of elderly people in the United Kingdom stood at 15% in 2006, compared with only 6.1% in 1921 and a projected increase to 23% by the year 2034. [2]

The young-old balance is shifting throughout the world. Another useful indicator to describe this change in young-old balance is the aging index, defined as the number of people aged 65 and over per 100 youths under age 15. The ageing index is projected to triple over the next half century. The ratio of people aged 60 or over to children younger than 15 has increased from 24 per hundred in 1950 to 33 per hundred in 2000. It is estimated that by the year 2050, there will be 101 people 60 years or older for every one hundred children (less than 15 years) in the world. [1] The UK is facing a similar demographic shift. In December 2009 the Office for National Statistics reported that the proportion of the UK population younger than 16 had dropped from 25% in 1971 to 19% in 2008. At the same time, the proportion aged 65 and over had risen to 16% compared to 13% in 1971. This trend is projected to continue. By 2031, 22% of the population will be aged 65 and over compared to 18% aged 16 or younger. [3]

1.2 Growing Number of the "85+ Year Olds"

The most striking feature of this population ageing is the progressive ageing of the older population itself. The "85+ years old" fraction of the population is the fastest growing fraction. At the global level, the 85+ fraction of population is expected to increase 155% between 2005 and 2030, compared to 104% increase in population 65 and above. (Figure 1.1) According to the United Nations the world population of 80 and above will reach almost 379 million by year 2050, having been less than 14 million in 1950 (Figure 1.2). In Europe the number of "85+ individuals" is expected to rise by 181% by 2050. [1] The 85+ year old age group is the fastest growing fraction of the population in the UK. Their numbers have doubled from just over 600,000 in 1983 to 1.3 million in 2008. This trend is projected to continue and by 2033 the number of people aged 85 and over will reach 3.2 million. [4]

1.3 Demographic Determinants Of Population Ageing

Underlying global population ageing is a process known as the "demographic transition" in which mortality and then fertility declines from higher to lower levels. Decreasing fertility along with lengthening life expectancy has changed the age structure of the population in most regions of the world by increasing the median age of the population and altering the young old balance. The role of international migration in changing age distributions has been far less important than the decline in fertility and mortality. [5] There are two main demographic factors causing these demographic changes:

1.3.1 Low / Declining Fertility Rate

Fertility decline is a global phenomenon but is happening at a faster pace in some countries than others, and is the largest contributor to population ageing in the world today. One of the most common measures of fertility is the 'total fertility rate (TFR)' – the average number of children that would be born to each woman if current age-specific fertility rates stayed constant across her childbearing years. We have seen a global fertility (TFR) decline from 5.02 per woman in 1950 to 2.55 per woman in 2005 and the TFR is expected to fall to almost 2.0 per woman in 2050 (Figure 1.3). [1]

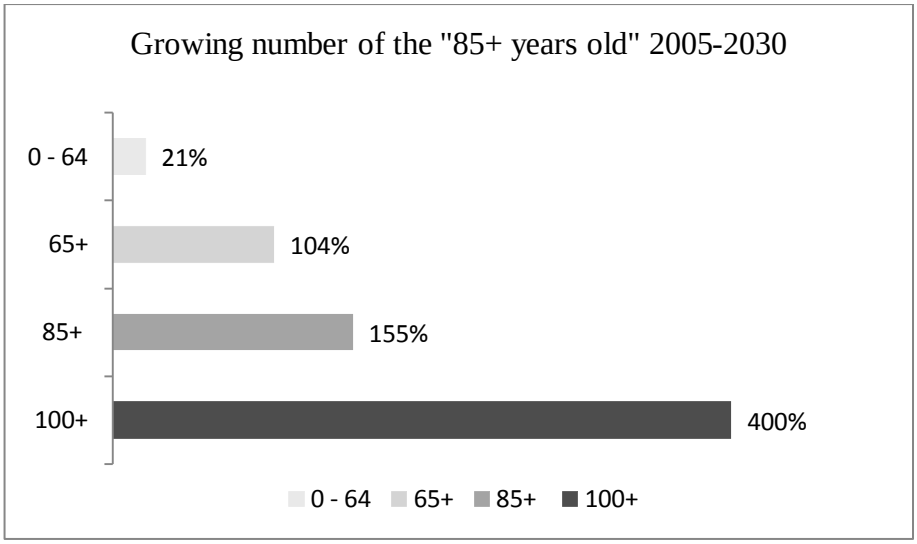


Figure 1.1: Projected increased in global population between 2005 and 2030

(Adapted from Paula J Dobriansky, Why Population Aging Matters: A Global Perspective. National Institute on Aging, ; 2007) [6]

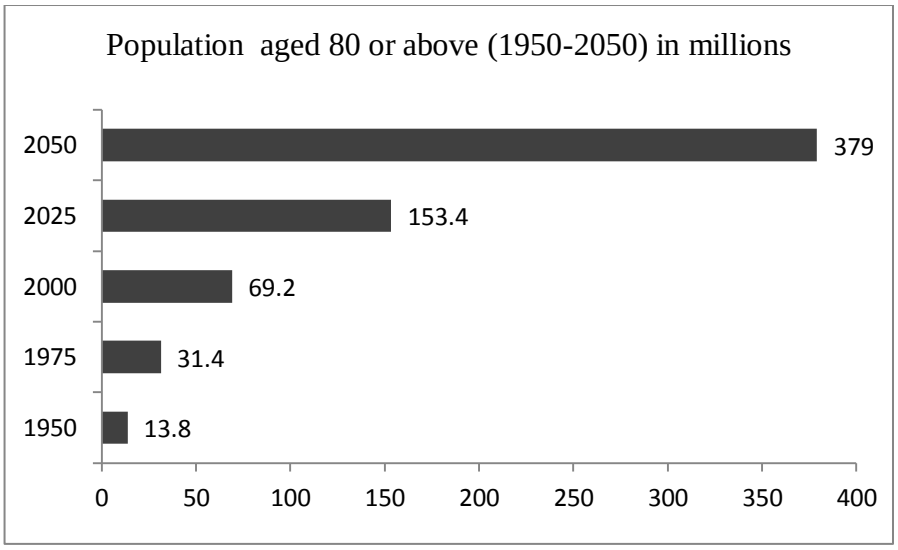


Figure 1.2: Estimated growth of "80+ years old" between 2005 and 2030

(Adapted from United Nations Department of Economic and Social Affairs Population Division. World Population Ageing: 1950-2050) [1]

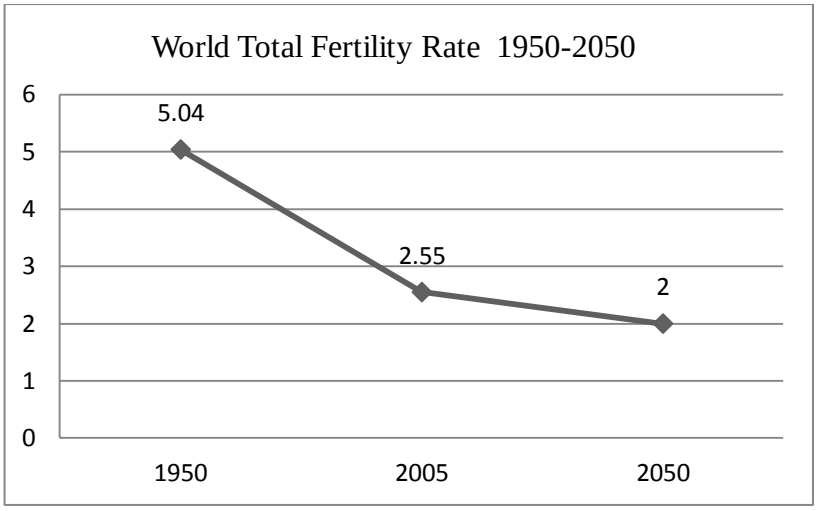


Figure 1.3 : Decline in global total fertility rate between 1950-2050

(Adapted from United Nations Department of Economic and Social Affairs Population Division. World Population Ageing: 1950-2050) [1]

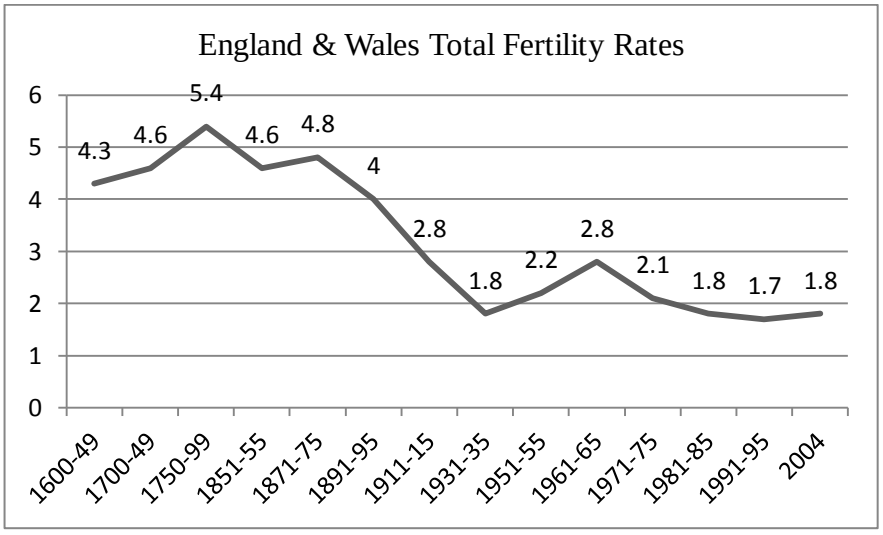


Figure 1.4: Trends in total fertility rate in England and Wales

(Source: E Wrigley & A Schofield The Population History of England 1981.Office of National Statistics)

Women in the UK like other countries are having fewer children than in previous generations. In 1871 the average woman was having 5.5 children but by 1971 this had gradually fallen to 2.1 children and presently it is below 2.0. (Figure 1.4) [7, 8]

1.3.2 Rising Longevity

Life expectancy is the average number of years that a person can expect to live if they experience the current mortality rate of the population at each age. Along with the decline in fertility, the increase in life expectancy as a consequence of declining mortality, especially at older ages, has played an important role in population ageing. In developed countries, where fertility is low for relatively longer periods, population ageing is primarily determined by improved survival at old ages. [9]

According to a United Nation's recent report (2007) life expectancy is increasing globally, although there is a marked variation between developed and developing countries. Overall, globally life expectancy at birth has risen by almost 20 years form 46.6 years in 1950-55 to 66 years in 2000-05 and is expected to increase by another 10 years to 76 years by 2050. This trend is slightly less marked in developed countries than developing countries. In the UK average life expectancy at birth increased from 69.2 years in 1950-55 (66.7 years male, 71.8 years female) to 79.4 years in 2005 (77.2 years male, 81.6 years female). The gain in life expectancy is projected be more marked in older ages, as we have seen an significant and accelerated improvement in the mortality in this group over last 25 years (Figure 1.5). This was probably the reason that official population projections underestimated the size of the elderly population, especially those in the oldest age groups.[10] The increase in the life expectancy at the age of 80 by 2050 is projected as 22% at global level, compared to 18% and 19% at the age 60 years and 65 years respectively. This relative gain in the life expectancy of the "oldest old" is projected to be more marked in the developed regions according to the United Nations. [1] In the more developed regions, average life expectancy at age 80 is projected to increase by 27% by 2050 as compared with 19% at age 60 and 9% at birth. Whereas, an average life expectancy at age 80 in the less developed regions is expected to increase by 28% as compared with 22% at age 60 and 17%at birth (figure 1.6).

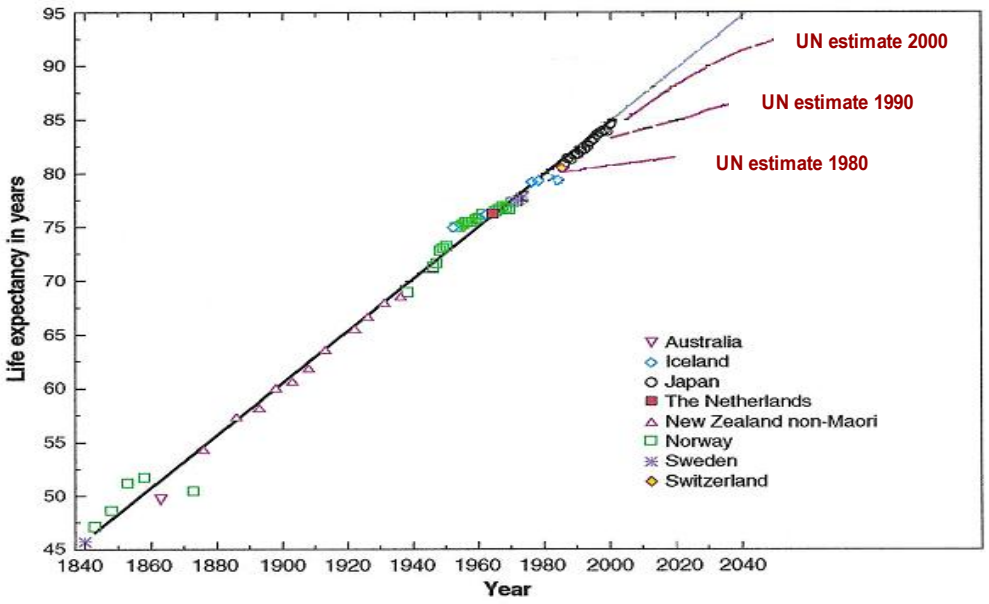


Figure 1.5: Life expectancy from 1840 to the present.

Dotted red lines show UN projection in females life expectancy, which clearly were underestimated the rise in life expectancy especially at older age.

(Adapted from Oeppen J, Vaupel JW. Demography. Broken limits to life expectancy. Science. 2002[10]

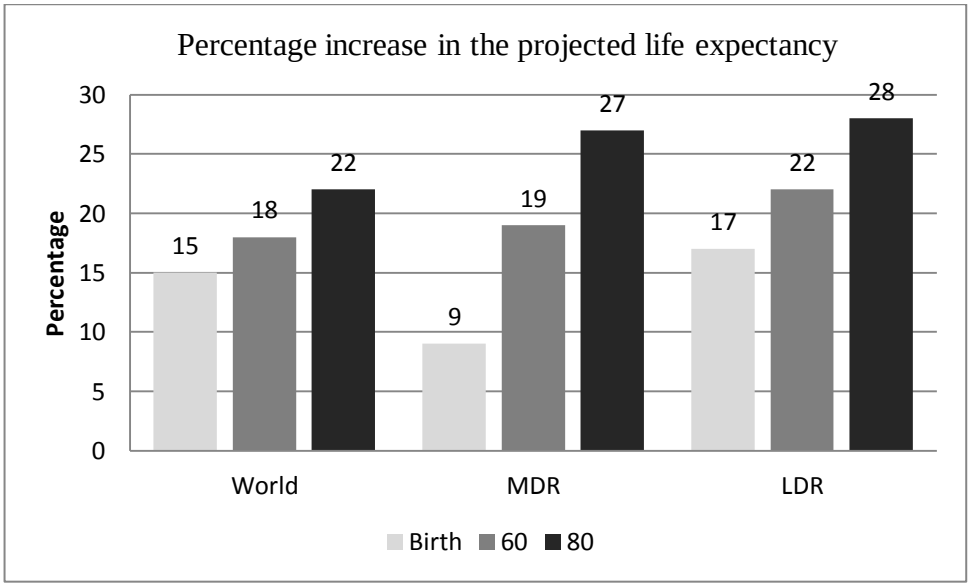


Figure 1.6: Highest gains in life expectancy are seen in the "oldest old" cohort.

(MDR = more developed regions and LDR = less developed region as per UN classification)

(Adapted from United Nations Department of Economic and Social Affairs Population Division. World Population Ageing: 1950-2050) [1]

1.4 Implication of Population Ageing

Population aging has a number of socioeconomic and health implications for a society. On the one hand, it shows "a great triumph of civilization" over disease and injury, which have constrained human life expectancy for thousands of years. [11] On the other, it presents various challenges to public institutions that must adapt to a changing age structure.

As populations age, the prevalence of disability, and burden of chronic illnesses including cardiovascular disease, cerebrovascular disease, malignancies and Alzheimer's disease increase significantly. Some experts raise concerns that mankind may become a "global nursing home". [12]The Health Survey for England (HSE) comprises a series of annual cross sectional surveys and is part of an overall programme of surveys commissioned by the Department of Health and designed to provide regular information on various aspects of the nation's health. Each of these surveys consists of a questionnaire and various anthropometric measurements and is an important source for monitoring population trends in disability over time. Figure 1.7 shows disability prevalence rates per 1000 adults by 5-year age intervals for adults aged 16 and over in the health surveys conducted in 1985, 1995, 1996 and 2001. All four surveys show a similar pattern of increasing disability with advancing age and a marked rise in the "oldest old" group. [13] The prevalence of non-communicable diseases including cardiovascular disease (CVD) also increases with age (Figure 1.8). [14] Cardiovascular diseases (CVD) are the leading cause of death and morbidity worldwide in all population and specifically in the "oldest old". Nearly 40% of all cardiovascular deaths were reported in the oldest old in the US in year 2005 (Figure 1.9). [15] In the US almost 8.6 million deaths were due to CVD in year 2005 and nearly 3.3 million deaths happened in the oldest old age group, which were four times higher than deaths due to malignancies in this age group. CVD is also the leading cause of death in England. In 2004 it claimed over 190,000 deaths (>92,500 IHD and >40,000 stroke deaths) in England and Wales, and 89% of these deaths occurred in people aged 65 and over. [14] In old age although the mortality from coronary heart disease has decreased since the 1970s, the prevalence, incidence and mortality from chronic heart failure has increased (Figure 1.10). [16, 17] In the ageing population, chronic heart failure (CHF) is an increasing public health problem with significant financial implication for healthcare system due to its association with frequent hospitalizations and the need for long-term

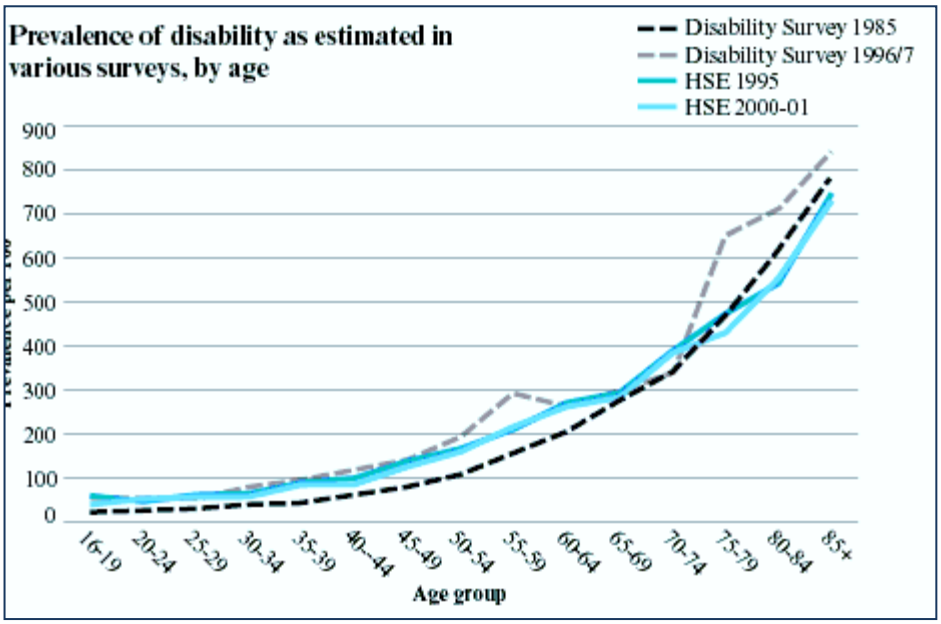


Figure 1.7: Trends in the prevalence of disability by age.

(Adapted from Health Survey for England (HSE) annual report 2001. Department of Health. [13]

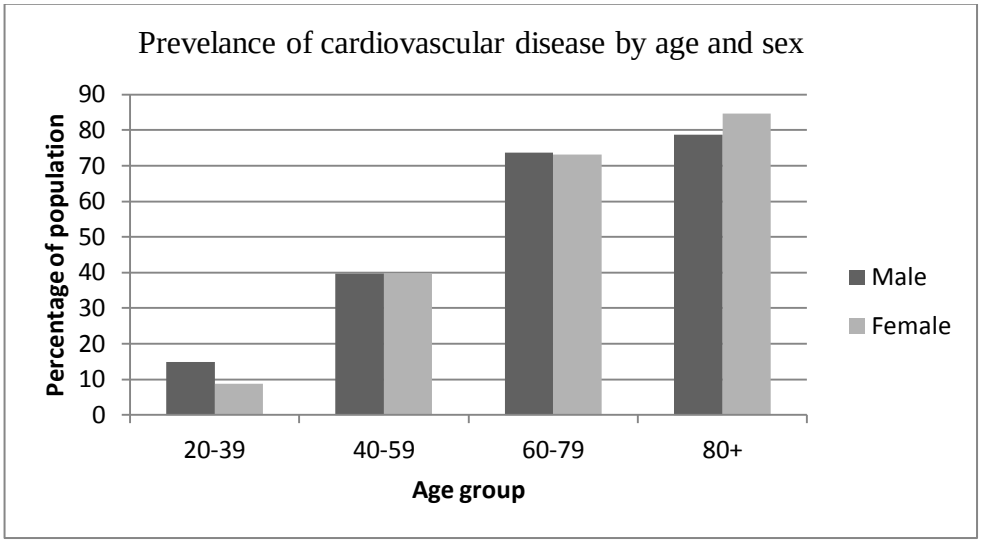


Figure 1.8: Prevalence of cardiovascular diseases by age.

(Source:Heart Disease and Stroke Statistics--2010 Update: A Report from the American Heart Association.) [15]

treatment. [16, 18, 19] Trends of population ageing and increasing burden of disease and disability with age probably explain why healthcare utilization also increases with age. In 2001-02 people of age 65 and over utilized £32 billion, almost 40% of the total health and community health expenditure (HCHE) in England. Total per capita healthcare spending also increased significantly with age. Per capita spending was highest in the "oldest old". The average per capita spending was £646 which rose to more than five times for people aged 85 and over (Figure 1.11). [20]

Life expectancy is continuously increasing with maximum gains in the "oldest old" fraction of the population despite higher prevalence of disease and disability. Health and cardiovascular phenotyping of the 85+ years old, which probably play an important role in the growing life expectancy in this cohort, is not very much studied in detail. The role of age associated stiffness of the arteries and its interplay with cardiac function and development of heart failure is discussed later in the chapter.

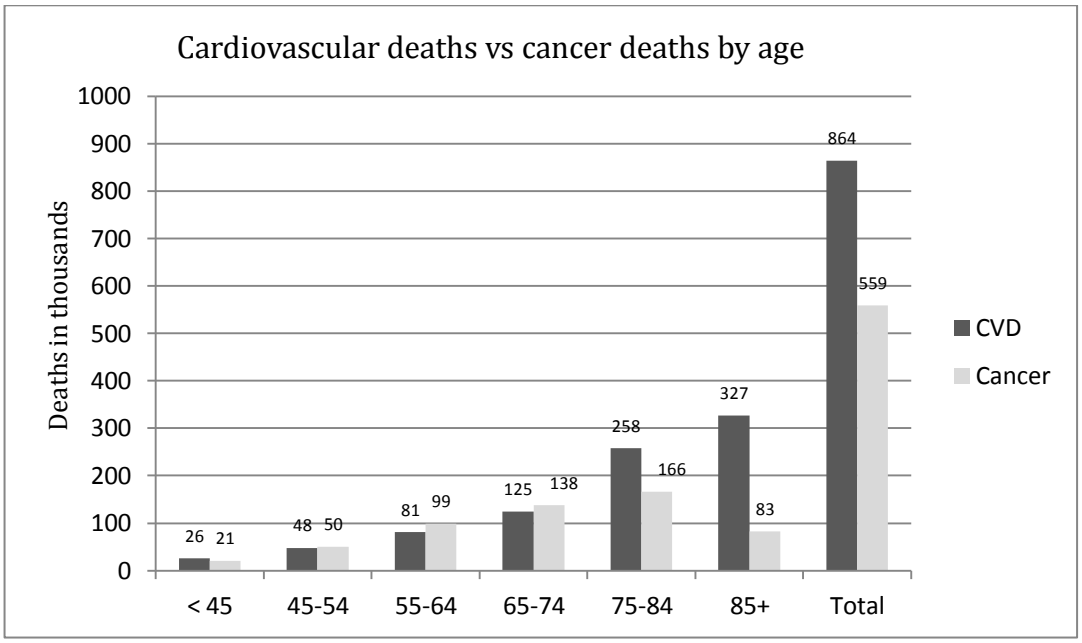


Figure 1.9: Mortality due to cardiovascular diseases by age.

(Heart Disease and Stroke Statistics--2010 Update: A Report from the American Heart Association.[15]

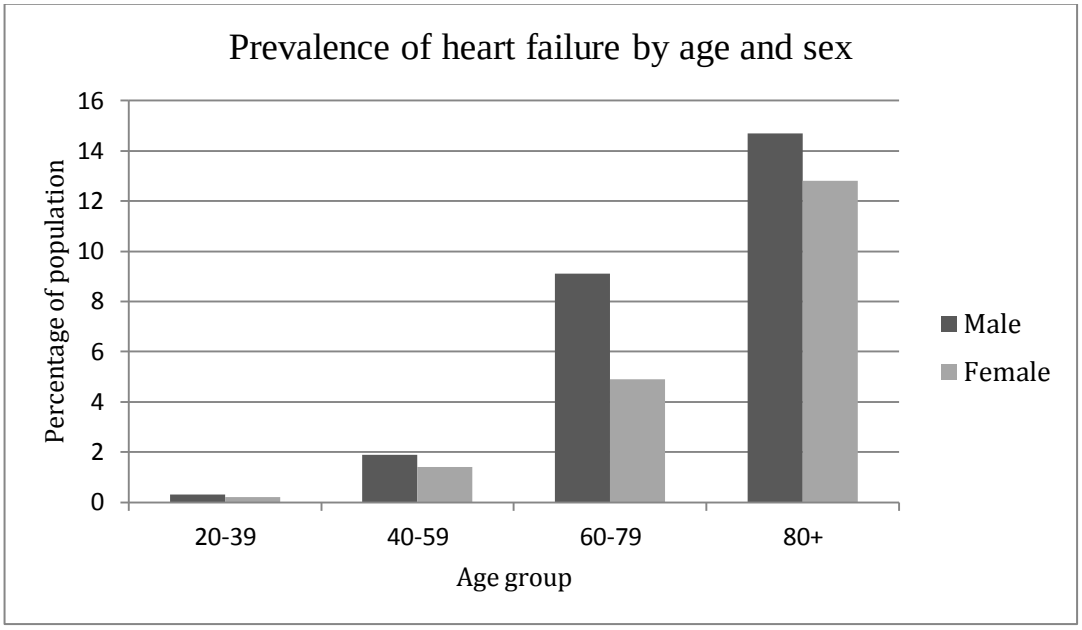


Figure 1.10: Prevalence of heart failure by age.

(Heart Disease and Stroke Statistics--2010 Update: A Report from the American Heart Association. [15]

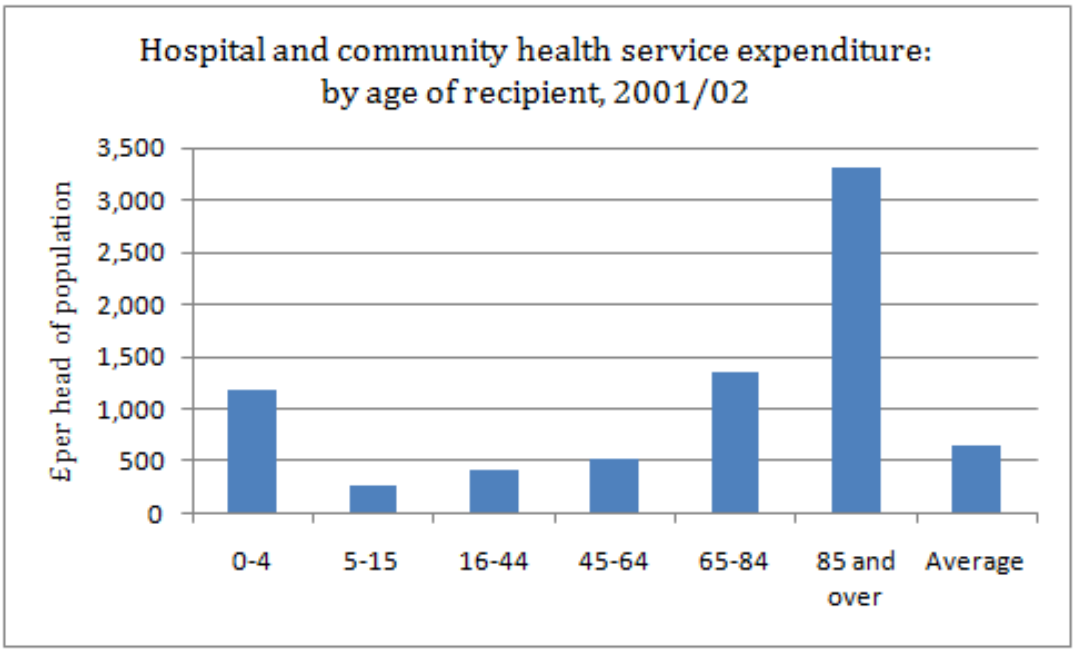


Figure 1.11: Hospital and community health service expenditure by age.

(Office for National Statistics. Hospital and community health service expenditure: by age of recipient, 2001/02: Social Trends 34. 2004) [20]

Chapter 2: Heart Failure and 85+ Year Olds

2.1 Brief Historical Background

The concept of heart failure (HF) is very old and has evolved throughout history. Some of the first descriptions of heart failure scenarios were recorded by ancient Egyptians, Greeks and Romans in 1500 BC. "Hydropsy" or "Dropsy" is a term that was used to describe this condition up through the middle ages. It is synonymous for oedema, a generalized swelling due to the accumulation of excess water. The ancient Egyptian physicians used to treat heart failure by "emptying the system" by bloodletting.[21] Even in the 19th century and early 20th century Southey's tubes were used to drain the fluid from oedematous peripheries. It was an introduction of organomercurial diuretics in 1920 and thiazide diuretics in 1958 that helped to treat fluid overload better by diuresis and ended the era of bloodletting to treat fluid overload. Discovery of X-rays by Rontgen and introduction of cardiac ultrasound in 1950's by Hellmuth Hertz improved the understanding and investigations of the condition.[22] Modern day echocardiography, cardiac catheterization and nuclear medicine have since improved the diagnosis of the patients with heart failure.

There are many definitions of heart failure but one of the most widely quoted definitions in literature was proposed by Eugene Braunwald as " a pathophysiological state in which the heart is unable to pump blood at a rate commensurate with the requirements of the metabolising tissues or can do so only from an elevated filling pressures"[23]

One of the difficulties in defining and diagnosing heart failure is the non-organ specific nature of most features of the condition, and there may be only a few features in the early stage of the disease. This has led modern day physicians to define heart failure as a clinical syndrome characterised by typical features, clinical signs and objective evidence of heart dysfunction. The Task Force on Heart Failure of the European Society of Cardiology has recently published guidelines (2008) on the diagnosis and treatment of heart failure, which require the presence of symptoms (breathlessness at rest or on exercise, fatigue, tiredness, ankle swelling), signs (tachycardia, tachypnoea, pulmonary rales, pleural effusion, raised jugular venous pressure, peripheral oedema, hepatomegaly) and an objective evidence of cardiac dysfunction (cardiomegaly, third heart sound, cardiac murmurs, abnormality on the echocardiogram, raised natriuretic

peptide concentration) [24]. Reversibility of signs and symptoms to appropriate therapy are also desirable but not essential. The echocardiogram is considered the gold standard investigation for the diagnosis of left ventricular dysfunction, the principal anatomical correlate of the clinical syndrome of heart failure.

2.2 Heart Failure with Reduced and with Preserved Ejection Fraction

Heart failure is often caused by 'pump failure' in which the left ventricle fails to pump enough blood into the circulation. This pumping ability of the heart is referred as 'systolic function'. Systolic function of the left ventricle is assessed by an echocardiography and is measured in terms of left ventricular ejection fraction (LVEF). LVEF is defined as the proportion of blood that is pumped into the circulation during systole, received by left ventricle during diastole. The term "systolic heart failure "is used when heart failure develops in the setting of left ventricular systolic dysfunction i.e. reduced LVEF. It is also termed as heart failure with reduced ejection fraction (HFREF).

Heart failure can also develop in the settings of normal or near normal ejection fraction. In this setting failure of the heart to relax during the diastolic phase of the cardiac cycle (diastolic dysfunction) is considered as the principal underlying cause for this clinical presentation of heart failure which is therefore termed "diastolic heart failure". This term was first used by Kessler in 1988.[25] Some other terms have been used in the literature to describe this clinical entity such as heart failure with normal ejection fraction (HFNEF) or heart failure with preserved systolic function (HFPSF). There is no consensus on the cut off values of LVEF for preserved systolic function. In a recent large population based US study in Olmsted County, LVEF 50% or above was used to describe preserved systolic function.[18]

Many recent population based echocardiographic studies from both US and UK have shown high prevalence of asymptomatic LV systolic and diastolic dysfunction, termed as 'preclinical systolic or diastolic heart failure'. Although this condition is not equivalent to heart failure, due to lack of symptoms, it has shown to be an important predictor of heart failure and other cardiovascular events. In the Olmsted County study preclinical systolic dysfunction was associated with increase in all cause mortality when compared with normal LVEF (HR, 8.31; 95%CI, 3.0 – 23.1). Preclinical diastolic dysfunction was also associated with increase in all cause mortality when compared to normal diastolic function (HR10.2; 95%CI, 3.9 – 31.0). [26-29] In the Cardiovascular Health Study the relative risk of heart failure in participants with abnormal baseline preclinical LV systolic or diastolic dysfunction was 2.84 (CI 1.63 to 4.93); in those with prevalent coronary disease it was 2.11 (CI 1.34 to 3.32).[30]

2.3 Epidemiology

Heart failure has been described as a growing and major public health problem in developed countries with ageing populations by many writers.[31, 32]

2.3.1 Prevalence

Prevalence of heart failure is increasing with estimated 15 million patients with heart failure in Europe and almost 5.7 million patients in USA. [24, 33] In UK prevalence of heart failure has been reported as 1-2% in MONICA study.[34] The "Heart of England" screening study assessed the prevalence of heart failure, in the West Midlands, England between 1995 and 1999. Prevalence of heart failure was reported as 3.0% in males and 1.7% in females.[35] Improved survival after acute myocardial infarction, better prevention of coronary artery disease and increasing longevity in the west is thought to be behind overall increase in the prevalence of heart failure. [32] Major evidence on the prevalence of heart failure in the population comes from the large population based cohort studies carried out in United States and Europe. Figure 2.1 summarises the reported prevalence of heart failure and mean age of the participants in these studies. Differences in reported prevalence across different studies is probably due to the mean age of the cohort, number of elderly people in the sample but most importantly the difference in the case definition employed. Heart failure is predominantly a disease of the elderly, with its prevalence increasing progressively with age. There is a sharp rise in prevalence especially after age of 75 years. Large cohort studies carried out in USA and Europe have established that fact. Figure 2.2 summarises the rise of prevalence in elderly cohort. In the Olmsted County study the prevalence of heart failure was 2.7%, increasing from 0.7% in people between aged 45 – 54 years old to 8.4% for 75 years and older.[18] In the Helsinki study where mean age of participants was 80 years, the prevalence of heart failure has been reported as 8.9%. [36]Much has been studied and learnt about the epidemiology of diastolic heart failure especially in last 2 decades. More than half of the diagnosed heart failure patients have been reported to have diastolic heart failure in recent cross-sectional population based echocardiographic studies. [37] In the Helsinki ageing study 72% of the heart failure patients had preserved systolic function.Figure 2.3 summarises the proportion of heart failure with preserved systolic function in major heart failure studies. Variation in the prevalence among various studies might reflect the difference in the definition used for "preserved" heart failure, methods used to assess LV function and mean age of the cohort.

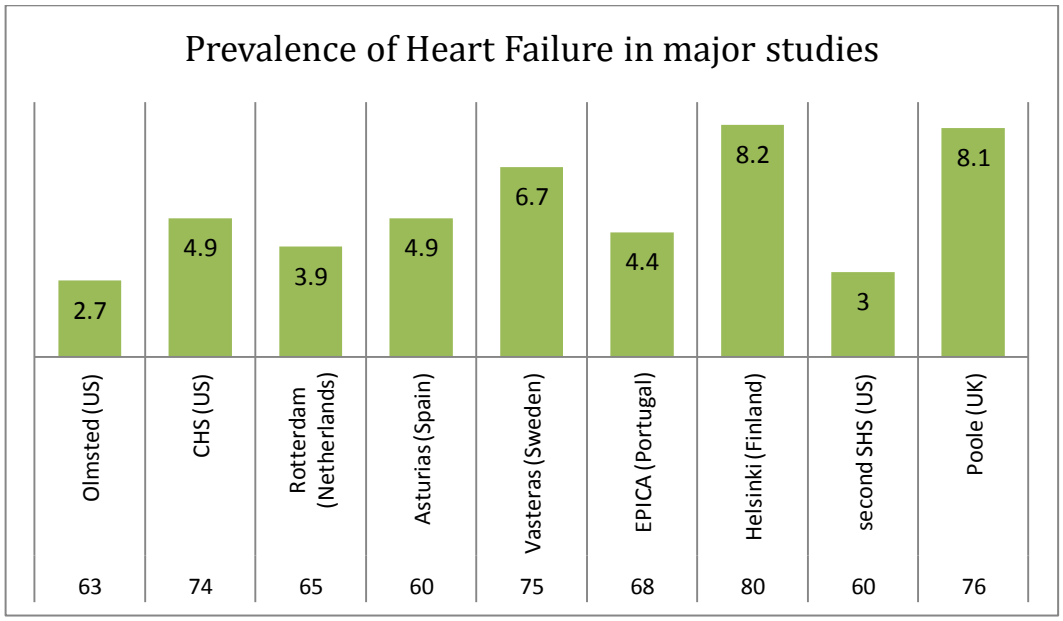


Figure 2.1: Prevalence of Heart Failure in major echocardiographic based studies. [16, 18, 36, 38-43]

(Height of the bars represents prevalence in % & mean age of participants in these studies is given at bottom of the table)

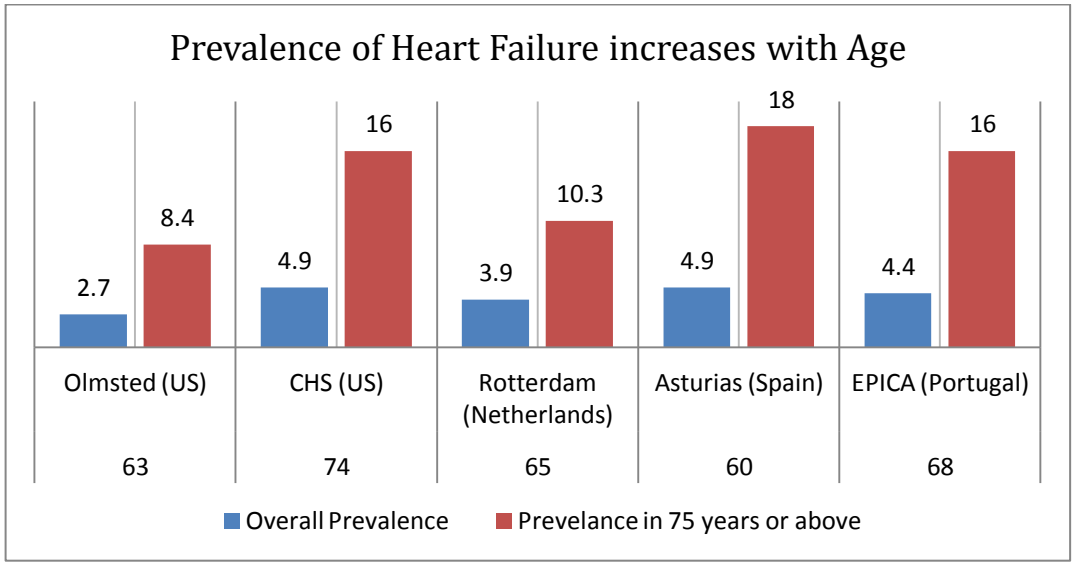


Figure 2.2: Prevalence of Heart Failure increases with age [16, 18, 38, 39, 41]

(Blue bars represent overall % prevalence of heart failure and red bars represent % prevalence in participants of 75 years or above age. Mean age of the cohort is given at the bottom of the figure)

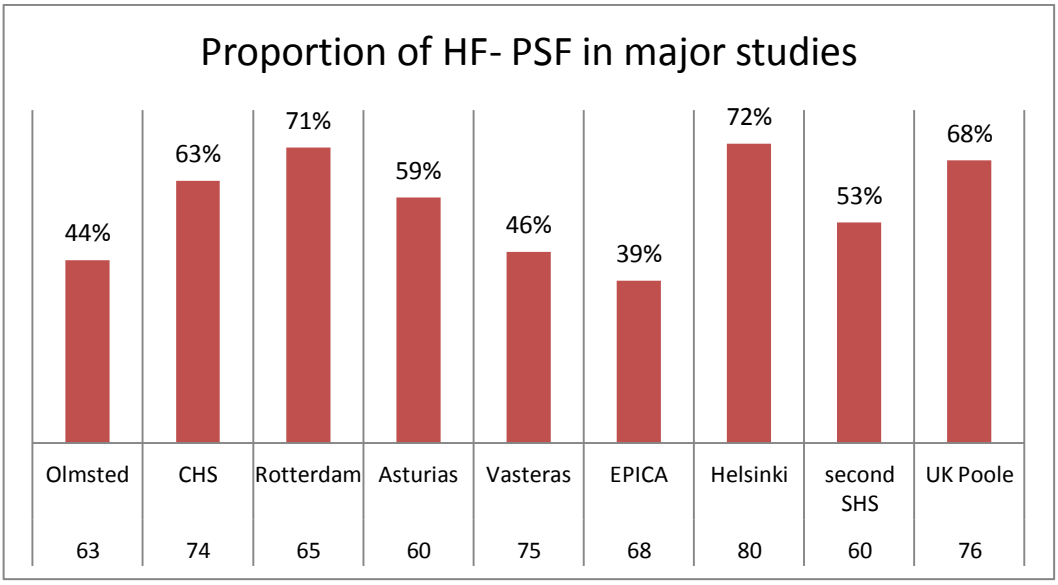


Figure 2.3: Proportion of heart failure with preserved systolic function in major population based echocardiographic studies. [16, 18, 36, 38-43]

(Height of the bars represents prevalence in % & mean age of participants in theses studies is given at bottom of the table)

2.3.2 Incidence

Relatively less information is available about the incidence of heart failure. Again difference in methodologies between studies makes comparison difficult.

In the Framingham heart study (US) the annual incidence of heart failure was 0.2% in women and 0.3% in men aged 50-59 years, rising to 2.2% in women and 2.7% in men aged 80-89 years. [44]

In Rotterdam (Netherlands) the incidence of heart failure increased from 0.25% per annum (age 55-64 years) to 4.4% per annum in aged 85 years and above. [17]

In the Hillingdon heart failure study (UK) the annual incidence of heart failure increased from 0.1% in women and 0.2% in men aged 55-64 years old to 1.0% in women and 1.7% in men aged 85 years and over. [45]

As noted, the overall incidence of heart failure was higher in men than women.

There is less data available in the literature about the incidence of diastolic heart failure. In the Olmsted county study 216 new cases of heart failure were reported in the year 1991. Of these 63% of patients had preserved systolic function. Patients with preserved systolic function were female (69% vs 41%) and older (78 vs 74 years). [18]

2.3.3 Aetiology and risk factors

There are many conditions that can cause heart failure including coronary artery disease (CAD), hypertension and valvular heart disease but, coronary artery disease is the most common initiating cause in almost 70% of the patients with heart failure.[24].

Table 2.1 lists the major causes of heart failure. It is difficult to be certain of a primary aetiological factor when multiple conditions co-exist.

Table 2.1: Aetiology of heart failure

- Coronary artery disease
- Hypertension
- Valvular heart disease
- Cardiomyopathies
- Tachyarrhythmias
- Non cardiac causes like anaemia, thyrotoxicosis, pulmonary hypertension etc

In the Framingham heart study (US) almost 53% of heart failure patients were reported to have ischemic aetiology. [44] In the Bromley heart failure study (UK) 52% of heart failure patients had an ischemic cause, which was established by using myocardial perfusion scan and coronary angiography for establishing the diagnosis.[46]

Risk factors for the development of HF have been examined by various studies, [17] which include hypertension, diabetes mellitus, advancing age, obesity, renal failure and COPD.

The Framingham heart study data suggests that hypertension was a very common risk factor in the HF patients. [44] Hypertension, diabetes, coronary artery disease, advancing age and obesity are common risk factors for both systolic and diastolic heart failure. However, in diastolic heart failure hypertension and in systolic heart failure coronary artery disease were more common risk factors.[47]

2.3.4 Prognosis

The survival after the diagnosis of HF, although improving with the advent of new medications, remains poor across the globe. Heart failure mortality rates are in excess of many common cancers (breast, colon and prostate).

Long-term prospective data from 44 years follow-up from the Framingham heart study (US) and 20 years follow-up of its off-spring cohort suggest high mortality from heart failure with 80 % of men and 70% of women under the age of 65 years diagnosed with heart failure dying from it within 8 years. In men after the diagnosis of heart failure mortality rates at one-years, five-year and ten-year were 43%, 75% and 89% respectively. In women the corresponding mortality rates at one, five and ten years were 46%, 62% and 79%. [33]

The Olmsted County study reported 1 year mortality from heart failure in men as 21% and 17% in women, and 5 year mortality was 50% in men and 46% in women. [17] This slightly better survival in The Olmsted county study might be due to the fact that patients were not hospitalized, implying that their symptoms were less severe.

In the Hillingdon heart failure study (UK) median follow-up time was 16 months (range, 6-26 months) and total 220 incident cases of heart failure (118 men, 102 women) were identified. During follow-up period 90 people died with overall 6, 12 and 18 months mortality of 30%, 38% and 43% respectively.[48]

In Rotterdam study median follow-up time was 7.1 years and total 725 incident cases of

heart failure (335 men, 390 women) were identified. Survival at one year of diagnosis of heart failure was 63%, 51% at two years and 35% at five years, with no significant difference between men and women (p=0.15). [49]

Mortality associated with systolic heart failure in population based studies in general has been higher than associated with diastolic heart failure. In recently published meta-analysis mortality among patients with diastolic heart failure was half that observed in those with systolic heart failure. In this meta-analysis 17 studies were included with 24501 patients (68% males, mean age 67 years) with heart failure. 38% patient (n=9299) died over a mean follow-up period of 47 months. LV systolic function was assessed by echocardiography in 16 studies. Definition of HF-PSF varied in the studies from LVEF 40-55%. Overall, 2468 patients died among the 7688 patients with HF-PEF compared with 6831 deaths among the 16 813 patients with HF-REF. Patients with HF-PEF had an OR for all-cause death of 0.51 (95% CI: 0.48, 0.55) compared with those with HFR-EF. [50]

Many determinants of prognosis in heart failure have been identified and were highlighted a in recent publication of Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology.[24] Major powerful predictors of poor prognosis include: advancing age, NHYA class III-IV, low LVEF, Hyponatraemia, markedly elevated plasma BNP and low peak VO2.

2.3.5 Healthcare burden

The cost of chronic health care in developed countries is rising significantly. Recently published data has suggested 4 times increase in total healthcare spending in US since 1989. In US total cost for HF in 2009 was $37.2 billion.[33] In European countries >2% of total healthcare spending is related to HF management and 70% of this cost is related to inpatient admissions.[24] In the UK heart failure management is estimated to cost NHS £625 million every year and over 60% of this cost is related to hospital inpatient care.[51]

2.4 Major Echocardiography Based Heart Failure Studies

2.4.1 The Olmsted County Study

Redfield et al carried out a cross sectional study of 2042 randomly selected residents of Olmsted County, Minnesota (US), aged 45 or older from 1997 to 2000.[29] Echocardiography was carried out in hospital. Systolic function of left ventricle was assessed by eyeball method, m-mode and biplane method. Diastolic function was assessed by using mitral valve inflow doppler velocities and tissue doppler velocities of mitral valve annulus. LVEF was available by eyeball method for 99% (n=2036) participants, by biplane method for 79.2% (n=1617) and by m-mode method for 78.0% (n=1593) participants. Diastolic function was classifiable as normal or abnormal (mild, moderate, severe) in 1779 (87.1%) participants. Diagnosis of heart failure was confirmed from hospital medical records using Framingham Criteria for the clinical diagnosis of congestive heart failure. [52] Mean (SD) age of the participants was 62.8 years (10.6) with only 290 participants aged 75 or above. The prevalence of heart failure was reported as 2.6% (95%CI, 1.9% - 3.3%). 44% of these people had HFPSF. The overall prevalence of LVSD (LVEF <50%) was 6.0% (95%CI, 5.0% - 7.1%), and this was higher in males than females ($p<0.001$). 20.8% (95% CI, 19.0%-22.7%) had mild, 6.6% (95% CI, 5.5% - 7.8%) had moderate, and 0.7% (95% CI, 0.3% - 1.1%) had severe diastolic dysfunction with 5.6% (95% CI, 4.5% - 6.7%) having moderate or severe diastolic dysfunction with normal LVEF. Prevalence of preclinical systolic dysfunction (LVEF <50%) was 4.9% (95%CI, 5.6% - 8.0%) and preclinical diastolic dysfunction (moderate-severe) was 16.5% (95%CI, 12.6% - 20.9%). Half of the participants with an LVEF <40% or with moderate to severe diastolic dysfunction did not had a validated diagnosis of heart failure.

2.4.2 The Cardiovascular Health Study

This major multi-center study recruited community –dwelling participants (n=5201, 43% males, 57% females) aged 65 or above from four US states (Forsyth County, North Carolina; Sacramento County, California; Allegheny County, Pennsylvania; and Washington County, Maryland).[53] Mean (SD) age of the participants was 73.3 (5.8) years for males and 72.4 (5.4) years for females. Echocardiography was carried out in hospital based centre. Systolic function of left ventricle was assessed by eyeball method and m-mode method. Diastolic function was assessed by using mitral valve

inflow doppler velocities. Heart failure was defined as self-report at baseline and later confirmed by medical records or heart failure medication. LVEF by m-mode method was unavailable in 1/3rd of the participants. Doppler mitral inflow measurements were available in 97% of cohort. The prevalence of heart failure was reported as 8.8 %, 55.0% of these normal LV systolic function (LVEF>55% on eyeball assessment).[54] Among women, 67% of participants with heart failure had normal systolic function versus 42% in men (p <0.001).[54]

2.4.3 The Helsinki Ageing Study

Kupari et al studied 501 randomly selected participants from Helsinki (Finland), aged 75 years or above (only 136 participants were 85 years or above). These participants underwent clinical examination by a cardiologist, chest X-ray (CXR) and 2D echocardiography. Heart failure was diagnosed in the presence of three out of four following criteria: (i) history of breathlessness, (ii) signs of HF (third heart sound, raised neck veins or palpable hepatomegaly) on physical examination (iii) presence of pulmonary venous congestion on CXR and cardiomegaly on CXR (cardio-thoracic ratio >0.55). LV systolic dysfunction was defined as fractional shortening (FS) < 0.25 (on m-mode measurements). HF-PSF was defined as fractional shortening > 0.25 and diagnosis of HF. Investigators reported prevalence of HF as 8.2%, 72% of these people had normal LV systolic function (FS >0.25). Prevalence of HF was slightly more (10.2%) in 85+ years old. Diastolic function was assessed by measuring mitral inflow velocities by doppler, but was not used to define diastolic heart failure. [55]

Regional wall motion of LV was not assessed before LV systolic function assessment, which could potentially lead to inaccurate measurement of LVEF or fraction shortening by m-mode assessment method.

2.4.4 The Rotterdam Study:

Mosterd et al recruited 5540 participants resident in Rotterdam (Netherlands) aged 55 years or above (mean age 65 years, only 29 participants 85+ years). Participants were interviewed at home and subsequently examined for signs and symptoms of heart failure at the research centre. In 2823 participants echocardiography was performed. LV systolic function was measured by m-mode method. In 19.7% of the participants m-mode measurements were inadequate due to poor echo windows (raised BMI or COPD). Heart failure was diagnosed by a physician in the presence of signs and

symptoms of HF. LV systolic dysfunction was defined as fractional shortening < 0.25. The overall prevalence of heart failure was 3.9% (95%CI, 3.0±4.7) and did not differ between males and females. LV systolic dysfunction (fraction shortening < 0.25) was 5.5% (95%CI, 4.1±7.0). 71% of the peoples with HF had normal LV systolic function. [16]

2.4.5 The ECHOES Study:

The Echocardiographic Heart of England Screening Study (ECHOES) was carried out in 16 general practices of the West Midlands region of England between 1995 and 1999. [35] Out of 6162 participants of the study, 3850 participants were randomly selected for the cardiac substudy. Mean (SD) age of the participants was 61 (10) years. Only 66 participants were 85 years or above. Participants were assessed by history and examination, electrocardiography, and echocardiography, which were carried out in a research centre. Heart failure was diagnosed by a specialist panel in accordance with the European Society of Cardiology (ESC) criteria.[56] LV systolic dysfunction was defined as LVEF < 40%. Heart failure was seen in 2.3% of the participants (95%CI, 1.9-2.8). Prevalence of heart failure was increased to 21.1% (10/66) in people aged 85 years or above. The overall prevalence of LVSD (LVEF <40%) was 1.8% (95%CI, 1.4 – 2.3), which rose to 3.6% in those aged 75 years or above. 43% of the people with LVSD had no symptoms of breathlessness (NYHA I). 45.6% of participants with heart failure had LVEF > 50%. [35]

2.4.6 The WHO MONICA Projects:

The MONICA (Multinational **MONI**toring of trends and determinants in **CA**rdiovascular disease) Project was established by WHO in the early 1980s in many Centres around the world to monitor trends in cardiovascular diseases, and to relate these to risk factor changes in the population over a ten year period. The Glasgow MONICA study and the Augsburg MONICA study are two important cross-sectional echocardiographic surveys that looked at the prevalence of LV systolic and diastolic dysfunction in general population. [34, 57]

The Glasgow MONICA study was carried out in 1997, in Glasgow (UK). It was a cross-sectional study of randomly selected 1640 participants aged 25-74 years. Participants completed a detailed questionnaire detailing current medication, history and symptoms of breathlessness. ECG and echocardiogram was performed in a research centre. LV

systolic function was assessed by biplane Simpson's method, which was measureable in 89.5% (n=1467) of participants. Definite LV systolic dysfunction was defined as LVEF ≤ 30%. Definite LVSD was present in 2.9% of the participants (males 4.0%, females 2.0%). Overall 113 (7.7%) participants had LVEF 35% or lower and 77% among those had no symptom of breathlessness. Diastolic function of LV was not assessed in this study. [34]

The Augsburg MONICA study was carried out in 2001, in Augsburg (Germany) to determine the prevalence of diastolic function abnormalities in the population. It was a cross-sectional study of randomly selected 1678 participants; aged 25-75 years (mean age, 51±14). LV systolic function was assessed by m-mode method and LV diastolic function was assessed by measuring mitral inflow doppler velocities including E/A ratio and IVRT (isovolumetric relaxation time). LV systolic dysfunction was defined as LVEF <45%. In this study validated symptoms score for the heart failure was not available. Echocardiography was available in 85.5% (n=1418) of the cohort. People with LVEF <45% (n=19, 2.3%) were excluded from the diastolic function analysis as those were not considered to have isolated diastolic abnormalities. Diastolic abnormalities were defined as proposed by the European Study Group on Diastolic Heart Failure. [58] According to the study group, diastolic abnormalities was considered to be present when $E/A_{<50years}$ was < 1.0, or $E/A_{>50years}$ was <0.5, or $IVRT_{<30years}$ was >92 ms, or $IVRT_{30\text{-}50years}$ was >100 ms or $IVRT_{>50years}$ was 105 ms in the presence of Preserved LVEF (LVEF ≥45%). Diastolic dysfunction was defined as echocardiographically derived diastolic abnormalities in the presence of diuretic therapy and/or left atrial enlargement (LA diameter > 45mm). Based on the cut-points, they identified 141 individuals with diastolic abnormalities (89 with prolonged IVRT, 68 with decreased E/A ratio and 8 people showed both prolonged IVRT and decreased E/A ratio). The overall prevalence of diastolic abnormalities was 11.1% (13.8% in males and 8.6% in females) and diastolic dysfunction was 3.1% (3.9% in males and 2.3% in females). Despite using age adjusted cut-points for diastolic abnormalities, the probability of diastolic abnormalities increased with age. In males it increased from 9 to 21% ($p<0.03$) and in females it increased from 5 to 14% with age ranges from 25 to 75 years. [57]

2.4.7 The Danish Study:

In 2001 Neilsen et al carried out a cross sectional study to estimate the prevalence of

heart failure and LV systolic dysfunction in the general population. They randomly selected a cohort aged 50 years and above (n=2158) registered with three general practices in Copenhagen. GP records and hospital notes were reviewed for any cardiac history. A medical questionnaire was sent to all eligible participants asking about shortness of breath, angina, any previous treatment or hospitalisation for heart trouble. On the basis of screening information participants were classified into one of three groups: Definite heat disease (Ischaemic heart disease, atrial fibrillation, and hypertension or valvular heart disease), suspected heart disease (pacemaker, cardiomegaly on CXR, paroxysmal supraventricular tachycardia or pulmonary embolism) and no apparent heart disease. People with signs and symptoms of heart failure were classified by a primary care physician using the modified version of the Boston index (score ≥ 5 points). [59] LV systolic function was measure by using m-mode method. LV systolic dysfunction was defined as a fractional shortening <26.0 or WMSI (wall motion score index) score ≤ 1.5. In the 38% (n=48) where m-mode measurements were unattainable WMSI method was used to assess LV systolic function. LV diastolic function was assessed by measuring mitral inflow doppler velocities including E/A ratio and IVRT and DT (deceleration time). Diastolic dysfunction was defined as two or more of three abnormal mitral inflow doppler velocity parameters (E/A ratio < 0.5, IVRT > 1.0, DT >0.224 sec).

The study population comprised of 2182 people among whom only 401 were > 80 years of age. Over all response rate for the screening questionnaire was 86% in people < 80 years of age, while only 48% (191 of 401) for people ≥ 80 years. Out of 357 people found to have some evidence of heart disease, only 126 (35.3%) people underwent echocardiography. People were excluded from echocardiography as they lived in nursing homes (n=38), declined the test (n=32), did not respond (n=56) or were unable to attend due to medical or physical disability. Of those dropping out 47% were aged 80 years and above.

The overall prevalence of heart failure in people aged 50 years and above was 6.5%, which increased to 11.9% in people aged 80 years and above. The proportion of heart failure with preserved systolic function (HF-PSF) in patients <70 years of age was 57 % as apposed to 75% in patients ≥ 70 years of age (p<0.0001). [60]

2.5 Pathogenesis

2.5.1 Pathogenesis of Heart Failure with Impaired Systolic Function

According to the current understanding it develops due to complex interplay of both beneficial and harmful affects of endogenous hemodynamic and neurohormonal mechanisms.

Haemodynamic Remodelling

Impairment of LV function and a subsequent fall in the cardiac output plays a central role in the pathophysiology of HF. Myocardium can be damaged by various cardiac insults including coronary artery disease, hypertension, cardiomyopathies, severe valvular heart disease and cardiotoxic agents. However most commonly myocardial injury especially in >50 years old, is related to myocardial infarction leading to impaired LV systolic contraction. This impairment of LV systolic contraction leads to chain of compensatory mechanisms to maintain cardiac output. These compensatory mechanisms are initially beneficial but later these overshoot or become exhausted leading to development of heart failure. [61] Myocardial damage impairs the ability of the LV to pump enough blood in the circulation leading to increased residual LV diastolic LV volume. This leads to increased LV wall stress. The myocardium responds to this increased wall tension by Frank-Starling principle by dilatation of LV and increasing preload.[62] This compensatory mechanism of stretching and dilatation is initially beneficial but progressive dilatation leads to thinning, necrosis and fibrosis of LV wall, restricting its ability to normalize stress. [63] This leads to an increase in left ventricular end diastolic pressure (LVEDP). Prolonged elevation of LVEDP leads to an increased left atrial (LA) pressure and dilation which in turn causes pulmonary capillary hypertension, causing pulmonary oedema. Over period of time pulmonary vascular remodelling causes pulmonary hypertension leading to increased right ventricle (RV) after load. The right ventricle deals with this increased pressure in a similar way and when RV decompensates, right atrium and systemic venous pressures rise causing peripheral oedema and characteristic features of right heart failure.

Neurohormonal Activation

Along with left ventricular haemodynamic remodelling several neurohormonal compensatory mechanisms also become activated to maintain cardiac output. Activation of the sympathetic nervous system with increased release of noradrenaline leads to increased heart rate, increased force of contraction and peripheral vasoconstriction.

Again this compensatory response is initially beneficial to restore cardiac output but prolonged activation exerts harmful effects. Noradrenaline release also activates renin angiotensin aldosterone system (RAAS), leading to arterial and venous constriction (increased preload and afterload) increased salt and water retention and further noradrenalin release. Angiotensin II acts both locally and systemically and leads to vasoconstriction in addition to some other effects as well. It promotes vasoconstriction, stimulates aldosterone and anti diuretic hormone (ADH) production, promotes growth factors leading to hypertrophy of vascular endothelium and cardiac fibrosis (increased cardiac fibroblast production) by acting on AT1 receptors while activation of AT2 receptors leads to cellular apoptosis. Apart from salt and water retention, aldosterone can also cause a loss of magnesium. Due to its steroid structure, it can also stimulate fibrosis by collagen production. This activation of the RAAS finally becomes maladaptive and results in fluid overload.[64] Apart from RAAS and noradrenaline, vasoconstriction is also caused by locally active endothelin produced by vascular endothelium further increases the left ventricular wall stress leading to increased atrial and ventricular pressures.[65] In response to atrioventricular stretch natriuretic peptides like ANP and BNP are released to counter the effects of noradrenaline. These natriuretic peptides also have direct vasodilator and natriuretic effects to reduce haemodynamic load on the heart.[66] However prolonged atrioventricular wall stress causes depletion of these natriuretic peptides and this normal compensatory response is blunted in heart failure.[67] High concentrations of noradrenaline and angiotensin also have direct toxic effects on myocardial cells leading to progressive cardiac dysfunction. It is also postulated that these activation of these neurohormonal responses cause release of pro inflammatory cytokines (interleukin 6, TNF alpha). These cytokines also increase production of increased oxygen free radicals. These cytokines and oxygen free radicals are involved in endothelial dysfunction by inhibiting nitric oxide production by vascular endothelium. [68] All these events lead to unopposed vasoconstriction and vascular dysfunction which in turn increases LV wall tension by affecting afterload. This profound neurohormonal activation, inflammatory activity and free radical production have been implicated as a major cause of the vascular dysfunction seen in the heart failure syndrome.

It is now believed that neurohormonal imbalance and abnormal haemodynamic remodelling are central in the progression of heart failure.

2.5.2 Pathogenesis of Heart Failure with Preserved Systolic Function

Pathophysiology of heart failure with preserved systolic function (HF-PSF) has been studied extensively in last two decades but not yet fully characterised. Many experts in the field believe that diastolic dysfunction play a major role in the development of HF-PSF. [69, 70] Recently it has also been proposed by some that extra cardiac factors such as interactions between left ventricle and systemic vasculature "ventriculo – vascular interactions" play an important role in the pathophysiology of HF-PSF. [71, 72]

Diastolic Dysfunction

The diastolic phase of the cardiac cycle mainly comprises of myocardial relaxation and filling of left ventricle making it ready for the next ejection. A detailed account of the physiology of diastolic function and the pathophysiology of diastolic dysfunction is beyond the scope of this introduction but I will summarise some important aspects of diastolic dysfunction. Many comprehensive reviews have been written recently by various writers.[73, 74]

Diastolic dysfunction is characterised by impaired relaxation and impaired filling with reduced distensibility of the LV. These abnormalities can exist regardless of LVEF and symptoms of heart failure. Diastole begins with relaxation of contracted myocardium. This is an active and complex process which consumes energy. In the normal heart rapid decline in the LV pressure by active relaxation produces a pressure gradient between LA and LV promoting the filling of LV chamber.

At the molecular level calcium (Ca^{2+}) haemostasis, active phosphorylation of troponin I and actin-myosin cross bridge detachments are major energy consuming events during this phase. Active relaxation depends on the restoration of Ca^{2+} levels in cytosol of myocardium which allows Ca^{2+} to detach from troponin and myofilaments to return to their resting length. This restoration of Ca^{2+} happens primarily through the ATP dependant reuptake of Ca^{2+} by the sarcoplasmic reticulum [74] These events rely on energy consumption and can be affected by myocardial ischemia resulting in impaired relaxation and diastolic dysfunction. This possibly explains the high prevalence of diastolic dysfunction in coronary artery disease and LVH. [73] It is also noted that ageing myocardium also displays prolonged relaxation, poor calcium haemostasis and reduced oxidative phosphorylation, possibly explaining increased prevalence of diastolic dysfunction in elderly population.[75]

Passive filling of LV is another important phase of cardiac diastole. It is dependent on

the intrinsic properties of LV wall – "distensibility" or "stiffness". In the normal heart after active relaxation the left ventricle is readily distensible with minimal resistance to additional LV filling. Myocardial stiffness is determined by changes in the extracellular matrix (ECM) composition with increased interstitial fibrosis. These changes can be reactive (increased afterload) or reparative (myocardial infarction). Myocardial ECM is composed of 3 important constituents: (1) fibrillar protein, such as collagen type I, collagen type III, and elastin; (2) proteoglycans; and (3) basement membrane proteins, such as collagen type IV, laminin, and fibronectin. [76] LV stiffness is determined by the absolute amount of collagen in ECM, ratio of collagen I to more compliant collagen III and the degree of collagen cross-linkages.

Ageing and diseases like hypertension, LVH and diabetes that are associated with diastolic dysfunction also display the altered myocardial ECM composition that is found in increased LV stiffness including increased fibrosis, increased collagen cross-linkages and decreased collagen I to collagen III ratio. Treatments that are successful in controlling diastolic function have also shown the restoration of ECM fibrillar collagen. This also strengthen the argument LV stiffness is an important factor in diastolic dysfunction. [77] Many other researchers have also found increased prevalence of raised LV stiffness in people with HF-PSF by using both invasive and non invasive methods. Zile et al carried out cardiac catheterisation to obtain left ventricular pressure-volume loops from 47 patients (mean age= 59±12) with HF-PSF.[71, 78] These patients also had echocardiographic assessments of LV diastolic function. 10 people (mean age=58±16) with no evidence of cardiovascular disease were selected as control. They demonstrated that LV diastolic pressure rise per unit rise in LV volume much steeper in patients with HF-PSF than health controls, suggesting increased LV stiffness in patients with HF-PSF. [77]

As a result of diastolic dysfunction LV diastolic pressures become elevated despite normal filling volumes. This elevated diastolic pressure can lead to increased pulmonary pressure, neurohormonal activation and clinical features of the heart failure syndrome. Activation of neurohormonal mechanism remains central to pathophysiology of both systolic and diastolic heart failure, probably explaining the frequent coexistence of these two clinical syndromes.

Ventriculo-Vascular Interaction – "Continuity Disease"

Although diastolic dysfunction plays an important role in the pathophysiology of HF-PSF, abnormal vascular function and interaction between systemic vasculature and the

left ventricle has also been implicated in pathophysiology of HF-PSF. Diastolic heart failure has also been described as a "continuity disease" characterised by ventricular as well as vascular stiffness.[72] According to this concept, the cardiovascular system is a continuous system comprising of heart and peripheral circulation in which pathology in one part affects all continuous parts. LV and vascular stiffness are commonly described in terms of LV end systolic elastance (Ees) and effective arterial elastance (Ea). Ea is a measure of arterial load derived from the ratio of LV end systolic pressure to stroke volume. Ees represents the LV end systolic pressure-volume relationship. Ea/Ees ratio represents the ventriculo-vascular interaction. [79] Ea and Ees both can be measured non-invasively (echocardiography) and invasively (cardiac catheterization).

A recent large cohort echocardiographic study found both ventricular and arterial stiffness more prevalent in elderly females, which is the most likely group to develop HF-PSF. In this study Redfield et al conducted a cross-sectional study on the residents of Olmsted County (Minnesota) aged 45 (n=2042) and above used non invasive techniques (echocardiography) to measure Ees and Ea, looking for age and gender related changes in ventriculo-vascular interaction. LV systolic elastance (Ees, mmHg/ml) was 1.86 in males and 2.21 in females at the of 55 years, while at the age 75 years it was 2.05 in males and 2.58 in females. Ees was significantly ($p<0.0001$) higher in older participants and females. Arterial elastance (Ea) was 0.61 in males and 0.83 in females at the of 55 years, while at the age 75 years it was 0.73 in males and 0.97 in females. Ea was also significantly ($p<0.0001$) higher in older participants and females. [80]

Increased arterial stiffness causes elevation in the afterload of LV, which act as a strong stimulus for the development of left ventricular hypertrophy (LVH). Two main pathological processes are involved in the development of LVH: myocyte hypertrophy and interstitial hypertrophy (discussed previously) can lead to the development of impaired relaxation and increased ventricular mass. However, the development of LVH in response to increased arterial stiffness may not be the only explanation of increased HF-PSF in people with increased ventriculo-vascular stiffness.

In Olmsted County Study Lam et al have shown that despite similar LV mass index HF-PSF patients had more impaired LV diastolic dysfunction. They compared vascular and ventricular structure and function in HF-PSF cohort (n=244, mean age 76years) with those observed in healthy (no cardiovascular disease, n=617, mean age 57 years) and hypertensive (HTN) controls without HF (n=719, mean age 66 years). They reported

that even after adjusting for age, sex and BSA, ventricular stiffness (Ees, mmHg/ml) was higher ($p<0.05$) in people with HF-PSF (2.39 ± 0.87) and HTN controls (2.30 ± 0.80) as compared to healthy controls (1.99 ± 0.59) but was almost similar in HF-PSF and HTN cohort. They have also reported that even after adjusting for age, sex and BSA, people with HF-PSF had significantly ($p<0.05$) more impaired relaxation (E/e´ = 18.43±9.65), compared to HTN (9.43±3.32) and healthy controls (7.55±2.29). This study showed that despite similar LV mass index, HF-PSF cohort (LV mass index = 102.1±29.0) had more impaired diastolic function (raised E/e´ ratio) compared with HTN cohort (LV mass index = 100.2±22.7). [81]

The exact pathophysiology of diastolic heart failure is not yet fully understood. However, this complex interaction between LV stiffness, diastolic dysfunction and vascular stiffness possibly play a key role in the pathophysiology of HF-PSF.

2.6 Diagnosis

The very essence of cardiovascular practice is the early detection of heart failure. [82] Diagnosis of heart failure is difficult to make especially in elderly female and obese subjects. Because most of the signs and symptoms of heart failure are non specific, a detailed history, through clinical examination and investigations are needed to establish diagnosis. Echocardiography is the single most useful diagnostic test in the evaluation of heart failure. [83] It should also be remembered that heart failure is never a sole diagnosis and every effort should be made to establish the aetiology and precipitating factors of heart failure.

2.6.1 Signs and Symptoms

Breathlessness, tiredness and oedema are the most typical symptoms of heart failure but are non specific. Other symptoms such as orthopnea and paroxysmal nocturnal dyspnoea (PND) are more specific but not very sensitive. Shortness of breath is 66% sensitive with 52% specificity whereas ankle oedema is 80% specific but only 23% sensitive. Tachycardia, basal crepitation, third heart sound , raised JVP, presence of ankle oedema and displaced apical beat are important clinical signs with high specificity but are not found in many patients with heart failure. [84]. Sometimes these signs are very subtle and may not be picked up by clinicians.[85]

There is a poor relationship between symptoms and the severity of left ventricular dysfunction. However the symptoms and exercise capacity of the patient may be used to classify severity of heart failure and has prognostic significance.[86, 87]

Table 2.2 New York Heart Association Functional Classification:[86]

NYHA I	No limitation during ordinary activity
NYHA II	Slight limitation by shortness of breath and/or fatigue during moderate exertion or stress
NYHA III	Symptoms with minimal exertion that interfere with normal daily activity
NYHA IV	Inability to carry out any physical activity without shortness of breath, which may be present even at rest

2.6.2 Diagnostic Techniques

According to recently published ECS guidelines to diagnose heart failure an echocardiogram should be performed to assess underlying cardiac systolic and diastolic dysfunction.[24]

A twelve lead ECG should be performed in every suspected patient with heart failure. Left ventricular systolic dysfunction is unlikely in the presence of normal ECG.[88]

Chest x-ray may also provide useful information. Cardiomegaly and pulmonary congestion may give important clue about the cause of breathlessness. However neither finding alone can confirm or refute the presence of left ventricular dysfunction.[89]

Echocardiography is a widely available non invasive and safe investigation that should be done on every suspected patient of heart failure to establish the diagnosis. Echocardiography can evaluate systolic function, diastolic function, valvular function and cardiac anatomy. A detailed role of echocardiography in heart failure is discussed in the later section of this literature review.

BNP and NT pro BNP assay levels are important tools in diagnosis and management of heart failure. Role of BNP in excluding the non cardiac causes of breathlessness has been described. [90] Detailed role of BNP in heart failure is discussed in the later section of this literature review.

Cardiac MRI, cardiac CT, Dobutamine and stress echocardiography can also provide useful information about cardiac function, anatomy, regional wall motion abnormalities. But these tests are limited because of availability and cost.

Six minute exercise test is also used to assess the functional capacity and to evaluate the response to treatment.

Coronary angiogram should be considered in heart failure patients with suspected underlying heart disease. Right heart catheterization is the gold standard investigation to assess filling pressures and diastolic function but due to advancement of non invasive tissue Doppler imaging it is used less frequently.

2.7 Role of Echocardiography In Management of Heart Failure

2D echocardiography is a well established non invasive modality in the assessment and management of heart failure. It can precisely assess LV function and can provide detailed information of cardiac anatomy.

2.7.1 Assessment of LV Systolic Function

2D echocardiography is important in the evaluation of LV systolic function which is calculated in terms of LV ejection fraction.

Four echocardiography methods are particularly of interest to calculate LVEF; M-mode, biplane volumetric method, wall motion index and a semi-quantitative 2-D approach (also known as 'eye balling').

M-mode is the longest established one dimensional method to calculate LVEF. M-mode is one dimensional assessment of LVEF and is dependent on the changes in ventricular dimensions during systole and diastole. This method can produce false results in the presence of wall motion abnormalities and aneurysms. [91] Therefore, presence of regional wall motion abnormalities limits the clinical utility of this method.

The biplane volumetric method is based on endocardial tracing of LV in apical two and apical four chamber views. This method can calculate LV volumes more accurately and can calculate LVEF even in the presence of regional wall motion abnormality. However endocardial borders may not be visible in majority of patients and this method may also not be better than eye balling. [92] Jensen-Urstad et al studied the usefulness of various methods of assessing LVEF for 96 patients (age= 64 ± 9 years) by eyeball assessment, wall motion score index (WMI) and biplane volumetric method by using trans-thoracic echocardiography and compared these with the reference method radionuclide imaging. The echocardiographic study was performed by two experienced physicians, independently of each another. Interobserver coefficient of variation for eyeball assessment of the EF was 10%, for biplane volumetric method 18%, and for the radionuclide EF 5%. In 45 patients (50%) biplane volumetric method was not possible due to poor tracing of endocardial borders. Wall motion score index and eyeball assessment of the EF correlated best with the radionuclide EF ($r = 0.72$ and $r = 0.71$), whereas biplane volumetric method had lower correlation with radionuclide EF ($r = 0.51$). [93] Regional Wall Motion scoring is a system that divides the left ventricle in 16 small segments and scores them individually[94] Each segment is scored according to both wall motion and thickening. Wall Motion Index (WMI) is a total score divided by

number of segments.[95] WMI X 30 reveals ejection fraction.[96]

Eye balling is the most commonly used method to assess LVEF in clinical practice. It is a visual estimate of global LV systolic function and if performed by an experienced person can be competitive to biplane volumetric method with respect to accuracy while being measurable in a greater proportion of the population. Eyeballing has also shown good correlation with gold standard radionuclide imaging and formal echocardiographic methods in previous studies. Royen et al recorded LVEF by eyeball assessment method and gold standard radionuclide angiography in 73 stable patients and reported that correlation of LVEF determined by both methods was good (r = 0.81) [81, 97]

LVEF and LV volumes do not correlate well with heart failure symptoms and exercise tolerance but are powerful prognostic indicators for future cardiac events.[98, 99]

2.7.2 Assessment of LV Diastolic Function

Doppler echocardiography is the most practical method for assessing diastolic function abnormalities. Doppler assessment of transmitral velocities provides useful information about LV diastolic relaxation and filling of left ventricle. Figure 2.4 shows various mitral inflow Doppler patterns which are useful in diagnosing and grading diastolic dysfunction.

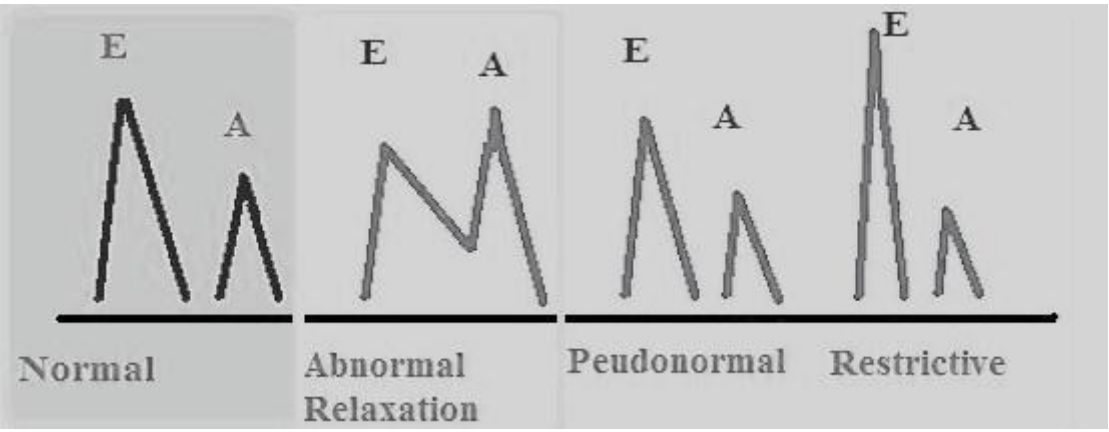


Figure 2.4: Transmitral Doppler (PW) flow patterns.

A typical transmitral flow consists of following two distinct waves:

i. E wave- corresponds to early diastolic flow
ii. A wave- corresponds to transmitral flow during atrial systole

The E velocity represents the early mitral inflow velocity and is influenced by the

relative pressure difference between the LA and LV. The A velocity represents the atrial contraction component of mitral filling and is mainly influenced by LV compliance and LA contractility. Time taken for the peak E velocity to reach baseline is called deceleration time, another useful parameter to assess diastolic function. DT correlates with the time of pressure equalisation between the LA and LV. Time interval between the end of A wave and the beginning of next E wave is called isovolumetric relation time (IVRT). PW mitral inflow parameters (E/A ratio, DT and IVRT) have been used to diagnose and grade the diastolic dysfunction into mild, moderate and severe categories as these can be obtained in nearly all the patients. However, these parameters also have few weaknesses as they are highly pre load dependent and difficult to measure at high heart rates. Another limitation of this technique is atrial fibrillation (AF) and paced rhythms, where A wave is lost and IVRT cannot be measured. Diastolic dysfunction is characterised by incomplete or delayed relaxation of LV, resulting in delay in the transfer of blood from LA to LV. Early in the evolution of the diastolic dysfunction, the delay in emptying is partially compensated by a more vigorous atrial contraction (A), resulting in reduced E/A ratio (grade 1 or mild diastolic dysfunction). Later LA pressure increases in face of further impaired LV relaxation, resulting in increase in E velocity and E/A ratio and mitral inflow velocity profile may look normal (grade 2 or moderate diastolic dysfunction – also called pseudo-normalisation). However, early diastolic myocardial velocity of mitral annulus (e´) velocity will remain reduced and will identify the underlying diastolic abnormality. With further impairment of LV relaxation, impedance to atrial emptying further increases the LA pressure. Along with this further increase atrial pressure and dampening of compensatory increase in atrial contraction results in very high E/A ratio (>2.0) resulting in grade 3 or severe diastolic dysfunction.

Mitral annular velocities measured by tissue doppler (TDI) techniques also reflect myocardial relaxation and are used alone or in combination with mitral inflow velocities to assess diastolic function. [100]

There are three components of the tissue Doppler profile that are routinely measured: the systolic myocardial velocity (S´); the early diastolic myocardial velocity (e´); and the late diastolic myocardial velocity (A´). The e´ is essential for classifying the diastolic function. Advantage of this technique is that it is not affected by preload and can also be used in AF. [101] Another benefit of this technique is that e´ decreases progressively with severity of diastolic dysfunction and there is no pseudo-normalisation. [100] E/e´ ratio correlates with LV filling pressures irrespective of LV

systolic function. [102] Due to these obvious advantages both European Society of Cardiology and American Society of Echocardiography have designated e´ and E/e´ indices as first line doppler parameter in the diagnosis and classification of diastolic dysfunction. [103, 104] However, TDI methodology is also influenced by local changes in wall motion (infarction) which may limit its use in some patients.

Pulmonary vein flow velocities are also used to assess diastolic function. This method has advantage over inflow velocity technique as it is not affected by HR and preload. However poor image availability of pulmonary veins in a substantial proportion of the population is the major limitation.[104]

LA volume can also provide morphologic and physiological evidence of chronic elevation in filling pressure and diastolic dysfunction, however in chronic volume overload conditions like anaemia and compensated valvular diseases LA volume can be raised in the presence of a normal LV filling pressure.

2.7.3 Assessment of Valvular Function and LV Dimensions

2D echocardiography also provides useful information regarding LV dimensions, and LV mass. Image quality in patients with poor echo window is however a major limiting factor in the accuracy of these measurements.[105]

Combination of 2D and doppler echocardiography reliably evaluate the valve structure and function. However poor alignment of Doppler signals can under estimate the valve pathology.[105]

2.7.4 Therapeutic Guidance

Echocardiography can also help to guide therapies in heart failure. For example aldosterone antagonism is normally recommended in patients with NYHA functional class III-IV with LVEF less than 35%. [106] Echocardiography is also used in monitoring LV systolic function in chemotherapy patients (e.g. Herceptin). Treatment is often discontinued if LV systolic function deteriorates.

Indications for implantable cardioverter-defibrillators (ICDs) and cardiac resynchronisation therapy (CRT) are very much reliant on specific cut-off value of LVEF measured by biplane volumetric method.

2.8 Treatment

Both the American and European associations have laid down the guidelines for the treatment of heart failure.[24, 83]. Like other treatments goal of heart failure treatment is symptom control, increased quality of life, decreased hospitalization and prolonging life. I will summarize the key points of heart failure management under the following headings.

- Life style modification
- Pharmacological treatments
- Invasive treatments

2.8.1 Life Style Modification

Despite recent advances in pharmacological treatment of heart failure life style modifications and patient education play a very important role in achieving the goals of heart failure treatment. Recently published guidelines for heart failure management highlighted the importance of cessation of smoking, weight reduction, dietary restriction of sodium, reducing or stopping alcohol consumption and modest aerobic exercise. These lifestyle modifications play an important role in heart failure management along with pharmacological treatment.[24]

2.8.2 Pharmacological Management

ACE inhibitors, beta blockers, ARBs, aldosterone antagonists and diuretics are key pharmacological agents that play important role in symptom reduction, decreased morbidity and mortality.

ACE inhibitors are the first line drugs recommended to treat heart failure. This group of medicines have shown improvement in survival when used in heart failure patients (CONCENSUS and SOLVD-treatments). [107, 108] ACE inhibitors have also shown to reduce mortality in patients with asymptomatic LV systolic dysfunction. [109] However, dry cough, electrolyte imbalance and renal impairment might limit their use. Angiotensin receptor blockers (ARBs) can be used if patient is intolerant to ACE inhibitors. ARBs have also shown decrease in mortality and morbidity when used in heart failure patients (CHARM and Val- HEFT).[37, 110]

Beta blockers are important medications that have shown significant improvement in

symptoms and survival in all (NYHA) classes of heart failure and should be added to ACE inhibitors. [111]. MERIT –HF, CIBIS, COPERNICUS and SENIOR are important randomized controlled trials that have proven beta blockers role in the treatment of heart failure. [112-115] However, bradycardia and hypotension are two important side effects that may limit their use.

Spironolactone and Eplerenon (RALES and EPHESUS) are two important medications, which act as aldosterone antagonist, have shown improvement in survival in moderate to severe heart failure. [116] However, electrolyte imbalance and renal impairment may limit their use and should be used with caution in people with renal failure.

Diuretics are mainly used to control symptoms of fluid retention and are most commonly used medications in heart failure. However diuretics have not shown any improvement in survival of heart failure patients.

Other agents like Digoxin are also used in heart failure patients with AF to control the heart rate. However, these have no effect on mortality but may reduce hospitalization. [117] Warfarin may also be used in patients with severe heart failure with or without atrial fibrillation and proven better than aspirin in reducing hospitalization and co-morbidity like stroke.[118] Statins may also play a role in reducing hospitalization in heart failure patients with ischemic aetiology. [119]

2.8.3 Invasive Treatment

Limited options of invasive treatment options are available for severe heart failure patients with limited benefit.

Cardiac resynchronization therapy (CRT) has shown benefit in patients with severe heart failure that show evidence of asynchrony between both ventricles. CRT maximizes the cardiac output by synchronising contraction of both ventricles. CRT has shown improvement in symptoms , quality of life and mortality.[84, 120]

More than 50% of deaths in heart failure are due to sudden cardiac deaths. Implantable cardiac defibrillators (ICDs) are better in preventing sudden cardiac deaths as compared to anti arrhythmic drugs. [121] Most of the trials to date on ICD and CRT have been in younger patients and the conclusive evidence of the benefits of this therapy in elderly is still awaited. However, age alone should not be a contraindication.

2.9 Treatment of Heart Failure with Preserved Ejection Fraction

No treatment has yet been shown to convincingly reduce morbidity and mortality in patients with HF-PSF. Unfortunately, very few large randomised controlled trials have looked at the patients with HF-PSF as compared with HF-RSF and hence, there is insufficient data on mortality benefit of medications used for patients with HF-PSF. [47, 70, 122, 123]

HF-PSF is typically common in elderly patients, who suffer with multiple co-morbidities like hypertension, diabetes, coronary artery disease and atrial fibrillation.[18, 37] It is believed among physicians and researchers that treating co-morbidities might help to improve survival. Therefore, mainstay of treatment remains on diuretics to control the symptoms and adequate control of blood pressure and ventricular rate. [24, 124] Two trials have suggested that ARBs (CHARM preserved trial) and ACE inhibitors (PEP-CHF trial) may reduce the hospitalisation in patients with HF-PSF. CHARM preserved trial was a randomised, double blinded controlled trial compared the effects of candesartan (vs. placebo) in patients with HF-PSF (EF>40%). The primary outcome for the whole study was cardiovascular death or hospital admission for CHF. Mean age of the participants (n=3023) was 67.1 ± 11.1 years. After 2 years of follow up, cardiovascular death did not differ between groups, but fewer patients in candesartan group were admitted to hospital (230 vs 279; p = 0.01). Again, even in this trial only 407 patients were aged 75 years and above.[70] In PEF-CHF trial 850 patients aged 70 years and above (76 ± 5 years) were recruited to see the effect of perindopril (vs. placebo) on all cause mortality and hospitalisation due to CHF in patients with HF-PSF. Median follow up was 2.1 years, however after 1 year most people withdrew from study and only 207 (24.4%) reached the primary end points. After 1 year of follow up cardiovascular death did not differ between groups, but fewer patients in perindopril group were admitted to hospital (HR 0.692; 95%CI 0.408 – 0.966; p = 0.033). Although this trial recruited predominantly elderly cohort but drop out in the follow up reduces the power of the study. [125] Still there is lot to learn about treatment of heart failure with preserved systolic function. Obviously more trial including elderly cohorts and more clinical research looking for treatment of HF-PSF is need but it is equally important to screen and treat the comorbidities like hypertension, diabetes, atrial fibrillation, chronic kidney disease and coronary artery disease.

2.10 Challenges In Treating Elderly Heart Failure Patients

There are many challenges in the treatment of heart failure in elderly population. The first challenge in treating elderly population is to correctly identify them. It has already been discussed that its quite difficult to diagnose heart failure in elderly population, especially in community due to non-specific symptom, multiple co-morbidities including COPD, anaemia and renal failure and limited excess to investigations like echocardiography. The biggest challenge in treating elderly patients with heart failure is that most of them suffer from heart failure with preserved systolic function (HF-PSF) and current treatments options have shown small or no benefit in improving morbidity and survival related with this condition as discussed previously. [70, 125]

Elderly people have always been under represented in heart failure (HF-PSF) drug trials. Mean age for most major randomised control trials is 58 to 71 years. [126]

Multiple co- morbidities like renal impairment and polypharmacy in elderly population may also increase the frequency and magnitude of heart failure drugs and decrease the compliance to the treatment. Polypharmacy in elderly can also lead to drug interaction, raising issues of efficacy and safety. [127, 128] Patients with heart failure may often have coexistent COPD leading to difficulty in diagnosis, due to similar symptoms and signs. It is important to have low threshold of suspension in this age group. Cognitive impairment in many elderly population with heart failure also has implications on drug compliance and titration of medication.[129]

However studies have shown that a multidisciplinary approach including patient and family education, social support, involvement of pharmacist and heart failure specialist nurse results in improvement in event free survival and quality of life in elderly patients.[122, 130-132] In an Australian randomised controlled study, CHF patients discharged home after acute hospital admission were randomly assigned usual care including (n=100) or a multidisciplinary, home-based intervention (n=100). Usual care included both inpatient and community-based contact with a cardiac rehabilitation nurse, dietitian, social worker, pharmacist, community nurse and an outpatient follow up with the cardiologist. In a multidisciplinary, home-based intervention group all of the usual care was included along with a structured home visit by a qualified cardiac nurse 7–14 days after discharge. During this visit the nurse assessed the patient's clinical progress since discharge, patient's adherence to the prescribed treatment regimen, ability to recognise changes in symptoms indicative of worsening heart failure, fluid and sodium intake, current amount of physical activity. On the basis of this comprehensive

home assessment, patients and their families received counselling targeting to improve treatment adherence, recognition of fluid overload or worsening of symptoms, introduction of a simple exercise regimen and where indicated. If indicated the medication regimen was also alter by the cardiac nurse after discussion with the cardiologist. Mean age of patients in usual care group was 76.1 ± 9.3 years and in intervention group 75.2 ± 7.1. 40% of patients in usual care group and 32% in intervention group had LVEF > 40%. During 6 months' follow-up there were 129 primary endpoint events in the usual care group and 77 in the intervention group (p=0·02). Overall, there were fewer unplanned readmissions (68 vs 118; p=0·03) and associated days in hospital (460 vs 1173; p=0·02) among intervention group patients. Hospital-based costs were Australian $490 300 for the intervention group and $922 600 for the usual-care group (p=0·16). [131]

Chapter 3. Arterial Stiffness

Arteries stiffen with advancing age and with other cardiovascular risk factors including hypertension, diabetes mellitus and coronary artery disease. [133, 134] Increased arterial stiffness is an independent risk factor for cardiovascular events. [133, 135] Arterial stiffness is a generalized term to describe rigidity of the arterial tree. Different terms are used to describe this property of the arterial system, some of which are explained in the following table 3.1.[136]

Table 3.1: Important indices of arterial stiffness

Term	Definition
Distensibility*	Relative change in the diameter/area for a given pressure change
Compliance*	Absolute change in the diameter/area for a given pressure change
Elastic modulus*	The pressure change required for theoretical 100% stretch from resting diameter (inverse of distensibility)
Young's modulus*	Elastic modulus per unit area
Pulse wave velocity	The speed with which pulse wave travels along a length of artery
Augmentation index	Percentage of central pulse pressure rise due to reflection of pressure wave

*Also requires pressure measurements

To understand pathological arterial stiffness one must understand the main functions of the arterial system and mechanisms affecting blood flow through arterial tree.

Cushioning and Conduit function of elastic vessels

The principal function of the arterial system is act as a conduit and deliver blood from left ventricle blood into the circulation to deliver oxygen and nutrients to metabolising tissues and the also transport the waste materials to the organs to eliminate them. Another important function of large vessels is to buffer the pulsatile blood flow from the left ventricle and convert it to steady and almost continuous flow to the peripheral vasculature. This is called the 'windkessel function'. [137, 138] This function is possible because arteries are compliant, with the ability to expand due to pressure and

the ability to recoil. Although the windkessel model of the circulation helps to understand the importance of elastic and conduit characteristics of arteries, this model assumes that the arterial tree has separate elastic and conduit compartments and also does not take the existence of wave reflection into account. In fact most of the arterial tree has both of these functions combined, although one or the other tends to predominate in any given arterial segment. That combination of function leads to pressure wave travel and reflection which is discussed in the following section.

The arterial pressure wave is generated with ventricular ejection which propagates through the arterial tree. The speed at which the arterial pressure wave travels along the arterial tree is termed the pulse wave velocity. Young originally described the relationship between arterial stiffness and pulse wave velocity in 1808 [139] but it is generally described by Moens - Korteweg equation: [140]

$$PWV = \sqrt{E \times h / 2R\rho}$$

"(Where E is Young's modulus of the arterial wall, h is thickness of arterial wall, R is radius and ρ is blood density)"

Arterial pressure wave reflection and waveform analysis

The arterial pressure wave is a combination of a forward wave generated by LV systolic ejection and a reflected or backward wave, from impedance points (vessel bifurcations)

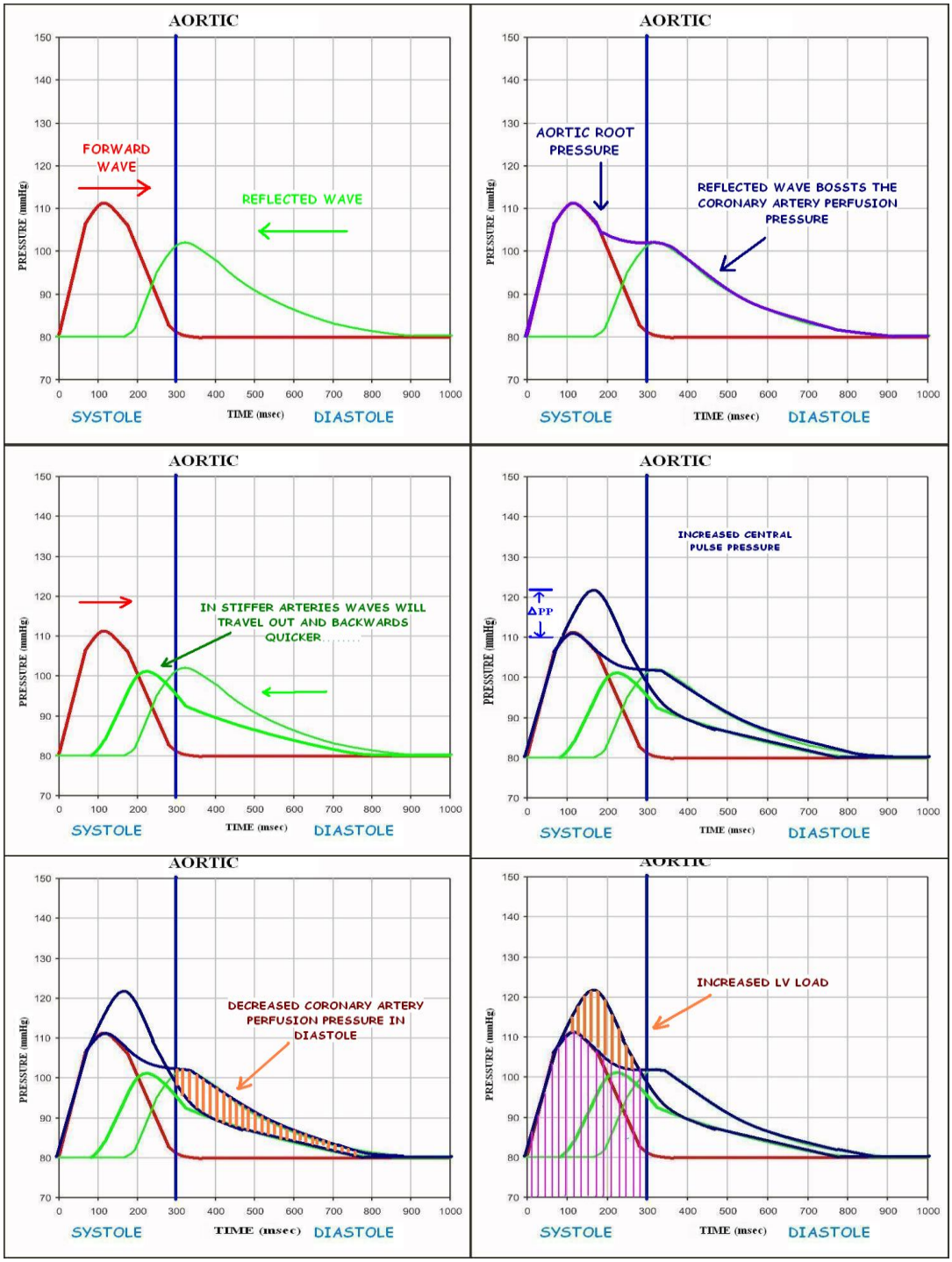


Figure 3.1: The central (aortic) pressure wave form formation- components, effects of arterial stiffness on pressure wave form.

of the peripheral arterial tree (Figure 3.1). Reflection of the backward wave depends on the speed with which the forward wave travels along the arterial tree, i.e. pulse wave velocity (PWV). [141] In youth and health the reflected wave arrives in the proximal aorta in diastole. This augments end diastolic aortic pressure and boosts the coronary perfusion. [142] However, PWV increases with arterial stiffness resulting in early return of the reflected wave in systole. This in turns augments systolic blood pressure, reduces diastolic blood pressure and widens the pulse pressure. [143] The proportion of this augmented pulse pressure is called augmentation index (AIx).

This augmentation of systolic pressure and decrease in diastolic pressure results in increased tension time index (TTI = area under the systolic half of the pressure waveform), increased LV workload (F) with increased oxygen demand.

3.1 Mechanisms Underlying Arterial Stiffness

Arterial stiffness is considered to be the result of simple wear and tear in the elastic arteries. With each cardiac ejection aorta distends and this stress is taken up by predominantly the elastic fibres in the vessel wall. On average the proximal aorta dilates by 10% with each heart beat. Repeated cycles of distension and elastic recoil are thought to cause fatigue fracture [140] of elastin in the vessel wall which results in depletion of elastin and replacement with collagen which is less elastic. [144] This results in increased arterial stiffness. This increase in arterial stiffness results in a positive feedback loop of elevated PWV, early return of reflected waves with further augmentation of systolic pressures and more vascular damage [143] Arterial stiffness is also influenced by the tone of smooth muscles in the vessel wall which is partly regulated by the vascular endothelium. [145] Vascular endothelium exerts that function possibly by means of nitric oxide. [146] Decline in endothelial nitric oxide production with age also plays some role in the development of age related arterial stiffness. [146] The process of arterial stiffness is accelerated in the presence of conditions like metabolic syndrome, renal failure and hypertension. [133] A number of genetic determinants of arterial stiffness have also been identified. Several genetic polymorphisms have been reported to influence PWV, including some in the fibrillin-1, angiotensin II type 1 receptor and endothelin receptor genes which are also related to arterial stiffness. [147] Still the precise mechanism underling arterial stiffness remains somewhat unclear and more work is needed in this regard.

3.2 Determinants of Arterial Stiffness

Arterial stiffness is influenced by many factors. Major physiological and pathological factors listed in the table 3.2 are discussed below.

Table 3.2: Major determinants of arterial stiffness

Physiological Factors	Pathological Factors
Age	Hypertension
Gender	Diabetes Mellitus
Height	Atherosclerosis
Heart Rate	Renal disease

3.2.1 Physiological Factors Affecting Arterial Stiffness

Age is the single strongest determinant of arterial stiffness. This is reflected by increase in PWV and AIx with advancing age. This has been described in many population based studies using various methods of assessment. Investigators of the Anglo-Cardiff Collaborative Trial (ACCT) have studied more that 4000 healthy community based participants between 20 to 90 years old. [148] They have showed that PWV, central aortic blood pressure, central pulse pressure, augmentation pressure (AP) and augmentation index (AIx) increase significantly with age for both men and women, although values for AP, AIx, central blood pressure and central pulse pressure were significantly higher in women than men. This was also shown by previous large cohort American studies like the Cardiovascular Health Study (CHS) and the Framingham Health Study. [149, 150] Increase in arterial stiffness with age is gradual and continuous with increase of 0.1 m/sec per year in PWV. [133] However investigators in ACCT and some others have shown that increase in PWV and AIx follow a non linear course, being more marked after age of 50. It is also shown that aging exerts differential effects on various vascular indexes. [148] For example, increases in central pulse pressure and aortic PWV were more marked in older subjects compared with younger subjects, whereas the age-related changes in AIx were more prominent in younger subjects. Ten years of ageing at 20 years old increases PWV by 0.48 m/sec and 0.35 m/sec in males and females respectively whereas a similar time period at 80 years of age raises PWV by 1.35 m/sec males and 2.35 m/sec in females. Similarly ten years of ageing, a rise in

AIx at the age of 20 years was 9% and 10% in males and females respectively, whereas AIx rise in 80 years old males was only 1% and no change was observed in 80 years old females. . The exact cause of this non linear rise and gender difference is not known, although a possible explanation for the non linear rise is elastin fatigue fracture and degradation, with resultant increased loading on stiffer collagen fibres and a marked increase in calcification of the aortic media with age, particularly after the fifth decade.[148] Augmentation index (AIx) is inversely related to height. [151] Smulyan and colleagues studied the relationship of height to various markers of arterial stiffness in a study including 402 subjects. 149 subjects had end stage renal failure (ESRF) (mean age = 52.9 ± 16.9 years) and 253 subjects had normal kidney function (mean age = 48.9 ± 20). AIx is also inversely related to heart rate. [152] Wilkinson and colleagues studied the relationship between heart rate and AIx in 20 young people (mean age = 47 ± 20) who attended the hospital for their electrophysiological investigations. Investigators found significant reduction in AIx when the subjects' heart rate was increased from 80 beats/min to 120 beats/min with incremental right atrial pacing ($r = -0.70$, $p < 0.001$). Investigators didn't observe any change in PWV with this incremental heart rate. [152] The relationship between heart rate and PWV is less clear. In a similar study, Lantelme and colleagues studied 22 subjects with a mean age of 77.8±8.4 (SD) years who attended the hospital for permanent cardiac pacing. In each subject, PWV was measured at 5 different pacing frequencies in the same session (60, 70, 80, 90, 100 beats/min). The average difference between PWV at 100 and 60 beats/min was 1.36 ± 2.9 m/s. This effect of heart rate on PWV was highly significant ($p = 0.01$). Those investigators believed that the predominance of elderly subjects in their cohort might have amplified the overall PWV-heart rate relationship because age is indeed known for its effect on arterial compliance. [153]

3.2.2 Pathological Factors Affecting Arterial Stiffness

Increased arterial stiffness is widely observed in the hypertensive population. Increased wave reflection (Tr) and AIx has also been widely reported among hypertensive subjects. [154] Similarly, higher PWV has been reported in hypertensive patients compared with normotensive controls across wide ranges of age. [155, 156] Asmar and colleagues studied 512 community based subjects to investigate the relationship of age, hypertension and PWV. They divided the subjects into three groups: group 1 included 124 normotensive subjects (mean age = 45 ± 13 years), group 2 included 224 untreated

hypertensive patients (mean age = 48 ± 13 years) and group 3 included 164 patients with well controlled hypertension (mean age = 59 ± 11 years). In group 2 all subjects had essential and uncomplicated hypertension and none of the patients had cardiac, neurological or renal involvement or arteriopathy of the lower limbs. Patients with valvular heart disease, arrhythmia or carotid artery stenosis were excluded from the study. Patients had been free of all medication for one month prior to the study. The mean duration of their hypertension was 3.8 ± 5 years (mean ± SD). In group 3 all patients were treated and classified as well controlled by antihypertensive medications (if their diastolic blood pressure had been below 90 mmHg during the 3 months preceding the study). The mean duration of the hypertension was 5.6 ± 4.8 years (mean ± SD). The mean duration of their treatment was 4.7 ± 4.3 years (mean ± SD). The mean duration of normalised diastolic blood pressure was 3.9 ± 4.1 years. PWV (carotid-femoral PWV) was measured in all the subjects. PWV in group1, 2, and 3 were 8.5 ± 1.5 m/sec, 11.8 ± 2.7 and 10.1 ± 2.1 respectively. Investigators found a significant correlation between age and PWV in all three groups (group 1: $r = 0.55$, $p < 0.001$; group 2: $r = 0.48$, $p < 0.001$; group 3: $r = 0.48$, $p < 0.001$). The comparison between the hypertensive and normotensive relationships of PWV with age shows that, at any given age, PWV was significantly higher in group 2 by comparison with group I ($p < 0.001$). Investigators also found that despite an adequate control of diastolic blood pressure, pulse wave velocity increased more with age in Group 3 than in group 1. [155] In this study effect of different antihypertensive medications on arterial compliance and PWV was not studied in detail due to the disparity within the treatment group regarding the form and duration of treatment, however pharmacological studies suggest that not all antihypertensive treatments improve arterial compliance and stiffness. Calcium channel blockers (nifidipine, nicardipine) and angiotensin converting enzyme inhibitors (ACE inhibitors like perindopril, captopril and enalapril) have shown to improve arterial stiffness and reduce the pulse wave velocity (PWV) in hypertensive patients in contrast with agents like beta blockers and diuretics. [157]

Hasegawa and colleagues measured PWV in 29 patients with hypertension, ranging in age from 37 to 73 years, 36 normotensive subjects with the same age range and in an additional series of 44 normal subjects aged 18-35 years. They found a linear rise in PWV with age for both normal subjects and patients with hypertension. There was a statistically highly significant ($p < 0.001$) increase in PWV in hypertension at all ages examined. [156] The exact mechanism for this relationship is not clear. Many believe

that this rise in arterial stiffness is due to an increase in the mean arterial pressures because if this pressure is normalized statistically or pharmacologically, aortic stiffness normalises. [158]

Arterial stiffness is also increased in individuals with diabetes mellitus (Type 1 & 2), it is even seen in people with even impaired glucose tolerance. [133, 159] Diabetes also has a differential affect by gender as women with diabetes or the metabolic syndrome have stiffer arteries than men. [159] The exact mechanism of this gender difference and cause of arterial stiffness in diabetes is unclear, however, one of the main mechanisms thought to be involved is the formation of advanced glycation end-products (AGEs) in the arterial wall, causing cross-linking of collagen molecules, which may lead to loss of collagen elasticity and a subsequent increase in arterial stiffness. [160] Endothelial dysfunction seen in diabetics with reduced availability of nitric oxide and increased activity of vasoconstrictors such as endothelin-1 may also play a role in the pathogenesis of stiff arteries in these individuals. [161-163]

Population based studies have shown strong association between arterial stiffness and atherosclerosis at various sites in the vascular tree. In the Rotterdam study more than 3000 elderly subjects aged 60 to 101 years were studied to see association between arterial stiffness and atherosclerosis. Significant associations between PWV and common carotid intima-media thickness ($p < 0.001$), plaques in the carotid artery ($p < 0.001$), and plaques in the aorta ($p < 0.001$) were observed even after adjusting for age, sex, mean arterial pressure, heart rate, and cardiovascular risk factors. [164]

Increased arterial stiffness is also seen in the patient with renal failure, and aortic PWV is a very strong predictor of cardiovascular mortality in patients with end stage renal failure [165], however an exact mechanism of aortic stiffness in renal failure is still unclear. Several potential mechanisms for aortic stiffening and dysfunction secondary to renal insufficiency have been described. Increased prevalence of abnormalities in endothelial function, oxidative stress, calcium homeostasis, activation of the RAAS and aortic calcification are often present in patients with renal dysfunction and may contribute to increased vascular stiffness in these patients. [165-168] Blancher and colleagues studied 110 patients (mean age = 54 ± 16 years) with stable end stage renal disease (ESRD) on dialysis and followed them up for 53 ± 21 months (mean ± SD). [168] They measured carotid intima-media thickness, carotid compliance, carotid distensibility, aortic pulse wave velocity, and the presence of arterial calcifications measured at the sites of the carotid artery, abdominal aorta and ilio-femoral arteries. The

presence of calcifications was analyzed semi-quantitatively, using ultrasonography as a score (0 to 4) according to the number of arterial sites with calcifications. During follow up 25 cardiovascular and 14 non-cardiovascular deaths occurred. Investigators showed that the presence and extent of vascular calcifications were strong predictors of cardiovascular and all-cause mortality. Risk of death increased with the number of vascular sites having calcifications (for 0 to 4 vascular sites with calcifications, risk of all-cause mortality was 3%, 17%, 31%, 50%, and 73%, respectively; $p < 0.001$). Adjusted hazard ratios of all-cause and CV mortality for an increase of 1 unit in calcification score were 1.9 (95% confidence interval, 1.4 to 2.6) and 2.6 (95% confidence interval, 1.5 to 4.4), respectively ($p < 0.001$ for both). [168]

There is still sparse data about how different variables of arterial stiffness alter in extreme ages in health and disease.

3.3 Assessment of Arterial Stiffness

There are several different methods to assess arterial stiffness. Each method has both advantages and limitations which I will discuss briefly in this section.

3.3.1 Pulse Pressure

Pulse pressure is simply a difference between systolic and diastolic blood pressures. It is usually measured by a standard sphygmomanometer.

Age associated changes in blood pressure tend to widen the pulse pressure beyond the age of 50-60 years. [169] Pulse pressure has been recognised as a valuable surrogate marker of arterial stiffness. [170]

Various studies have shown pulse pressure as better predictor of ischemic heart disease that either systolic or diastolic blood pressure alone, in elderly patients. [171, 172] In Framingham Heart Study (FHS) pulse pressure was shown to be a strong predictor of coronary heart disease in an elderly population based cohort (mean age of FHS cohort was about 63 years). According to the investigators of FHS there might be a selection bias in their study as they excluded people on antihypertensive treatment at baseline, which was 30% of their total cohort. Wider pulse pressure has also predicted stroke and mortality in elderly hypertensive patients. [173]. This study has demonstrated an 11% increase in stroke risk and a 16% increase in risk of all-cause mortality for each 10-mm Hg increase in pulse pressure (mean age of the cohort was 72 years).

Pulse pressure is the simplest method to predict arterial stiffness and is readily available in clinical settings however; it has its own limitations. Arterial stiffness is more marked in central and elastic arteries than peripheral arteries therefore pulse pressure from the brachial artery does not accurately reflect central aortic pulse pressure. [174] Central pressure is a more accurate predictor of cardiovascular risk and is a strong determinant of left ventricular load and resultant left ventricular hypertrophy. [140, 175]

The Prospective Studies Collaboration conducted a meta-analysis of over a million individual participants' data on blood pressure and cardiovascular death from 61 separate prospective studies. They used various blood pressure indices including systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (SBP-DBP), mean arterial pressure (2/3DBP + 1/3SBBP) and mid blood pressure (1/2 SBP + ½ DBP). Cause-specific mortality was noted during five decades of life (40-49, 50-59, 60-69, 70-79, and 80-89). During 12.7 million person-years at risk 56000 vascular deaths were noted (12000 stroke, 34000 IHD) at ages 40-89 years. It was noted that

during ages 40-69 each 20mmHg SBP difference was associated with more than twofold difference in stroke, IHD and other vascular death rates. However, at ages 80-89 these differences were less marked (nearly half) as at the ages 40-69. [176] They also found that SBP was better predictor of stroke or IHD mortality as compared to DBP or pulse pressure. However, they also reported mid blood pressure (average of both SBP and DBP) was informative in predicting stoke and IHD mortality than either alone. [176]

3.3.2 Pulse Wave Velocity

Pulse wave velocity (PWV) is simply the speed at which the pressure wave transited from aorta travels through the vascular tree. There are a number of different ways to measure PWV. The arterial pulse wave is recorded at proximal artery (carotid) and a more distal (brachial or femoral) artery. Time delay between the feet of these two waveforms is obtained either by simultaneous (Vicorder & Complior) or separately with ECG synchronization (SphygmoCor). The distance travelled by the pulse wave is measured over the body surface and PWV is than calculated as distance/time. Different devices use various techniques to record pulse wave like pressure sensitive transducer (Complior), applanation tonometry (SphygmoCor) and volume displacement technique (Vicorder, Arteriograph).[177-179] Pulse wave velocity measured by these devices shows a good correlation, however one device might give slightly higher value than the other. Vicorder is the most portable and is almost operator independent. The carotid-femoral PWV (cf PWV) reflects the aortic PWV and is considered as a "gold standard" for the measurement of arterial stiffness. [180] The carotid-femoral PWV has been shown to be an independent predictor of cardiovascular morbidity and mortality in the general population, hypertensive patients, and renal failure patients and in elderly cohort as mentioned in previous sections. Only one previous study has studied relationship of PWV with cardiovascular events in elderly cohort (85+ years) in suburbs of Paris. This study included 141 hospitalised individuals from geriatric wards with mean age of participants 87 years (87.1 ± 6.6 years). This study showed PWV was a strong independent predictor of cardiovascular death with an adjusted odd ratio of 4.60 (95% confidence interval, 1.4 to 15.7) when PWV was >17.7 m/s. However, that significance disappeared with PWV less than 17m/s. [181]

PWV measurement has become very simple, inexpensive and quick due to modern devices. However accurate estimation of path length (arterial distance between

recording sites) can be difficult as the aorta tends to become more tortuous with age. PWV can also be measured non-invasively by using MRI, which provides actual measurement of the path length but this method is more time consuming, expensive and not widely available. [182]

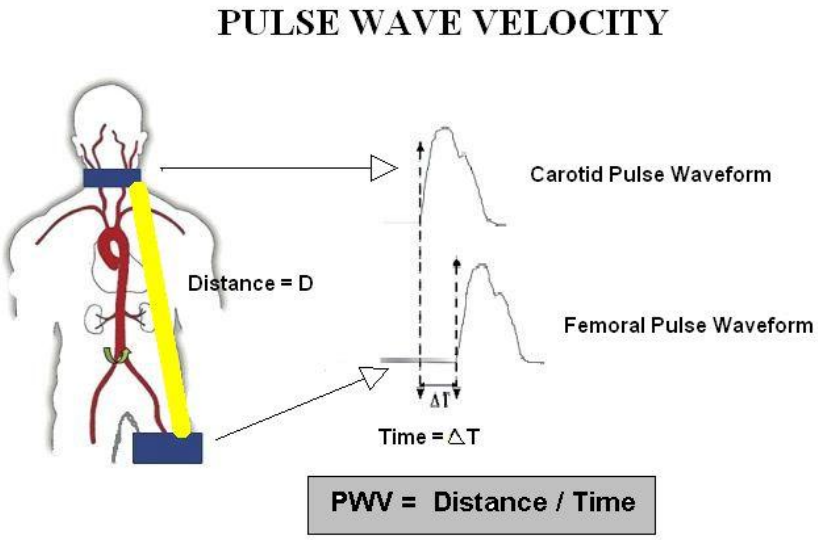


Figure 3.2: Pulse wave velocity (PWV) calculation using the foot-to-foot method

3.3.3 Pulse Wave Analysis

Arterial stiffness can be measured by analysing various components of the arterial pressure waveform. Different devices use various techniques to record peripheral pressure waveform including applanation tonometry and photoplethysmographic (PPG) signals. Mostly the radial pressure waveform is recorded, calibrated to brachial blood pressure measured with a sphygmomanometer. The central pressure waveform and central pressures are derived from this peripheral waveform and blood pressure by using a generalized transfer function. [31] Augmentation index (AIx) is calculated from the central pressure waveform and central blood pressure values (ratio of augmentation pressure to pulse pressure). Generalized transfer factor in SphygmoCor device has been validated by simultaneously recording central invasive pressure waveforms and peripheral non-invasive waveforms. [31, 183-185] In a validation study 30 patients (56±9 years; 21 men) underwent diagnostic coronary angiography and simultaneous recordings of the derived central pressure waveform using SphygmoCor device. There was good agreement and high correlation between invasive and non-invasive techniques with a mean difference (±SD) for central systolic BP of −1.3 ± 3.2 mm Hg. [185] Augmentation index also increases with age and traditional cardiovascular risk factors including diabetes, hypertension and hypercholesterolemia. [186-188]

Pulse wave analysis not only provides central pressures and augmentation index (AIx) but also measures the duration of systole (ejection duration) and diastole. The diastolic phase is characteristically shortened in elderly people and in diastolic heart failure [189]. AIx and AP have been shown as strong independent marker for coronary artery disease (CAD). Weber and colleagues studied 465 individuals undergoing coronary angiography for suspected CAD. Arterial stiffness was assessed by applanation tonometry at the radial artery. They reported, a higher AIx was increased risk of CAD (OR OR, 4.06 for the difference between the first and the fourth quartile [1.72 to 9.57; $P<0.01$]). This association remained significant even after controlling for age, height, presence of hypertension, HDL cholesterol, and medications (OR, 6.91; $P<0.05$). [190] AIx has been also independently associated with cardiovascular events in patients with end stage renal failure, coronary artery disease. [191] Although PWV has larger body of evidence to predict mortality, AIx has predicted mortality even in patients with normal PWV in small group of patients with end stage renal failure. [192] In this study London and colleagues measured arterial PWV and AIx in people with end-stage renal failure (ESRF) being treated with haemodialysis. 180 patients were included with mean age

54±16 years (range, 14 to 88 years). Risk ratio (RR) for AIx was 1.51 (95% CI, 1.23 to 1.86) for all-cause mortality and 1.48 (95% CI, 1.16 to 1.90) for CV mortality (cardiovascular). When they selected people with normal PWV (<11.0m/sec), risk ratio for AIx remained significant (p=0.0058) for CV mortality (RR=1.84). [192]

PWA is a simple, quick, inexpensive and non-invasive validated measure of arterial stiffness. PWA using radial tonometry also requires very little training and has more freedom from operator bias. [147] A correctly obtained pressure waveform by radial tonometry has been described as virtually identical to waveform recorded with invasive techniques including coronary angiography. [110]

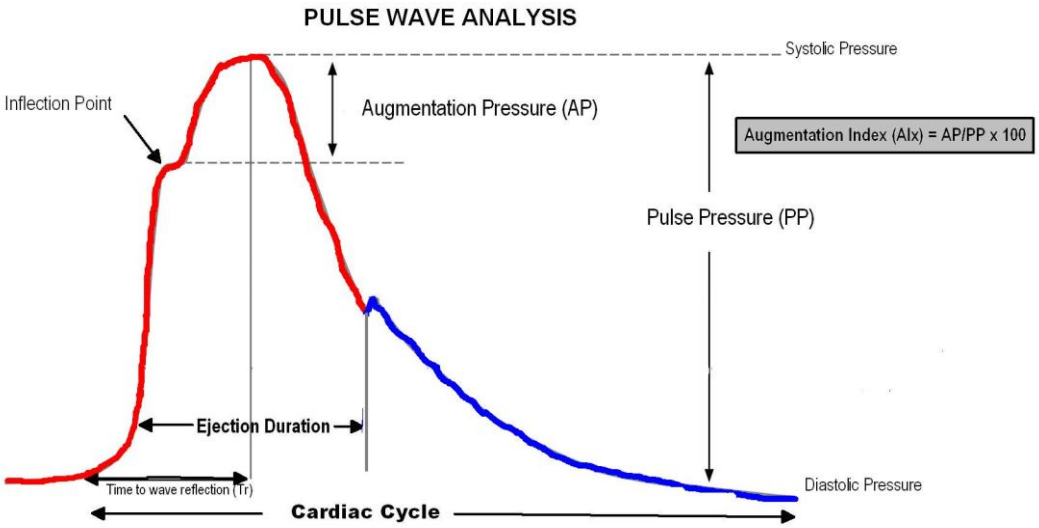


Figure 3.3: Features of Central aortic pressure waveform.

3.3.4 Arterial Ultrasonography

Arterial ultrasound and MRI can also be used to measure change in arterial diameter for a given pressure change to provide the direct measures of arterial stiffness. Arterial distensibility (relative change in diameter for a given pressure change), compliance (absolute change in diameter for a given pressure) and elasticity (elastic modulus) are important parameters that are calculated with this method. However, interpretation of these parameter can be complicated because their dependence on blood pressure. Many studies have shown elasticity and distensibility of the carotid artery is important predictors of cardiovascular events. [168, 193] However Oliver et al have suggested that use of peripheral rather than central BP was major limitation of these studies. [147]

Ultrasound techniques require substantial expertise and are time consuming. Another problem with the use of this modality is limited resolution of vessel wall to detect small changes in the arterial diameter. However, the latter problem can be solved by using high definition echo-tracking devices, which track the vessel wall by using inbuilt software and can detect small changes in the arterial diameter with precision.

3.3.5 Invasive Assessment

Central blood pressure and central pressure waveform can be recorded invasively by left heart catheterization. Similarly arterial distensibility and compliance can be measured by simultaneously measuring arterial pressure and diameter using intra-luminal catheters and intravascular ultrasound. This is the most accurate method of recording the central pressure and pressure waveform, however a major limitation is invasive nature of the procedure. It is also expensive, time consuming and requires substantial training and resources.

3.3.6 Measurement of Intima Media Thickness

Local arterial stiffness of superficial arteries can be assessed by measuring combined thickness of the arterial intima and media layers (IMT). MRI has been used by some researchers to measures intima media thickness of deeper arteries like aorta. Carotid Intima Media Thickness (CIMT) describes the combined thickness of the inner two very thin layers of the lining of the carotid arterial wall – the intima and the media. This corresponds to the inner and outer echogenic lines seen on the B-mode ultrasound image. In order to standardize measurements between subjects, the 'region of analysis' has been recommended as the 1cm section of the artery situated 1 cm proximal to the start of the bulb by Touboul and colleagues in the Mannheim Intima Media Thickness consensus document (Figure 3.5). [194] Most of the recent ultrasound equipment has automated computerized edge-detection software that allows faster evaluation of CIMT with lesser variability for all carotid segments. The manual measurement of CIMT measurement is however the most common technique used in clinical practice, which is time-consuming and prone to errors by the lack of expertise.

CIMT is considered as a surrogate marker of atherosclerosis [195] but it also provides useful information about arterial stiffness. Age dependent increase in IMT has been documented even in the absence of atherosclerosis. [196-198] There is a substantial body of evidence from large cohort studies to suggest strong association of increased CIMT with cardiovascular events including mortality and stroke. In the Cardiovascular Health Study (CHS) over 4000 participants 65 years of age or older (mean age 72 years) were followed over a median period of 6.2 years, and the baseline CIMT was associated with cumulative survival free of myocardial infarction and stroke. For a 1 SD increase in baseline CIMT, relative risk for the combined end point increased by 35% to 44% (adjusted for age and sex). [199] In the Rotterdam Study nearly 1600 people elderly people (mean age 72 years) had assessment of CIMT of the common carotid artery and were followed up for a median period of 2.7 years. The risk of stroke increased gradually with increasing common carotid intima-media thickness. The odds ratio for stroke per SD increase was 1.41 (95% CI, 1.25 to 1.82). In men, the odds ratio per SD increase was 1.81 (95% CI, 1.30 to 2.51) and in women, an odds ratio of 1.33 (95% CI, 1.03 to 1.71) per SD increase was observed. [44]

Carotid plaque area or volume has also been considered better predictor of cardiovascular events than CIMT [200-202] but the evidence is still debatable. [203, 204] Atherosclerotic plaque appears quite late in the disease and is probably better

predictor of cardiovascular events in patients with known cardiovascular disease. [205] However, increased CIMT has also shown to be a strong predictor of stroke and cardiovascular events even in asymptomatic people. [203, 206] Many researchers argue that age associated increased CIMT represents an early stage of atherosclerosis. However, recent studies have shown both carotid plaque and increased CIMT were independently associated with increased risk of stroke. [203, 207]

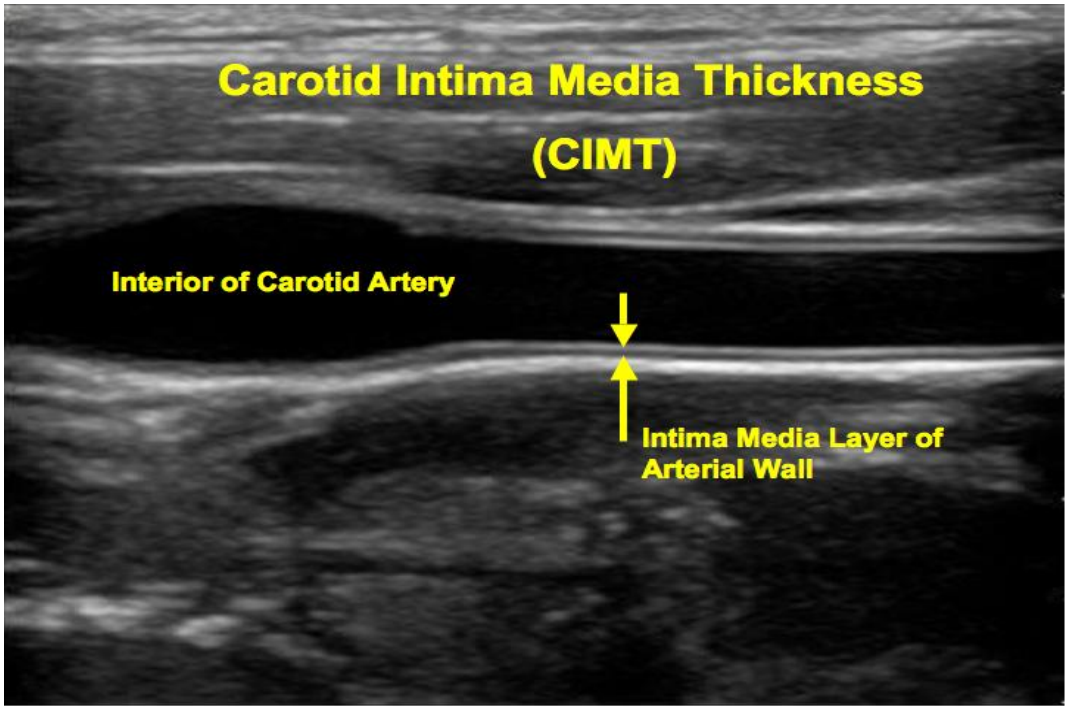


Figure 3.4: Longitudinal view of CCA and carotid bulb. The arrow marks the region of analysis

3.3.7 Endothelial Dysfunction

There are several methods for the assessment of arterial endothelial function. Almost all of these methods are based on the fact that endothelial derived nitric oxide release due to various stimuli results in vasodilatation. Detailed description of the assessment of endothelial dysfunction is beyond the scope of this thesis, but I will briefly outline the available methods with their pros and cons.

Intra coronary injection of acetylcholine (endothelial dependent vasodilator) during coronary angiography to measure the secondary dilatation is considered as a gold standard test for endothelial function. [208] This method allows direct and detailed quantification of endothelial function in the vascular bed, however the invasive nature, cost and risks associated with coronary catheterization limits its use.

The most widely used invasive method involves brachial artery catheterization and injection of acetylcholine or sodium nitroprusside, combined with forearm venous occlusive plethysmography to assess changes in forearm blood flow. [209-211] Brachial circulation is more accessible than coronary circulation, probably explaining the wider use than coronary catheterization. The main limitation for this technique is still the invasive nature and risk associated with procedure like neurovascular damage.

Brachial artery ultrasound with flow-mediated dilatation (FMD) is most widely used non invasive test to assess endothelial dysfunction. This involves Upper-arm occlusion with blood pressure cuff for five minutes, which results in reactive hyperaemia after the cuff is released and this increase in shear stress results in flow-mediated dilatation. This post ischemic reactive hyperaemia is predominantly influenced by arterial endothelial function [212]. Main advantage of this technique is the non invasive nature of this test. Brachial artery flow-mediated dilatation (FMD) has also been shown to correlate with measures of coronary endothelial function. [208] This technique is highly operator dependant and requires very high resolution images to detect small changes in the vascular diameter. Although flow-mediated dilatation is safer, faster and is a non invasive method but still discomfort associated with prolonged cuff occlusion will limit its use in elderly frail cohort.

In elderly population where direct assessment of endothelial function is difficult, measures of arterial stiffness such as pulse wave analysis (PWA) and pulse wave velocity provide useful insight to their endothelial function.

In a recently published work by Saga and colleagues augmentation index (AIx) was significantly correlated with flow mediated dilatation (FMD) ($r=-0.38$, $p<0.0001$) and FMD was a significant independent predictor of augmentation index ($p<0.05$). [213]

McEniery and colleagues have also studied relationship between endothelial function (brachial FMD) and definitive measures of arterial stiffness and wave reflections such as PWV, AIx and central pulse pressure in 309 community based healthy individuals (18-81 yrs). They showed significant and inverse correlation between flow-mediated dilatation and aortic PWV ($r=–0.39$; $P<0.001$) even after correcting the confounding variables. [214]

These findings suggest that increase in arterial stiffness is associated with grade of endothelial dysfunction and that AIx and PWV may be an index of not only arterial stiffness but also endothelial function.

3.4 Consequences of Increased Arterial Stiffness

Increased arterial stiffness has many clinical implications and is an independent cardiovascular risk factor.

Increased arterial stiffness is associated with increased pulse wave velocity and early wave reflection, which results in increased pressure in systole and decrease diastolic pressure. Increased systolic pressure and after load causes ventricular remodelling and is associated with increased LV mass and LVH. This increase in afterload and LVH increases myocardial O2 demand with impaired coronary perfusion on the other hand due to decreased diastolic pressure leads to increased predisposition to myocardial ischemia and angina. This mechanism links LVH to myocardial ischemia quite independently of coronary narrowing. [140, 215]

Increase in systolic and decrease in diastolic pressure with age related arterial stiffness leads to wider pulse pressure, which probably explain the high prevalence of isolated systolic hypertension in the elderly population. Data from both Framingham Heart Study and NHANES survey has shown widening of pulse pressure with age and that isolated systolic hypertension accounts for 60-75% of cases of hypertension in the elderly. [169, 216] Persistent increase in ventricular afterload due to increased arterial stiffness also induces left ventricular remodelling leading to increased left ventricular mass and left ventricular hypertrophy (LVH), an important independent risk factor for cardiovascular mortality. [217, 218] LVH is also implicated in the pathogenesis of diastolic dysfunction and heart failure with preserved systolic function (HF-PSF). [37] The role of altered vascular stiffness and its interaction with ventricular remodelling in the pathogenesis of HF-PSF has already been discussed in chapter 2. (Ventriculo-vascular interaction)

Increased arterial stiffness is strongly associated with increased incidence of cerebrovascular events. The Rotterdam study has shown that increased aortic PWV was a strong and independent predictor of coronary artery disease and stroke in population based apparently health people (n = 2835, mean age 71 years). This association persisted even when other risk factors of cerebrovascular disease (hypertension, age, diabetes, hypercholesterolemia, smoking, CIMT) were accounted for. [219] People who lived in nursing homes were not included in this study.

The exact mechanism how increased large arteries stiffness affects microcirculation of the brain is still unknown. It is postulated that once cushioning function of aorta or large vessels is lost due to arterial stiffness, pulsatile flow extends into the microcirculation

(which normally is steady and continuous) and probably damages the microcirculation. [116, 149, 220] Presence of severe microcirculatory lesions in the brain and kidney of older people supports this hypothesis. These lesion include endothelial damage with thrombosis and damage to media with oedema, haemorrhage and inflammation. [221, 222]

Chapter 4: Brian Natriuretic Peptides in Cardiovascular Disease

Natriuretic peptides are a group of hormones with potent natriuretic, diuretic and vasodilator properties. There are three major peptides in this family: atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C type natriuretic peptide (CNP). All 3 peptides share a common 17-amino acid ring structure and play an important physiological role in countering the effects of hypertension and plasma volume expansion.

4.1 Background

In 1956 Henry and Pearce described an increased urinary flow after mechanically stretching the canine left atrium. Twenty five years late, in 1981 de Bold and colleagues made a very significant observation that injection of extracts of atrial tissue into rats caused a copious sodium excretion and urinary flow (de Bold et al. 1981). This subsequently led to the isolation of atrial natriuretic peptide (ANP), a factor with potent natriuretic, diuretic and vasodilatory properties. In 1988 a peptide with similar properties was identified in the porcine brain and therefore named brain natriuretic peptide (Sudoh et al. 1988). Although present in the human brain, highest concentrations are in fact found in the cardiac ventricles. Since then, C-type natriuretic peptide, a third compound with similar structure and pharmacological spectrum has also been discovered (Sudoh et al. 1990). Plasma levels of CNP are very low in humans.

4.2 Physiology

Both ANP and BNP are released from the heart, ANP preferentially from atria and BNP from ventricles. However, both can be secreted from either chamber in certain pathological conditions including myocardial infarction and left ventricular dysfunction [223]. The ventricle is the main site of BNP secretion. Myocardial wall stretch due to volume expansion or pressure overload, acts as a major stimulus for synthesis and release of both ANP and BNP [66, 224]. Elevated levels of angiotensin 2 also stimulate secretion of BNP. Both of these hormones are realised as prohormones, which subsequently are cleaved by the trans-membrane enzyme “Corin” into their active form (carboxyl terminal) and N-terminal fragment [225]. ProBNP is a 98 amino acid peptide, which is cleaved upon release

into an active 32 amino acid BNP and a 76 amino acid containing N-terminal-proBNP (NT-proBNP) [224].

The biological actions of these natriuretic peptides are mediated through membrane bound natriuretic peptide receptors (NRPs) [66]. Three natriuretic peptide receptors have been identified in humans [226]. Type A (NRP-A) and type B (NRP-B) are guanylate cyclase receptors and both are present in the lung, kidneys and adrenal glands. NRP-A has a greater affinity for ANP than BNP and is most abundant in large blood vessels. NRP-B primarily binds CNP and is predominately found in the brain. Type C (NRP –C) receptor is mainly involved in the clearance of peptides. All three natriuretic peptides bind to NRP-C with equal affinity and are subsequently internalized and enzymatically degraded. [224, 227, 228].

In the cardiovascular system the natriuretic peptides reduce sympathetic tone in the peripheral vasculature causing fluid shifts by increasing the permeability of the vascular endothelium and increasing venous capacitance. These actions lead to a decrease in pre-load and blood pressure. In the kidney the glomerular filtration rate (GFR) is increased through a combination of dilation of the afferent renal arterioles, constriction of the efferent renal arterioles, and relaxation of the tubular mesangial cells. The peptides have a direct natriuretic effect in the renal tubules, but also cause a reduction in plasma renin and aldosterone concentrations. In the brain stem, the natriuretic peptides serve to decrease sympathetic tone and inhibit vasopressin secretion. Centrally there is suppression of thirst and salt appetite [66, 224].

BNP has a plasma half-life of 22 minutes. The NT proBNP in contrast has a longer half life of approximately 60-120 minutes, leading to higher circulating levels and slower fluctuations compared with BNP [227]. Its concentration increases with age and is higher in women than in men [229, 230]. BNP is less affected by age and renal function than its precursor pro-BNP which can also be measured in plasma [227, 231].

4.3 Normal Value of NT-pro BNP

Plasma levels of natriuretic peptides increase with age and are usually higher in female gender. [229, 232, 233]. However, in elderly cohort (aged ≥ 75 years) natriuretic peptide levels have been reported higher in male gender. [229, 230, 234] This effect of age and gender is independent of the age associated increase in prevalence of diastolic dysfunction and renal impairment. This is the reason that age and gender specific cut-off values of natriuretic peptides are used in the detection of various cardiovascular diseases including heart failure. Many studies have reported the normal range of NT-proBNP across various age groups, however little is known about the normal reference range of NT-proBNP in the 85+ years old fraction of the population for LV systolic and diastolic function.

Glasko and colleagues [232] studied a random sample subjects aged 45 and above (n = 1205, 671 male, 534 female, median age 61 years, range 45–91 years) from the general population to establish the normal range of NT-proBNP across various age groups. All patients had a full risk factor assessment including lipid profiles, a full biochemical profile including renal and liver function tests and an echocardiogram with measurement of their ejection fraction. This was one of the first clinical studies to calculate the upper reference values (97.5th percentile) for NT-proBNP.

A population with no cardiovascular risk factors, no structural heart disease and a LVEF of greater than 50% was defined and used as a reference normal population. They identified 389 individuals who had no risk factors, creatinine < 120 μmol/l, no ECG changes, no evidence of structural abnormalities or wall motion abnormalities on echocardiography and with an LVEF >50%. It was also important to note that only 111 participants of this sample were aged 65 or above (mean age = 55 ± 8 years) and none of the participants was aged 80 or above. They defined the age and gender specific upper reference cut-off values of NT-proBNP in this "normal" population. The study found the following cut-off values: 100 pg/ml and 172 pg/ml for men aged 45-59 years and 60+ years respectively. The cut-off values for women aged 45-59 years were 164 pg/ml and 225 pg/ml respectively. Investigators of the study believed that possible explanation for increased NT-proBNP levels with age was increased age related subtle diastolic dysfunction. Although the normal subjects had diastolic heart failure excluded, normal subjects ≥ 60 years old still had

significantly lower E/A ratios than the normal subjects < 60 years old (1.0 vs. 1.2; p <0.0001). The underlying cause for higher levels of NT-proBNP in females was unclear.

Another study of the community based residents aged 45 years and above (mean age = 62 ± 10) in Olmsted County, Minnesota has shown similar results [229, 230]. The investigators considered participants as clinically "normal" when they had no history of cardiovascular, pulmonary, or renal disease; had no diabetes; took no cardiovascular medications; had normal echocardiograms for systolic and diastolic function; and were in normal sinus rhythm.

NT-proBNP levels in normal participants were higher in females and also increased with increasing age (Figure 1). In normal participants (n = 746), female gender (r =0.287, p < 0.0001) and increasing age (r =0.537, p < 0.0001) were the strongest independent predictors of higher NT-proBNP levels. It was also interesting to note that even in that study there were only 20 people aged 75 years and above in the normal group and nearly 250 people in the overall study. Investigators of the study believed that the possible explanation for increased natriuretic peptide levels in females was probably related to use of oestrogen as BNP levels were 21% higher in women on HRT than in women not on HRT (CI 6% to 40%, p < 0.005). Investigators of the Dallas heart study (Texas, USA) studied 682 community based young women (35 years to 49 years) for any possible association between gonadal hormones (including estrogens and testosterone) and natriuretic peptides [235]. Subjects with heart failure and renal disease (creatinine >2 mg/dl) were excluded. Investigators found no significant difference in NT-proBNP levels of pre-menopausal and post-menopausal women. Among post-menopausal women, there was no difference in NT-proBNP levels among estrogen users and non users. The median NT-proBNP levels in estrogen users were 38.8 pg/dl (interquartile range 22.0 to 79.0) and 38.4 pg/dl (interquartile range 18.4 to 74.1) in nonusers (p = 0.70). Investigators from this study suggested a strong inverse relationship between serum testosterone levels and natriuretic peptide levels (for BNP: r = -0.155, p < 0.0001; NT-proBNP: r = -0.233, p < 0.0001). However, an exact explanation for higher NT-proBNP levels in females is still unclear.

Costello-Boerrigter et al also studied NT-proBNP levels as its ability to detect LVSD in community dwelling 45 years and above cohort. The also reported 'normal' cut off values of NT-proBNP for different age ranges. Participants were considered clinically normal

when they had no history of cardiovascular, respiratory, or renal disease; had no diabetes; were not taking cardiovascular medications; had for systolic and diastolic function; and were in normal sinus rhythm. In this study 275 people were aged 75 years and above out of which only 20 participants were in 'normal' group. In this age group values of NT-proBNP levels were 124pg/ml; 42 - 587 pg/ml (Median; 5th–95th Percentile) in females (n=18) and 57pg/ml; 46 - 68pg/ml (Median; 5th–95th Percentile) in males (n=2).[230]

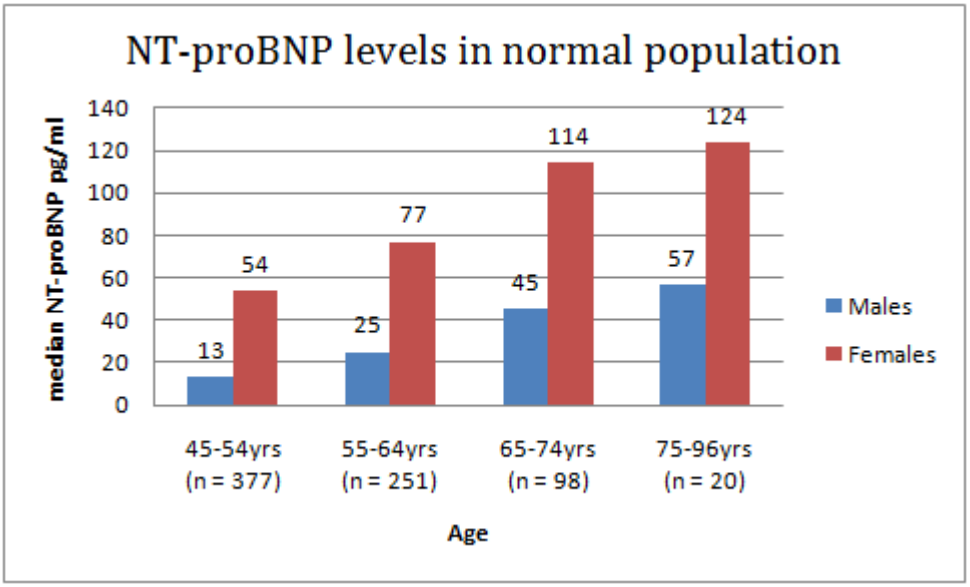


Figure 4.1: Age and gender specific median levels of NT-proBNP levels in "healthy population".

(Blue) males, (red) females; Total number of people in each age group are mentioned at the bottom of each bar. [230]

Apart from age and gender, many other factors including renal function, valvular heart disease, coronary artery disease, arrhythmias, pulmonary hypertension and sepsis also cause increase in plasma levels of natriuretic peptides.

4.4 Diagnostic and Prognostic Role of NT-ProBNP In Heart Failure

Plasma natriuretic peptide (BNP/NT-proBNP) levels have reliably shown to identify the left ventricular systolic dysfunction (LVSD), left ventricular diastolic dysfunction (LVDD) and also have been shown to have an important diagnostic role in patients with heart failure. Plasma BNP/NT-proBNP levels are also strongly correlated with the severity of the symptom (NYHA status) of the heart failure patient.

BNP and NT-proBNP plasma concentrations have been shown to be reliable markers of CHF, displaying similar diagnostic accuracy [236-239]. Reference intervals and decision limits of BNP and NT-proBNP have already been described in old healthy subjects [240]; however, the diagnostic accuracy of BNP and NT-proBNP has been little investigated in 85+ years old patients especially in community settings.

The PRIDE study [239] was a prospective and blinded study of 600 patients (mean age = 64.8 ± 14.8) presenting to the emergency department at Massachusetts General Hospital with complaints of dyspnoea. Exclusion criteria for the study were severe renal insufficiency (serum creatinine level > 2.5 mg/dl, dyspnoea after chest trauma, dyspnoea secondary to severe coronary ischemia that was identified as > 0.1 mV ST-segment elevation or ST-segment depression on a 12-lead electrocardiogram if performed at presentation), > 2-hour delay after urgent intravenous loop diuretic administration and unblinded natriuretic peptide level measurement.

Patients were assessed clinically by taking a detailed history, performing a clinical examination and diagnostic studies in the emergency department, such as ECG, chest x-ray, and standard blood tests. An additional blood sample was collected for NT-proBNP measurement as well. At the end of the standard clinical assessment and with the knowledge of the results of all clinical tests except NT-proBNP levels, the managing emergency department attending physician was asked to estimate the likelihood that acute heart failure (HF) was the cause of the patient's dyspnoea. The emergency department discharge diagnosis was also recorded. The diagnosis for each patient was later confirmed by the study cardiologists after reviewing all hospital records (including admit/discharge notes, results of laboratory and radiologic testing, cardiac tests such as echocardiograms). Patients were classified by diagnosis at presentation into 1 of 3 categories: acute HF, noncardiac dyspnoea in a patient who had previous HF, or no HF. NT-proBNP was found

to be sensitive and specific for the diagnosis of acute HF with the area under the receiver operating characteristic curve (AUC) = 0.94. Figure 2 shows NT-proBNP also had higher diagnostic accuracy than the ED physician in diagnosing CHF with AUC = 0.96 ($p = 0.006$). Patients with acute heart failure had median NT-proBNP over 4000 pg/ml (interquartile range 1,675 to 10,028), compared with 115 pg/ml (interquartile range 46 to 433) in those without heart failure ($p < 0.001$). The difference remained significant when comparing NT-proBNP levels of those who had acute HF with those who had noncardiac dyspnoea and previous HF (whose median NT-proBNP level was 1,175 pg/ml, $p = 0.02$). Multivariate analysis showed an increased NT-proBNP level was the strongest predictor of acute HF (OR 44.0, 95% CI 21.0 to 91.0, $p < 0.0001$).

An NT-proBNP cut-point of 300 pg/ml was proposed to 'rule-out' a diagnosis of HF, whereas the optimal cut-points for ruling in acute CHF were suggested as 450 pg/ml (for < 50 years) and 900 pg/ml (for ≥ 50 years), with an excellent area under each receiver-operating characteristic curve (0.98 and 0.93, respectively; $p < 0.0001$).

NT-proBNP levels also significantly correlate with the NYHA functional class in patients with heart failure and increase with the severity of symptoms (Figure 3). In the patients with NYHA II median levels of NT-proBNP were 1591pg/ml (interquartile range 1066 pg/ml to 2488 pg/ml), NYHA III median levels of NT-proBNP were 3438 pg/ml (interquartile range 1337 pg/ml to 9502 pg/ml) and NYHA IV median levels of NT-proBNP were 5564 pg/ml (interquartile range 2274 pg/ml to 12187 pg/ml). [69, 239]

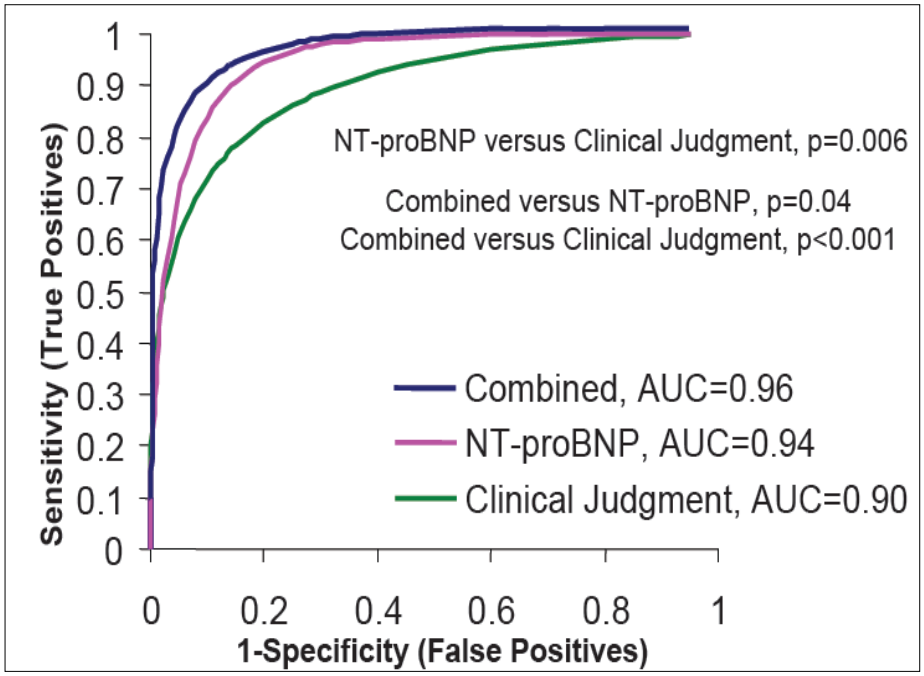


Figure 4.2. Receiver-operating characteristic (ROC) curve comparison of NT-proBNP versus clinician-estimated likelihood for the emergency department diagnosis of acute CHF. (adapted from Januzzi et al) [239]

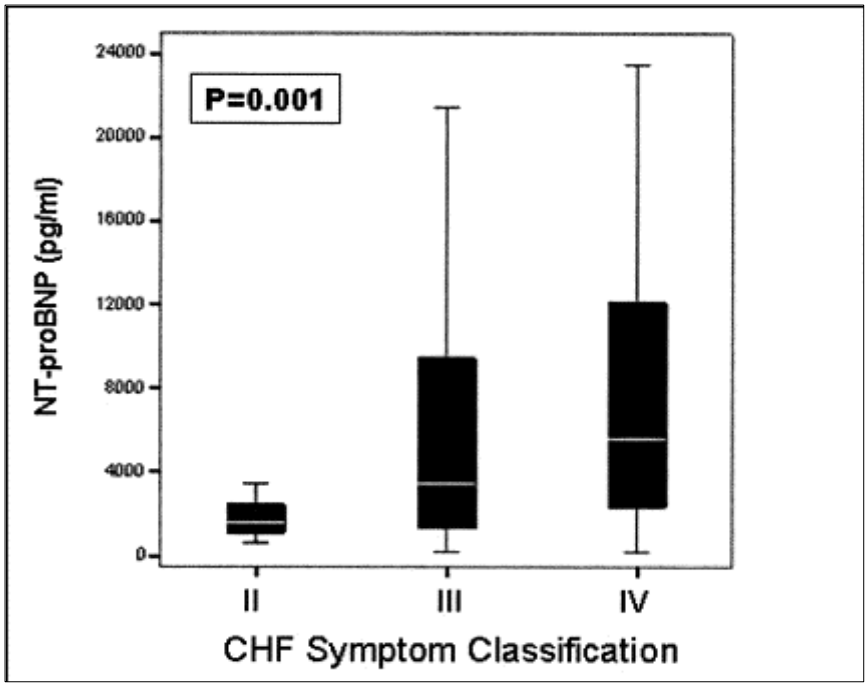


Figure 4.3: Correlation between median NT-proBNP levels and symptom severity based on New York Heart Association symptom classification. Boxes, interquartile ranges; whiskers, 5th and 95th percentiles. Data from the PRIDE study. (adapted from Januzzi et al) [239]

The International Collaborative of NT-proBNP Study (ICON) [69] is an international pooled analysis of 1256 patients (mean age = 68.3 ± 15 years) presenting in Emergency Department (ED) from four similar studies of NT-proBNP testing from Christchurch (New Zealand), Barcelona (Spain), Boston MA (USA) and Maastricht (Netherlands). NT-proBNP diagnostic cut-points for diagnosing acute HF were determined with the use of logistic regression analyses, with resulting receiver operating characteristic (ROC) curves.

Of the 1256 dyspnoeic subjects in this pooled analysis, 720 (57.3%) had acute HF, whereas 536 (42.7%) did not. Of those without acute HF exacerbation at the time of enrolment, 55 subjects (4.4% overall) had a prior diagnosis of HF. The median NT-proBNP concentration of those patients with acute HF exacerbation (4639 pg/ml) was significantly higher than those with neither acute nor prior HF (108 pg/ml, $p < 0.001$). Among those patients <50 years (n = 184), 50–75 years (n = 537), and >75 years of age (n = 535), NT-proBNP had an area under the ROC curve of 0.99, 0.93, and 0.86 for the diagnosis of acute HF (all $p < 0.0001$).

Investigators suggested an age-independent approach for 'ruling out' acute HF with a single cut-point of 300 pg/ml (95% CI=241–369) demonstrating a sensitivity of 99%, a specificity of 60%, and an NPV of 98%. The optimal cut-points of NT-proBNP levels for diagnosing acute HF (with 95% CI) were suggested by ROC curve analysis to be 450 pg/ml (145, 1463 pg/ml), 900 pg/ml (676, 1244 pg/ml), and 1800 pg/ml (1281, 2641 pg/ml) for the identification of acute HF in subjects aged <50, 50–75, and >75 years, respectively. Investigators didn't find any gender difference in NT-proBNP levels in patients with acute HF so they based the cut-off limits only based on age. This was the first study that included more than 500 people with age 75 years and above but so for no study has described the optimal cut-off NT-proBNP levels for the diagnosis of chronic heart failure in 85+ year old community residents.

The predictive value of natriuretic peptides in detecting in LVSD has been studied across different age ranges; however 85+ years old, especially in community settings were probably under represented in such studies. Redfield and colleagues studied the role of NT-proBNP in detecting LVSD in a random sample of 2042 participants aged > 45 years (mean age = 62±10 years), who were residents of Olmsted county, Minnesota [230]. Medical records review and detailed two-dimensional and colour Doppler echocardiography were

done on participating residents (n = 2042). Plasma NT-proBNP levels were available in 1869 participants. Participants who had no history of cardiovascular, pulmonary, renal disease or diabetes, who took no cardiovascular medications, who had normal echocardiograms for systolic and diastolic function and who were in normal sinus rhythm were considered clinically normal (n = 749, mean age = 57±10 years). Participants with LVEF < 50% were considered to have left ventricular systolic dysfunction (LVSD). There were 115 participants with LVEF less than 50% and 37 participants were identified to have LVEF below 40%. A receiver operating characteristic (ROC) curve analysis was performed to establish the predictive value of NT-proBNP for detecting LVSD. The results of ROC analysis for the detection of LVSD showed the AUC was higher in the overall population for the detection of LVEF ≤ 40% (AUC = 0.94; sensitivity = 86.5 and specificity = 86.0; NT-proBNP cut-off levels of 228 pg/ml) than LVEF blow 50% (AUC = 0.78; sensitivity = 73.9 and specificity = 73.8; NT-proBNP cut-off levels of 129 pg/ml).

In another study Tschöpe and colleagues [241] studied the role of NT-proBNP in diagnosing isolated diastolic dysfunction. They investigated 118 patients who had preserved LV function (LVEF ≥ 50%) and normal LV dimensions as determined by echocardiography and ventriculography. Sixty-eight patients (mean age 51±9) had exertional dyspnoea and isolated diastolic dysfunction while the remaining 50 patients (mean age 49±10) had normal diastolic function (control group). Patients with atrial fibrillation, lung diseases, renal dysfunction, significant heart valve disease, or other severe concomitant diseases were excluded from the study. Medications that can influence haemodynamics (diuretics, beta-blockers, calcium-blockers, and ACE inhibitors) were all stopped for 48 hours before examinations were performed. LV systolic and diastolic function was assessed by echocardiography, tissue doppler imaging (TDI), and left and right heart catheterization. Plasma NT-proBNP levels were determined simultaneously.

NT-proBNP levels were four-fold elevated in patients with diastolic abnormalities when compared with control patients (189.54 pg/ml vs 51.89 pg/ml; $p < 0.001$). NT-proBNP levels also increased significantly according to the severity of overall diastolic dysfunction (figure 4). In mild diastolic dysfunction or impaired relaxation (grade 1) median NT-proBNP levels were 151.6 pg/ml (interquartile range from 90.6 pg/ml to 278.1 pg/ml), moderate diastolic dysfunction or pseudonormal filling (grade 2) 308.1 pg/ml (interquartile

range from 261.7 to 568.2) and severe diastolic dysfunction or restrictive filling (grade 3) 2307.1 pg/ml (interquartile range from 1592.0 to 6440.1).

Diagnostic accuracy of NT-proBNP in diagnosing isolated diastolic dysfunction was almost as good as the LVEDP (invasive) and TDI and better than the E/A ratio of Doppler echocardiography. ROC curve analyses revealed an AUC for NT-proBNP of 0.83, between the AUCs of LVEDP (0.84) and TDI (0.81), whereas AUC for IVRT, DT and E/A were 0.63, 0.59 and 0.70 respectively. At a cut-off value of 110 pg/ml, NT-proBNP showed a high sensitivity of 72%, a specificity of 97%, a positive predictive value of 84%, and the negative predictive value of 94%. Because this was study done in relatively young subjects, this cut off value may not be valid in the older age groups.

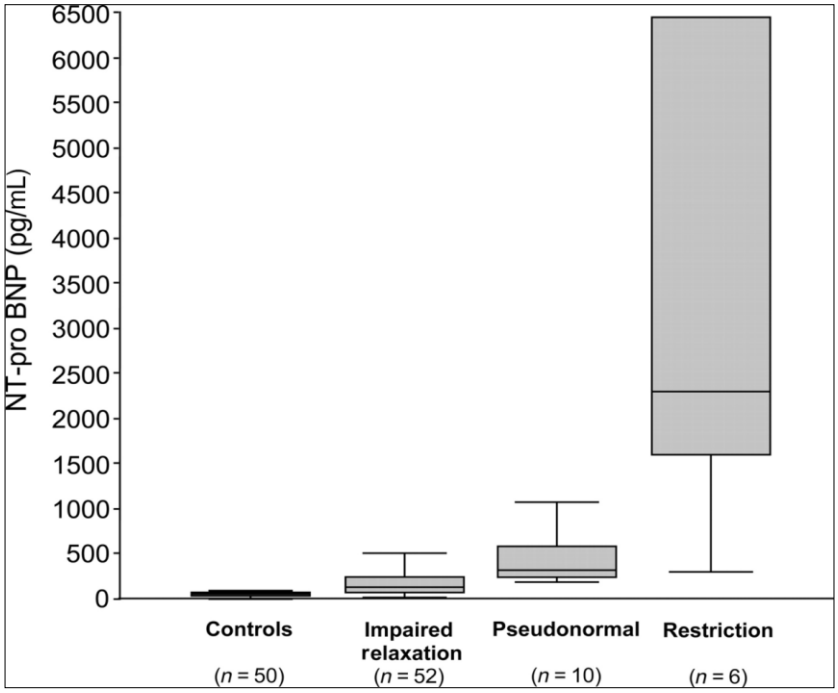


Figure 4.4: NT-proBNP levels in the patients with LV diastolic dysfunction are significantly elevated and correlate with the severity of disease. (adapted from Tschöpe et al, Eur Heart J. Nov 2005; 26(21): 2277-2284) [241]

BNP and NT-proBNP have been shown to be important prognostic indicators. McDonagh and colleagues [65] assessed the long-term prognostic role of BNP concentration in 1653 subjects aged 25–74 randomly sampled from north Glasgow. Patients were followed up for 4 years during which 80 people died resulting in all-cause mortality of 4.9%. The median BNP concentration in those patients who died was significantly higher than in survivors (16.9 vs. 7.8 pg/ml) and a BNP level of greater than 17.9 pg/ml ($p = 0.006$, hazard ratio 2.2 (95% CI 1.2 to 3.8), was an independent predictor of mortality in sub-group analysis.

In another study analysing the prognostic value of natriuretic peptides, Wang and colleagues [242] studied a cohort of patients from the Framingham offspring study, excluding patients with a history of heart failure or biochemical renal impairment. BNP and NT-pro BNP concentration were measured in 3346 patients who were regularly monitored for the occurrence of cardiovascular events or death. Follow-up was prospective and investigators were blinded to plasma natriuretic peptide levels. Median follow-up was 5.2 years during which 119 participants died and 79 had a first cardiovascular event. In multivariate analysis, increasing plasma natriuretic peptide levels were significantly associated with an elevated risk of death, stroke, first cardiovascular event, atrial fibrillation and heart failure, the association being strongest with the last two. After adjustment for cardiovascular risk factors, each increment of 1 SD in log B-type natriuretic peptide levels was associated with a 27% increase in the risk of death ($p = 0.009$), a 28% increase in the risk of a first cardiovascular event ($p = 0.03$), a 77% increase in the risk of heart failure ($p < 0.001$), a 66% increase in the risk of atrial fibrillation ($p < 0.001$), and a 53% increase in the risk of stroke or transient ischemic attack ($P=0.002$). There was however no association between natriuretic peptide levels and coronary heart disease events (MI, unstable angina).

4.5 BNP Versus NT-pro BNP

Although NT-proBNP has different pharmacokinetics as described earlier, its performance characteristics are similar to BNP. There are not many studies with head to head comparison of BNP and NT-proBNP. In general, BNP and NT-proBNP levels are reasonably correlated, and either can be used. However the absolute values of these assays are not interchangeable.

One recent community based study from Olmsted County has suggested NT-proBNP performed at least equivalently to BNP in detecting LV dysfunction and was superior in some subgroups (elderly, females) in detecting LV systolic dysfunction [230].

Sanz and colleagues [243] have compared the diagnostic accuracy of NT-proBNP and BNP to detect the LVSD in patients presenting with dyspnoea to the emergency department with ROC analysis. They found no significant difference ($p < 0.001$) in the AUC for NT-proBNP (0.98) and BNP (0.975). They also described a strong correlation between NT-proBNP levels and BNP levels in the detection of LVSD ($r = 0.89$). In a similar study Lainchbury and colleagues [244] also described the similar results with strong correlation ($r = 0.902$, $p < 0.001$) between the results of the N-terminal brain natriuretic peptide (N-BNP) assay and the brain natriuretic peptide assay (BNP). (Figure 5)

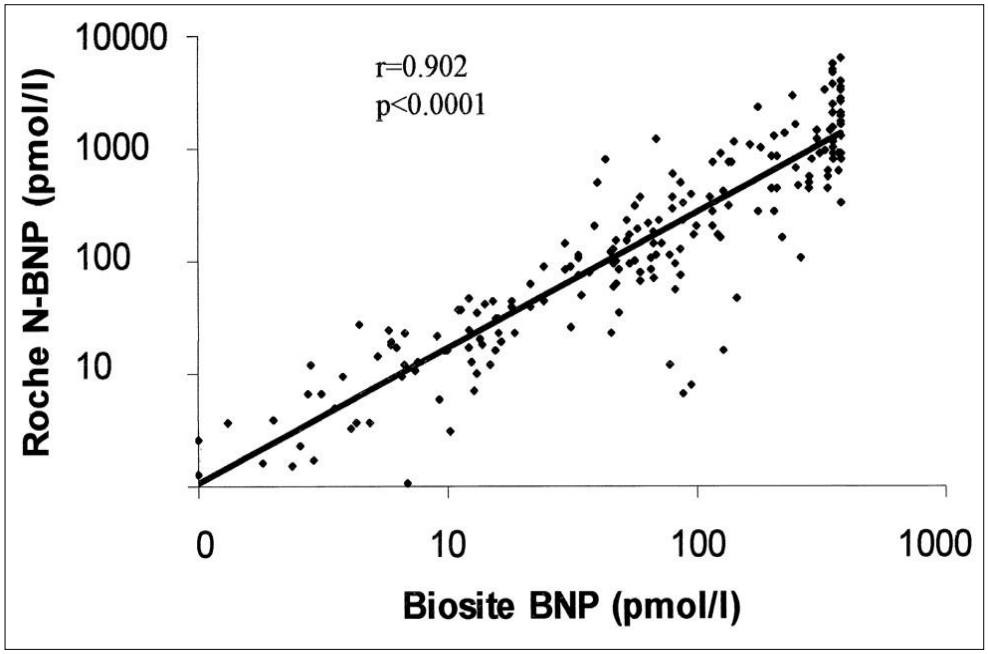


Figure 4.5: Correlation between the results of the Roche N-terminal brain natriuretic peptide (N-BNP) assay and the Biosite brain natriuretic peptide (BNP) assay (adapted from Lainchbury, et al) [244]

Data from the Olmsted county study suggest that NT-proBNP is probably better in detection of LVSD in people older than 65 years of age and in female patients [230]. For comparison purpose they divided the cohort (n = 1869) into smaller sub groups: people < 65 years, people ≥ 65 years, males, females and also people with LVEF ≤ 50% and LVEF ≤ 40%. Results from ROC curve analysis showed that for detecting an LVEF ≤40%, NT-proBNP had a significantly higher AUC in comparison with BNP in the total population (0.94 vs. 0.89; p = 0.0087) and for the subgroups of male patients (0.95 vs. 0.91; p =0.01) and patients ≥65 years old (0.92 vs. 0.87; p = 0.036). For detecting an LVEF ≤50%, the AUC for NT-proBNP was significantly higher than that for BNP in all patients (0.78 vs. 0.72; p < 0.001), patients ≥65 years old (0.85 vs. 0.79; p = 0.001), patients <65 years old (0.65 vs. 0.56; p < 0.0001), male patients (0.80 vs. 0.73; p < 0.001), and female patients <65 years old (0.75 vs. 0.64; p = 0.02).

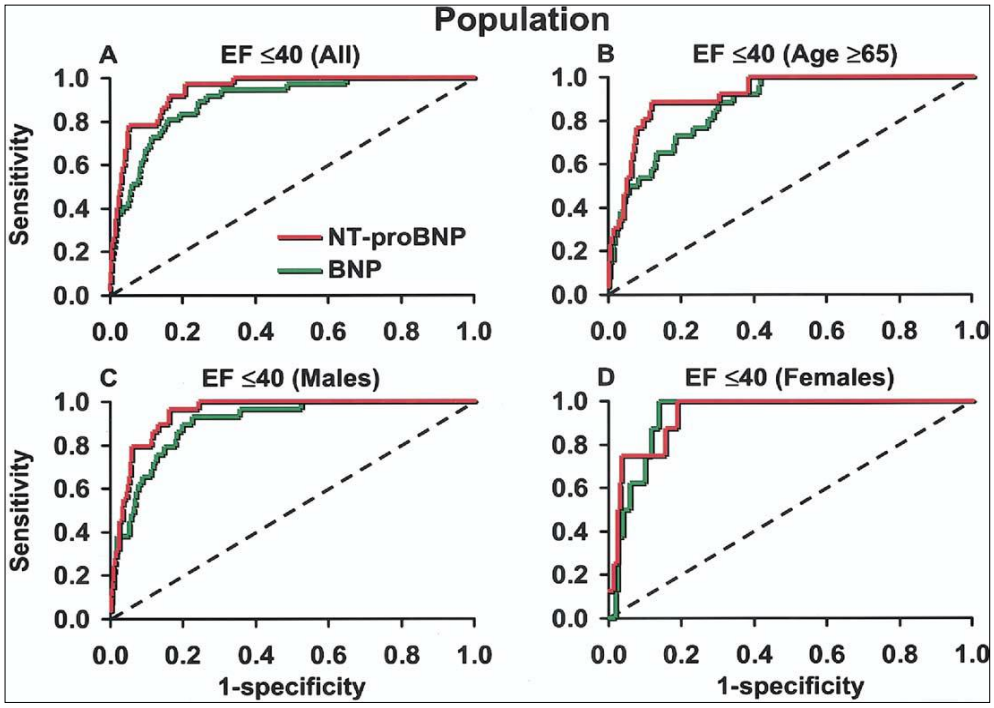


Figure 4.6: The receiver operating characteristic (ROC) curves of amino-terminal pro-B-type natriuretic peptide (NT-proBNP) (red) and BNP (green) for detecting an ejection fraction (EF) ≤40% for the entire population (all) (A), patients ≥65 years old (B), male patients (C), and female patients (D). (adapted from Costello-Boerrigter et al) [230]

Diagnostic performance of natriuretic peptides to detect LVSD and heart failure in elderly population has been reported as less robust as compared with younger population. In a meta-analysis of natriuretic peptides in diagnosis of heart failure and screening of LVSD in community Ewald et al have reported the age related decrease in the performance of NT-proBNP and BNP. At a given cut point, which would give sensitivity of 85% for BNP to detect underlying LVSD, the associated specificity would decrease from 90% in people aged 55 years to 54% in people aged 85 years. The values for NT-proBNP decrease more steeply. [245] In another systemic review, Vaes et al also found limited evidence of diagnostic utility of natriuretic peptides to detect LVSD and heart failure in community dwelling elderly patients aged 75 and over. [246] Hildebrandt et all have recently suggested to use age specific cut off of NT-proBNP to detect LVSD in community dwelling residents (median age 62 years, range 18-100) from different pooled studies, which collected data on NT-proBNP or BNP and LV systolic function on echocardiographic assessment. 19% of cohort was aged 75 yrs and above. They suggested that NT-proBNP is probably better in detection of LVSD if different cut-off values are used rather than a single value for all age groups. They overall area under the curve (AUC) was 0.89 when a single cut-off NT-proBNP value was used. When looking at different age groups, AUC was highest (0.95) for <50 years and lowest (0.82) for aged 75 years and above. [247] However, no study in 85+ year old community dwelling people has so far been reported to assess NT-proBNP diagnostic ability to detect LVSD, diastolic dysfunction and heart failure.

4.6 NT-proBNP and Arterial Stiffness

As discussed in the previous section of this chapter both increased levels of NT-proBNP/BNP and increased markers of arterial stiffness including PWV, augmentation pressure and augmentation index are associated with increased cardiovascular morbidity and mortality. BNP/NT-proBNP are predominantly released due to increased LV wall stress and increased arterial stiffness is also associated with increased LV afterload. Excessive and premature wave reflection has a deleterious effect on left ventricular systolic and diastolic function, leading to atrial and ventricular remodelling and hypertrophy. Little is known about the relations of natriuretic peptides and arterial wall stiffness in the community in any age group especially in the 85+ years old.

Levy and colleagues [248] have studied the relationship of plasma N-terminal atrial natriuretic peptide (NT-ANP) and brain natriuretic peptide (BNP) to arterial stiffness in participants in the Framingham Heart Study. Different variables of arterial stiffness including PWV and central pulse pressure were assessed in a total of 1962 participants (mean age, 61 years; 856 men, 1106 women). Plasma levels of NT-ANP and BNP were also measured in all individuals. They described increasing levels of NT-ANP and BNP were associated with carotid-femoral PWV (men: $r = 0.043$ and $p < 0.001$, respectively; women: $r = 0.037$ and $p = 0.04$). Plasma BNP levels were also associated with central pulse pressure (men: $r = 0.129$ and $p = <0.001$).

Shroff and colleagues [249] have also reported similar findings. They studied 55 (mean age = 51 ± 11 years) consecutive patients with chest pain and negative troponins admitted to a cardiology observation unit in a tertiary care hospital. Patients with acute coronary syndrome, decompensated heart failure, unstable arrhythmias and patients with end-stage renal disease were excluded from the study. A venous blood sample was taken of all the participants for measurement of hs-CRP and BNP. Carotid distensibility was measured using B-mode-guided M-mode ultrasonography and Stiffness index β (marker of carotid artery stiffness) was calculated. They reported suggested a strong relationship between carotid stiffness index β and age ($r = 0.56$, $p < 0.0001$), BNP ($r = 0.45$, $p < 0.004$) and hs-CRP ($r = 0.26$, $p = 0.06$), respectively. This relationship between arterial stiffness and BNP existed even after controlling for age and hs-CRP. Shroff and colleagues believe that the

relationship between arterial stiffness and BNP is probably due to altered ventriculo-vascular coupling leading to the development of diastolic dysfunction and increase in BNP levels as I have discussed in previous section in detail.

4.7 Aims

This Thesis will look at the following questions:

1- What is the prevalence of LV systolic and diastolic dysfunction in community dwelling 85+ years old?
2- What is the extent of symptomatic LV dysfunction?
3- What is the extent of undiagnosed and mis-diagnosed LV dysfunction?
4- Is there any association of markers of arterial stiffness and LV systolic and diastolic function?
5- What is the prevalence of valvular heart disease in community dwelling 85+ years old?
6- Feasibility of domiciliary echocardiography?
7- What is the normative range of NT-proBNP in community dwelling 85+ years old?
8- What is the diagnostic performance of NT-proBNP to detect LV dysfunction in community dwelling 85+ years old?
9- What is the prevalence of vascular disease in community dwelling 85+ years old?
10- What is the extent of undiagnosed and mis-diagnosed vascular disease?

Section II
Materials and Methods

Chapter 5. Materials and Methods

This chapter describes a brief outline of the core Newcastle 85+ study and a full description of the design and measures used in the cardiac sub-study which is the subject of this thesis. The cardiac sub-study was nested in the core study and took place during the 1st and 2nd follow-up assessments of the core study.

5.1 Core Newcastle 85+ Study

The Newcastle 85+ study is a population-based longitudinal study of an inception cohort of 85 year olds living in Newcastle upon Tyne and North Tyneside in north east England.

The main aims of the study are to study in detail the health spectrum of an unselected cohort of the 'oldest old':

- to follow health trajectories and outcomes as the cohort ages
- to enhance the understanding of factors contributing to healthy ageing
- to enhance understanding of the biological mechanisms of ageing.

Participants were recruited through general practices. All 64 general practices in Newcastle upon Tyne and North Tyneside NHS Primary Care Trusts (PCTs) were approached to participate in the study and 53 (83%) agreed; participating and non-participating practices were similar across key practice variables. All people born in 1921, who turned 85 in 2006 when recruitment commenced, and permanently registered with a participating general practice constituted the sampling frame. General practitioners (GP) were asked to review patient lists before mail-out and to exclude only those with end stage terminal illness and those who might pose a safety risk to a nurse visiting alone. Excepting these exclusions, all those remaining in the sampling frame were invited to participate in the study, whether living at home or in an institution and regardless of their state of health. Written informed consent was obtained from participants and where the participant lacked the capacity to consent, an opinion was sought from a "consultee" in accordance with the UK Mental Capacity Act.[250] Participation in the core study at baseline entailed a detailed multidimensional health assessment and a review of medical records held by the general

practice; participants could decline elements of the protocol. 851 participants (59% of those eligible) were recruited for both health assessment and review of general practice (GP) medical records; an additional 188 (13% of those eligible) were recruited to GP record review only and three people (0.2%) agreed to health assessment only (Appendix 1-2).

Participants were assessed in their current place of residence (home or institution) by a research nurse. The assessment was detailed and multi-dimensional including an extensive range of questionnaires, measurements, functional tests and blood tests. Details of the core study assessments at baseline are outlined in appendix 3.

In addition to the multi-dimensional health assessment at baseline, the research nurse reviewed the participants' general practice medical records and extracted data on pre-existing diagnosed diseases including heart failure, hypertension, ischaemic heart disease (angina or myocardial infarction or coronary artery bypass grafts or coronary angioplasty or coronary stent), cerebrovascular disease (stroke or transient ischaemic attack or carotid endarterectomy), peripheral vascular disease and diabetes mellitus and current medication and use of general practice services.

The recruited core study cohort was assessed at baseline, 18 months (phase 2) and 36 months (phase 3). Figure 5.1 shows the timelines of the core Newcastle 85+ Study. Phase 2 (18 months from baseline) spanned 18 months during which recruitment and re-assessment took place of surviving participants; 630 participants were recruited to phase 2 of the study. Phase 3 (36 months from baseline) again spanned 18 months; a total of 484 participants were recruited to Phase 3. Drop out for non-death reasons between the first two phases was around 10% but reduced to 7.6% between phases 2 and 3 with the remaining loss due to deaths. Re-assessment of the participants in Phases 2 and 3 took place in a similar manner to baseline with some minor changes. General practice medical records were not reviewed in this phase 2 but Phase 3 included a repeat review for the entire cohort recruited at baseline (estimated n=1021, taking account of withdrawals) to capture incident disease/events and use of GP services. Appendix 4 details the assessments for the core Newcastle 85+ Study in each of the three phases.

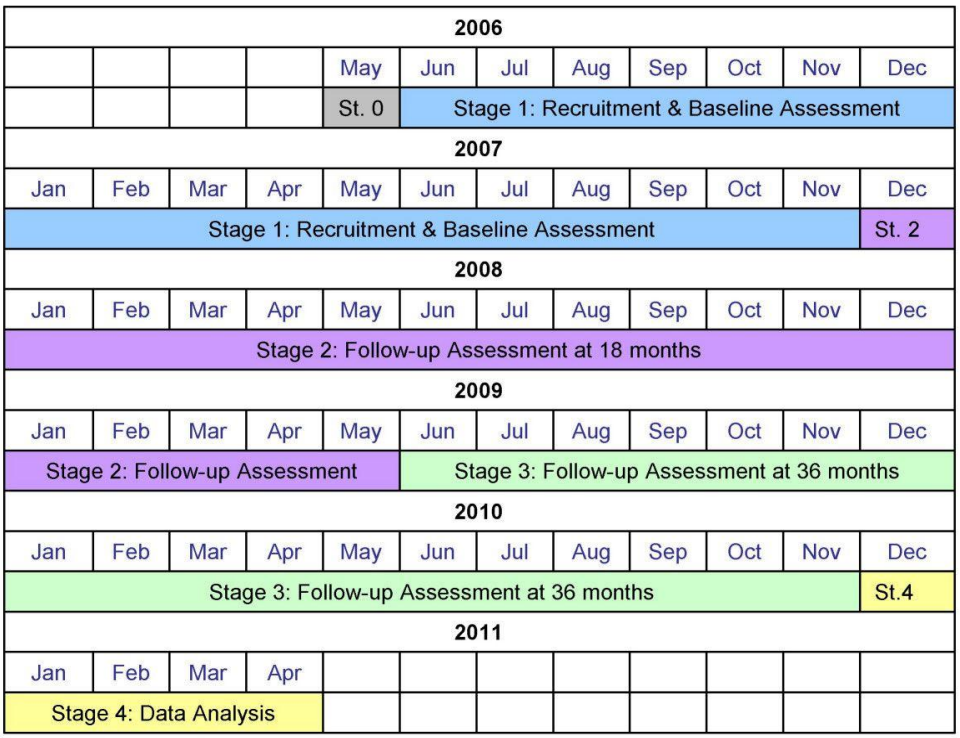


Figure 5.1: Different phases and recruitment timeline of the core Newcastle 85+ study[249]

(Adapted from The Newcastle 85+ study: biological, clinical and psychosocial factors associated with healthy ageing: study protocol. BMC Geriatrics – An open access journal)

5.2 Cardiovascular Phenotyping of Newcastle 85+ Cohort

The cardiovascular phenotyping sub-study was divided into the following three phases.

1- Training phase (3 months):

2- Data collection phase (14 months):

3- Data preparation and analysis phase (7 months)

Training phase involved training, piloting and designing the protocols. Before commencing this research project I had three years experience of heart scanning and had passed the British Society of Echocardiography written examination. During the initial three months I received additional training as follows:

- To standardize my echo technique I spent 40 hours in the Freeman Hospital (FRH, The Newcastle upon Tyne Hospitals NHS Foundation Trust) echocardiography department (annual caseload 5000 cases/year) under the supervision of Dr Antoinette Kenny.
- I received hands on training in carotid intima media thickness CIMT measurement in the Vascular Physics Department of the Freeman Hospital under the supervision of Mr. Crispian Oates (Chief Vascular Physicist, FRH).
- I received training in vascular assessment using the SphygmoCor and Vicorder technologies from a representative (Mr Simon Dickinson) from Smart Medical UK.

Following this training, I designed a cardiovascular phenotyping protocol in collaboration with Professor Bernard Keavney and performed five test runs on healthy volunteers at the Institute of Ageing and Health (Newcastle University) to master the technique. Once I had perfected conducting these assessments within 60 minutes I arranged five ‘dummy’ test runs within the community on six healthy volunteers aged between 65 and 85.

The Cardiovascular phenotyping of the Newcastle 85+ study cohort took place during phase 2 or phase 3 (2nd or 3rd follow-up visits) of the core Newcastle 85+ study. The original plan had been to phenotype a sub-set (n= approximately 400) of the core Phase 2

participants i.e. those participants recruited in the final 12 months of Phase 2. However, due to a delay in securing funding the start date for the cardiac study was delayed and an insufficient number of participants were recruited to the cardiac study during Phase 2. Therefore the decision was made to extend recruitment into Phase 3 and those participants not offered the opportunity to participate in the cardiac study in Phase 2, who were still alive and participating in the core study at Phase 3, were invited to join the cardiac study in Phase 3.

The core study participants from phase 2 and phase 3 were invited to take part in the cardiac study as a part of their invitation to take part in the core 85+ study. The research nurse team sent surviving participants from baseline a letter of invitation along with a detailed information pack and photographs of the research staff involved in home visits. The information pack detailed the nurse-conducted multidimensional health assessment and in addition the cardiovascular assessments. Participants were subsequently approached by a research nurse, either by a phone call or home visit, to ensure that they had received all the information to enable them to make an informed decision about whether to participate and to answer any queries regarding their participation and the tests involved. If they wished to participate, written informed consent (Appendix 13 & 14) was then obtained by the research nurse in the same manner as at baseline; in participants who lacked the capacity to consent, a 'consultee' (a carer or relative) approval was obtained according to the requirements of the UK Mental Capacity Act.[250] Consent for the cardiac study was included as part of the consent process for the core Newcastle 85+ Study. [251]. Those participants who agreed to remain in the core study were specifically asked whether they also wished to take part in the cardiac sub-study. Only those core study participants agreeing to remain in the core study could take part in the cardiac study. Verbal approval was also taken at the start of home assessment (by myself) to see if participants were still happy to go ahead with the cardiovascular assessments.

Participants were visited in their homes or their places of residence. The community based sample and domiciliary design of the study were very important. In previous cardiac studies of a similar age group, participants were assessed in hospital settings, creating a potential

selection bias. In the Newcastle 85+ pilot study around 50% of the participants said they would have refused to attend hospital setting for assessment. [252]

Each visit comprised a detailed cardiac assessment including an echocardiogram, carotid scan to measure carotid intimal media thickness (CIMT) and a comprehensive vascular assessment including pulse wave analysis, pulse wave velocity and ankle brachial pressure index (full details are mentioned in the subsequent sections of this chapter). The time burden on participants had to be taken into account imposing a total limit of 60 minutes for all the cardiovascular assessments. A chaperone accompanied me on certain visits, if requested by the participant. Details of the visit were noted down on a visit information sheet (Appendix 17). These details included three patient identifiers (PID, date of birth and gender), duration of visit, missing assessments and reasons for refusal or not doing the assessment. It also included the heart rhythm at the time of assessment and any notifiable echocardiographic finding to the general practitioners (Appendix 6).

5.3 Details of Cardiac Assessment by Echocardiography

The Vivid i (Vivid i BT06, GE Healthcare, USA) with i2 Performance Package was used to perform detailed cardiac imaging. The i2 Performance Package allowed us to conduct a full range of quantitative analyses, including tissue doppler imaging (TDI). 3S-RS sector phased array cardiac ultrasound probe was used, which had a small footprint (21 x 15mm), a broad bandwidth (1.5 – 4Mhz) and a 90 degree field of view (GE healthcare, USA) for imaging. This cardiovascular imaging system was a fully featured and high performance machine in a very lightweight (only 5 Kg) and miniaturized design. These features made it highly portable, which was a core necessity for assessing the study participants in their own home.

Participants were placed in the left lateral decubitus position. Most of the scanning was done in that position apart from the subcostal view, which was done in the supine position. If the participant was too immobile to achieve an appropriate position for study, the actual position was noted but the data, as far as possible, were recorded.

An echocardiogram for each participant was recorded according to a standardized protocol based on the British Society of Echocardiography (BSE) guidelines 2009.[253, 254] It was initially recorded in a cineloop format on the hard drive of Vivid I and later backed up in three copies according to the study protocol. Analysis was performed in three consecutive sinus beats (five in the case of atrial fibrillation) using an inbuilt Vivid I image-analysis system equipped with customized computer algorithms. Each examination was comprised of parasternal, apical 4 chamber, apical 2 chamber, apical long axis and subcostal views.

5.3.1 Assessment of LV Systolic Function

LV systolic function is normally expressed in terms of LV ejection fraction (LVEF). Four different echocardiographic methods were used for assessment of LV ejection fraction (LVEF); M-Mode, Simpson biplane volumetric method, Wall Motion Index (WMI) and semi-quantitative 2D (“eyeball”) method.

M-Mode measurements of systolic and diastolic chamber dimensions and wall thickness were obtained according to the recommendations of the British Society of Echocardiography.[253] Left ventricular volumes were calculated using the Teicholz formula (Where *D* stands for diameter): [255, 256]

$$Volume = 7D^3 / (2.4 + D)$$

LVEF was then derived using the following formula:

$$EF = (LV\ end\ diastolic\ volume - LV\ end\ systolic\ volume) / LV\ end\ diastolic\ volume$$

The biplane method was initially developed to calculate LV volumes during contrast ventriculography and subsequently applied in echocardiography as well. In this method left ventricular endocardial borders are manually traced in diastole and systole in paired apical 4 and 2 chamber views. The traced area is divided into a series of discs, stacked on each other. The volume of each disc is calculated by using the formula:

$$Volume\ of\ disc = \pi r^2 (disc\ area) \times h\ (disc\ height)$$

LV volumes are then calculated by summing all these discs. The left ventricular end diastolic volume (LVEDV) and the left ventricular end diastolic volume (LVESV) in apical 4 chamber and apical 2 chamber views were used to calculate the ejection fraction by Biplane Simpson's method.[95] Biplane ejection fraction is calculated as:

$$LVEF\ (biplane) = (LVEDV - LVESV) / LVEDV \times (100\%)$$

The Vivid I software is designed to define and calculate each disc automatically once endocardial borders of LV are traced in both apical 2 and 4 chamber views. This method was at times difficult due to inadequate endocardial resolution of LV anterior wall. This method was only used if more than 80% of the endocardial border was visible.

Regional Wall Motion scoring is a system that divides the left ventricle in 16 small segments and scores them individually.[94] Each segment is scored according to both wall motion and thickening. Each segment is graded as 1 = normal, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic and 5 = aneurysmal. Wall Motion Index (WMI) is a total score divided by number of segments.[95] (3-WMI) multiplied by 30 gives LVEF. [96] This

method gives information about both the regional and global contractility of the left ventricle.

"Eyeballing" is a visual estimation of LVEF from a combination of parasternal and apical views. The eye of an experienced observer has been considered highly comparable with more sophisticated methods of EF calculations.[257, 258] However, it might be biased by other measures of LVEF estimation if these were performed by the operator prior to making the eyeball assessment. In order to prevent this bias, eyeball assessment was always done prior to other estimations of LVEF.

5.3.2 Assessment of LV Diastolic Function

LV diastolic function can be assessed by using different echocardiographic modalities by means of Pulsed Wave Doppler (PWD) and Tissue Doppler Imaging (TDI). Transmitral blood velocities using PWD were assessed from the apical 4 chamber view and four variables were recorded: E wave (peak early diastolic transmitral flow velocity), A wave (peak late diastolic transmitral flow velocity), E/A ratio, IVRT (isovolumetric relaxation time) and DT (early filling deceleration time).

Mitral valve annular motion using TDI from the apical 4 chamber view was also assessed and four variables were recorded: s´ lateral (peak systolic wave, lateral annulus), s´ septal (peak systolic wave, septal annulus), e´ lateral (early diastolic wave, lateral annulus) and e´ septal (early diastolic wave, septal annulus). E/e´ ratio was automatically calculated by the software. Lateral annular e´ velocity was used in analyses as it has been shown more reproducible than e´ septal [259] unless the participant had a lateral wall infarct. In case of lateral wall infarct, septal variable (e´ septal) was used provided there was no septal infarct. If both lateral and septal infarcts were present, e´ was not recorded. Mitral annular TDI early diastolic velocity (e´) is essential for classifying diastolic function. A major advantage of this technique is that it is not affected by preload and can also be used in AF. [101] Another benefit of this technique is that E/e' decreases progressively with severity of diastolic dysfunction and there is no pseudo-normalization. [100] E/e´ ratio correlates with LV filling pressures irrespective of LV systolic function. [260] Due to these advantages

both European Society of Cardiology and American Society of Echocardiography have raised e´ and E/ e´ indices as first line doppler parameter in the diagnosis and classification of diastolic dysfunction. [103, 104]

LV diastolic function was classified into normal, mild, moderate and severely impaired using combination of transmitral flow velocity (E/A, DT, IVRT) and mitral annular motion variables. Participant in whom only one criterion suggestive of moderate/severe, were classified as indeterminate diastolic function. Participants with paced rhythm were excluded from analysis. Classification scheme is shown in figure 5.2 and 5.3. The classification scheme was based upon the recommendations of the British and American Societies of Echocardiography [refs] and was very similar to that used in the Olmsted County community-based study of heart failure. [18] However, owing to the difficulty of obtaining reliable pulmonary venous flow signals in these elderly participants in the home setting, which we had established in a previous pilot study, pulmonary venous flow, which was used in the Olmsted County study, did not constitute part of the scheme. The rationale of the diastolic function classification scheme is that E/e' is used as the "top level" classifier, and thereafter agreement is required between two out of three of the parameters E/A ratio, DT, and IVRT for diastolic function to be assigned to a particular class. Where such agreement was not present, diastolic function was classified indeterminate.

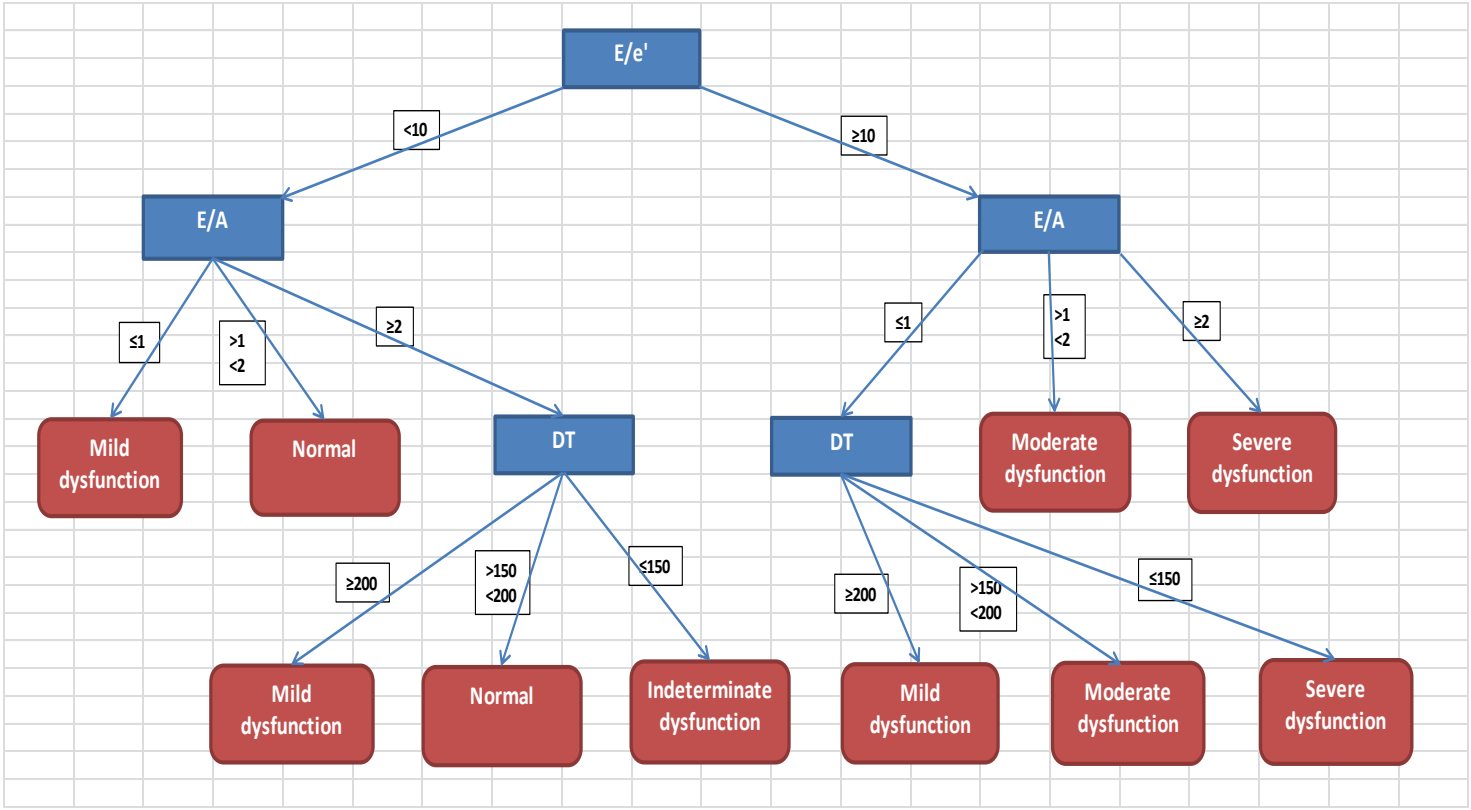


Figure 5.2: Classification scheme for diastolic function (Sinus Rhythm)

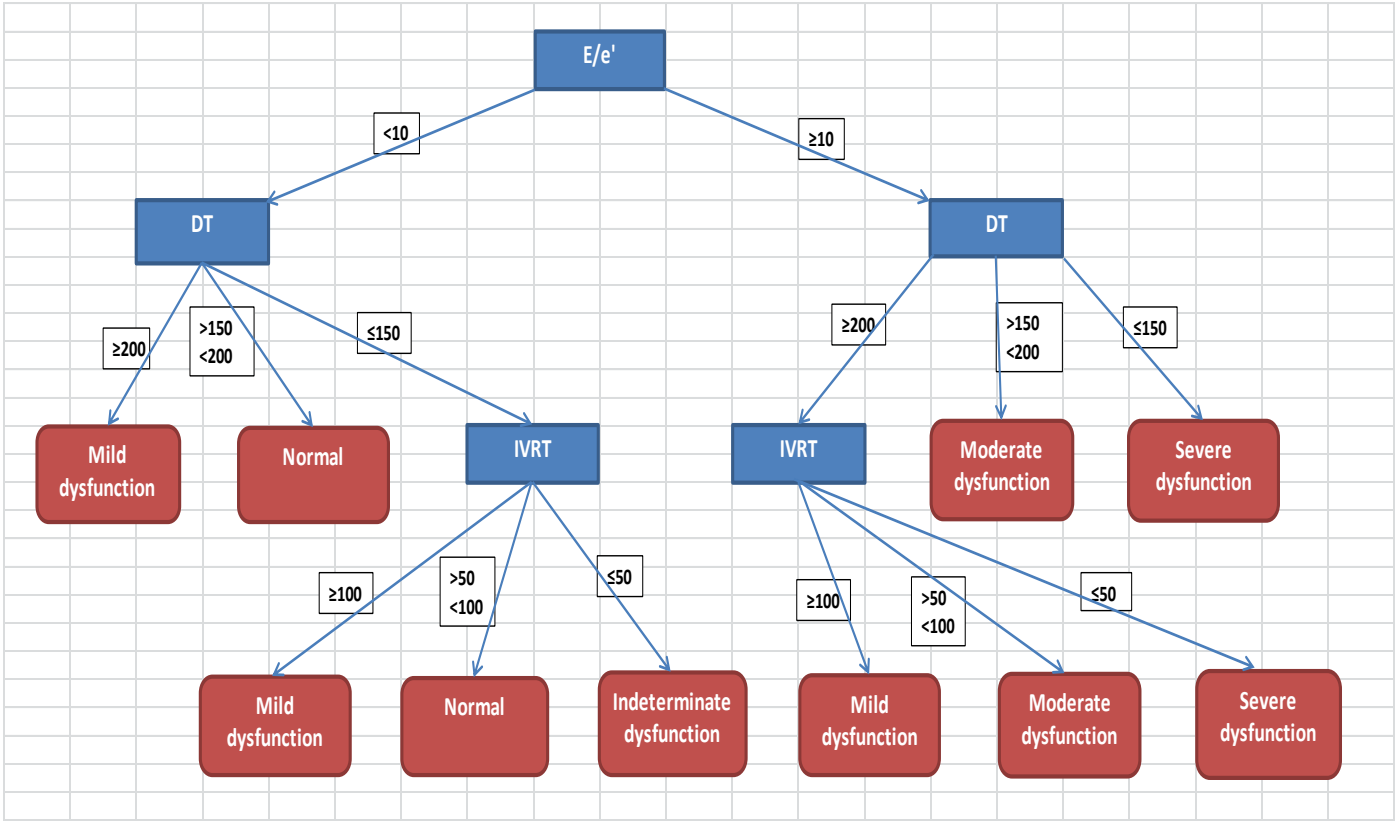


Figure 5.3 Classification scheme for diastolic function (Atrial fibrillation)

5.3.3 Assessment of RV Systolic Function

RV function was assessed qualitatively by eyeballing in various views. M-Mode measurement Tricuspid Annular Plane Systolic Excursion (TAPSE) in the apical 4 chamber view also recorded. To determine TAPSE, the M-mode cursor was oriented to the junction of the tricuspid valve plane with the RV free wall using the apical 4 chamber view. TAPSE has been shown as a very reproducible index of RV performance, which has strong prognostic value in patients with chronic heart failure.[261]

5.3.4 Chambers Quantification

Two dimensional M-mode measurements of systolic and diastolic LV chamber dimensions and wall thickness were obtained according to the recommendations of the British Society of Echocardiography (BSE).[253] LV volumes and mass were derived automatically by inbuilt formulae. LV mass was also calculated by using both the Penn formula[262] and ASE (American Society of Echocardiography) formula [263].

$$LV\ mass\ (Penn)\ =\ 1.04\ ([LVID\ +\ PWT\ +IVST]^3 -\ [LVID]^3)\ -13.6\ g.$$

$$LV\ mass\ (ASE)\ =\ 0.8\ (1.04\ ([LVID\ +\ PWT\ +IVST]^3 -\ [LVIDD]^3))+\ 0.6\ g.$$

(Where LVID = left ventricle internal dimension in diastole, PWT = LV posterior wall thickness in diastole and IVST = interventricular septal thickness in diastole)

The internal dimensions of RV were recorded according to latest BSE guidelines. Three variables RVD1 (basal RV diameter), RVD2 (mid RV diameter) and RVD3 (base to apex length) were measured from apical 4 chamber view at ventricular end systole.

M-mode left atrial (LA) diameter was recorded from the parasternal long axis view. LA volume was also measured using the biplane volumetric method from apical 4 chamber and apical 2 chamber views at ventricular end systole. 2D diameter of (right atrial) RA in apical 4 chamber view, extending from lateral border of RA to interatrial septum in a plane perpendicular to long axis of RA.

5.3.5 Assessment of Valves

All four valves were assessed in accordance with the latest recommendations of the British Society of Echocardiography.[253]

- **Mitral Valve**

The morphology of the mitral valve annulus and both leaflets was looked at in detail and any prolapsed, thickening, fusion or calcification was commented on. I also commented on Mitral valve stenosis (MS) by using 2D, M-Mode, continuous wave doppler (CW) and pulse wave Doppler (PW) assessments in various views. MS was graded as absent, mild, moderate or severe. Mitral valve area (MVA) was also calculated by pressure half time (PHT) method (empirical formula):

$$MVA = 220/PHT$$

Mitral regurgitation was also graded as absent, mild, moderate or severe semi – quantitatively by looking at the LA size (2D), regurgitant jet area (colour flow), vena contracta width, jet density (CWD) and mitral inflow profile (PWD).

- **Aortic Valve**

Morphology of the aortic valve (AV) was looked at in detail and cusp count, thickening, calcification and cusp mobility was commented on. I also commented on AV stenosis (if present) by using 2D, M-Mode, continuous wave doppler (CW) and pulse wave doppler (PW) assessment in various views. Aortic stenosis (AS) was graded as absent, mild, moderate or severe. The severity of AS was assessed by using AS jet velocity, mean pressure gradient across AV and aortic valve area (AVA). AS jet velocity was measured by CWD aligned parallel to the antegrade systolic flow across the aortic valve. The Bernoulli equation was used to measure the pressure gradient across the aortic valve;

$$\Delta P = 4v^2$$

The mean pressure gradient was auto-calculated by the software from the velocity curve. AVA was calculated both by continuity equation (AVA_{VTI}) and simplified continuity equation (AVA_{Vmax}):

$$AVA_{VTI} = CSA_{LVOT} \times VTI_{LVOT} / VTI_{AV}$$
$$AVA_{Vmax} = CSA_{LVOT} \times Vmax_{LVOT} / Vmax_{AV}$$

(where CSA = cross sectional area, VTI = velocity time integral, LVOT = left ventricular outflow tract and Vmax = maximal velocity across the valve)

Aortic regurgitation was also graded as absent, mild, moderate or severe semi – quantitatively by looking at the LV size (2D, M-mode), regurgitant proximal jet width (colour flow), jet cross-sectional area in LVOT (Colour Flow & Colour M- mode), jet density (CWD) and jet deceleration time - PHT (CWD).

- **Tricuspid and Pulmonary Valves**

The morphology of both the tricuspid and the pulmonary valves was assessed from various views. Tricuspid regurgitation was also graded as absent, mild, moderate or severe semi – quantitatively by looking at the right atrial & right ventricle (RV) size (2D), inferior vena cave (IVC) size (M-mode), jet area (colour flow), jet density and contour (CWD).

Pulmonary regurgitation was graded as absent, mild, moderate or severe semi – quantitatively by looking at the RV size (2D), jet width and length (colour flow).

5.3.6 Reproducibility

If a measurement such as echocardiography cannot be consistently replicated by the same observer or between different observers trained to the same standards, errors can be introduced. These errors can be (i) systematic (e.g. when one observer always reports higher than other) (ii) random or (iii) both.

In our pilot study intra-operator agreement has been tested, which showed good agreement and compared with the studies in hospital. In pilot study people (n=67) who

consented for echocardiography were examined at the place of their residence by a trained echocardiographer. One month later 19 participants were visited again for a second echocardiographic examination performed by a different trained echocardiographer. Two examinations were reported independently. Reproducibility of domiciliary echocardiography was assessed by calculating the correlation coefficient, coefficient of variation, and repeatability coefficient. The reproducibility of M-mode EF measured in the home was similar to previously published hospital-based data in mixed populations (r=0.85; CV=12.5%; repeatability coefficient 16.62%). [252] We were therefore satisfied with respect to the protocol for data acquisition in domiciliary settings. In order to check my interpretation of data acquired during domiciliary echocardiography assessments, 25 randomly selected echocardiograms (from participants performed during my study) were independently analyzed by me (FY) and a very experienced BSE (British Society of Echocardiography) accredited technician (Ms Julie Schuster) at the Freeman Hospital. The following echocardiographic variables were measured by both FY and JS (on the same scans performed by FY) were analyzed for agreement.

- LV systolic function by M-mode, visual estimate or eyeball method, and wall motion score index.
- LV diastolic function by measuring E/e´ (lateral)
- RV structure and function by semi-quantitative method (graded as normal, mild, moderate or severely impaired/dilated)

We used kappa statistics (Cohen's kappa – κ) to assess the repeatability for categorical data (RV structure and function) in this comparison exercise. [264] Kappa values measure the level of agreement in excess of what would be expected by chance. Kappa values can range from -1 to 1, with values close to zero indicating the agreement is close to that expected by chance. Values below zero suggest a negative agreement and those closer to 1 indicated a better agreement. (Table 2.1)

Bland Altman plot and Pearson's correlation was used to assess degree of agreement between two reviewers (FY and JS) for numerical variables (LV systolic and diastolic function .i.e. EF (m-mode, eyeball, wall motion score index) and E/e´. [265, 266] The bias or mean difference and 95% confidence interval (1.96 SD) were calculated.

Table 5.1: A Guide to Cohen's kappa value (κ)

Kappa Value (κ)	Strength of agreement
< 0.0	No agreement
– 0.20	Poor
0.21 – 0.40	Fair
0.41 – 0.60	Moderate
0.61 – 0.80	Good
0.81 – 1.00	Very good

5.4 Measurement of Carotid Intima Media Thickness

Vivid i (Vivid i BT06, GE Healthcare, USA) with the IMT analysis package was used to measure carotid intima-media thickness (CIMT). A12L-RS high-frequency linear array transducer was used for the carotid imagining.

Participants were placed in a supine position with the head rotated by 45° to the left/right, with their arms rested at their sides. If the participant was too immobile to achieve an appropriate position for study, the position was noted but the data, as far as possible, were still recorded.

Carotid Intima Media Thickness (CIMT) describes the combined thickness of the inner two very thin layers of the lining of the carotid arterial wall – the intima and the media. This corresponds to the inner and outer echogenic lines seen on the B-mode ultrasound image. In order to standardize measurements between subjects, the 'region of analysis' (Figure 5.4) was set as the 1cm section of the artery situated 1 cm proximal to the start of bulb as suggested by Touboul and colleagues in the Mannheim Intima Media Thickness consensus document.[194] CIMT assessment was performed in the plaque-free arterial wall (an atherosclerotic plaque being defined as an echogenic structure protruding into the vascular lumen with a thickness greater by at least 50% than neighbouring sites.[21]

Firstly, a transverse image showing the carotid artery in the short axis as a rounded vessel was obtained. Next the common carotid artery (CCA) and its bifurcation were identified in a transverse image. Then a longitudinal image showing the carotid artery in its long axis as four parallel lines was obtained. Finally the 'region of analysis' as mentioned above was identified.

The automated edge detection software in the Vivid – I CIMT analysis module was used to calculate CIMT. CIMT was measured on the both near and far walls of the CCA in the 'region of analysis'. Mean, maximum and minimum CIMT readings were calculated for both carotid arteries.

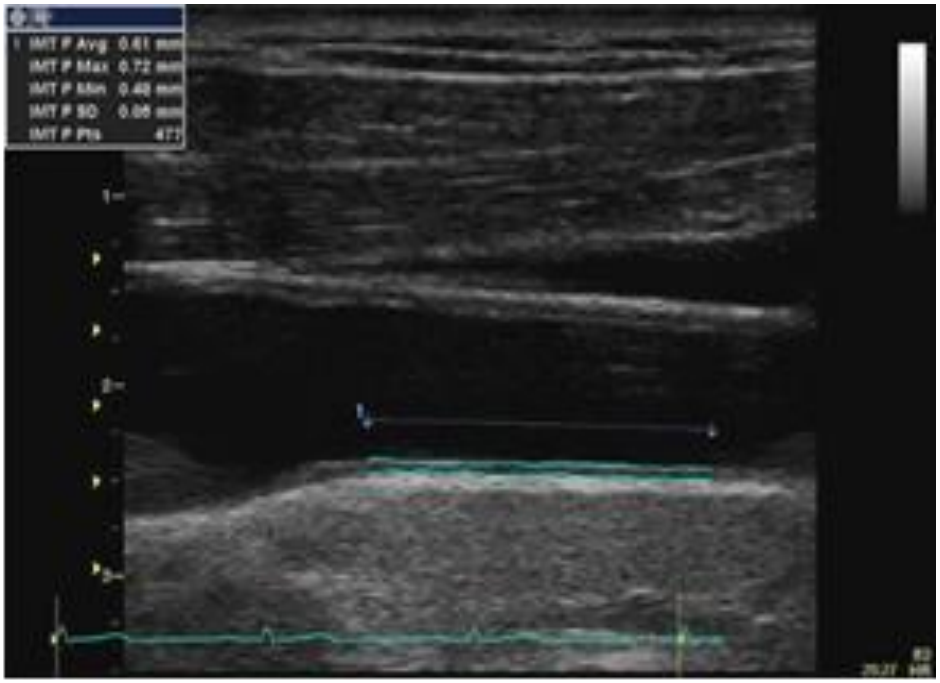


Figure 5.4: Longitudinal section of common carotid artery and 'region of analysis'

5.5 Assessment of Vascular Stiffness

Vascular stiffness was assessed by pulse wave analysis (PWA) and measuring pulse wave velocity (PWV). Ankle brachial index (ABI) was also recorded to look for any peripheral vascular disease. All these assessments were performed in supine position.

5.5.1 Pulse Wave Analysis

Pulse wave analysis (PWA) was done using a hand-held tonometer probe (Millar tonometer, Houston, TX, USA) attached to a SphygmoCor device (SCOR-Px; AtCor Medical Pty, Sydney, Australia). The SphygmoCor device takes a 10 second snapshot of the radial arterial pressure wave and, by using an inbuilt conversion algorithm derives the ascending aortic pressure wave. It provides important cardiovascular measurements including central blood pressure, central augmentation pressure, aortic augmentation index, ejection duration and subendocardial viability ratio (SEVR). Previous studies have shown good repeatability and low interobserver variation for tonometry and its derived indices.[267-269] Blood Pressure (BP) was measured using a validated automatic oscillometric BP machine (Omron 705 IT IntelliSense BP monitor; Omron Healthcare Europe BV, Kruisweg, Hoofddorp, Netherlands). BP was measured at the right brachial artery. The BP cuff was placed on the right arm 1-2 cm above the cubital fossa and measurement was taken in accordance with manufacturer's instructions. The BP was measured twice and the mean value was used for the PWA analysis.

PWA was undertaken by placing the hand held tonometer probe on the strongest pulse at the radial artery of the participant's wrist. The tonometer was gently pressed (applanated) into the skin, perpendicular to the wrist until a waveform signal appeared on the screen. Waveforms were captured for 10 seconds after achieving a consistent waveform. The SphygmoCor software automatically derived central aortic waveform and displayed the required measurements i.e. aortic systolic pressure, aortic pulse pressure, central augmentation pressure, central augmentation index, ejection duration and SEVR.

The quality of PWA was assessed using the device's in-built quality index score 'Operator Index'. We used examinations with an operator index of 80 or above for our

analyses as suggested by the manufacturer. Participants with poor quality trace (operator index < 80) were excluded from analysis.

5.5.2 Pulse Wave Velocity

Vicorder system (Skidmore Medical, Bristol, UK) was used for measuring pulse wave velocity. It measures simultaneous pressure waveforms by a volume displacement technique, using blood pressure cuffs placed around the sites of interest. Pulse wave velocity (PWV) is defined as the time taken by a pressure or flow wave to travel a given distance (Velocity = Distance/Time). Femoral and the carotid artery flow waveforms were simultaneously recorded by using the equipment. The Vicorder system calculates transit time by using a foot-to-foot methodology with the distance measured along the surface of the body between the recording points with a tape measure. It requires very little operator training and is almost operator independent.[270]

Measurements were obtained using the Vicorder device by placing a 100mm wide blood pressure cuff around the upper thigh to measure the femoral pulse and a 30 mm partial cuff around the neck at the level of the carotid artery. Both cuffs were simultaneously inflated to 65mmHg, and high-quality waveforms were recorded simultaneously for 3 seconds using a volume displacement method. Path distance "L" the distance between Supra-sternal notch and the top of thigh cuff in centimetres was measured with a measuring tape. The foot-to-foot transit time 'TT' was determined using an in-built cross-correlation algorithm. PWV is automatically calculated by the software as the distance (L) between the two recording sites divided by the time delay (TT) between the feet of the two waveforms at each site. (Velocity = Distance/Time). Participants with Atrial Fibrillation were excluded.

5.5.3 Ankle Brachial Index

Vicorder system (Skidmore Medical, Bristol, UK) was also used for measuring the ankle brachial pressure index (ABPI). It uses a digitally filtered photoplethysmoghraphic (PPG) signal displaying the linear characteristics of the flow wave. During the deflation cycle of the measurement, the system automatically selects the first appropriate PPG flow signal and references the cuff pressure.

The dual channel features of the Vicorder allow rapid collection of bilateral PPG waves, providing a quick method of obtaining systolic pressure measurements bilaterally, thereby speeding up ABPI measurements.

Wide blood pressure cuffs (100mm) were placed on both arms (just above the cubital fossa) and PPG sensors on the largest finger on each hand. Both cuffs were simultaneously inflated. Once systolic pressure was achieved the PPG signal disappeared and reappeared when the cuff again reached systolic pressure in its bleedback phase. During the deflation cycle of the measurement, the system automatically selects the first appropriate PPG flow signal and references the cuff pressure. Although automatically picked, the first appropriate PPG flow signal could also be selected manually. Measurements from both legs were also recorded by applying cuffs just above the both ankles and PPG sensors on both big toes. ABPI for both left and right sides were automatically calculated by the software by using the following formula:

ABPI = Ankle systolic pressure/Brachial systolic pressure

5.6 Electrocardiogram (ECG)

A 12 lead electrocardiogram was recorded on a Burdick Atria 6100 ECG machine (Bothell, WA, USA) and transmitted to the ECG Core Laboratory at Glasgow Royal Infirmary for automated Minnesota Coding, a service set up by Professor Peter MacFarlane.[271] [272]The portable size and inbuilt modem in this machine made it ideal for domiciliary use and subsequent transmission of the ECG for Minnesota coding.

Electrocardiograms were recorded in a supine position by a trained research nurse according to the study protocol. Firstly the procedure was explained the participant. Afterwards they were asked to lie down on the bed or sofa as per their convenience. Four limb electrodes were attached to the outer surface of wrists and ankles. Six chest electrodes (V1 – V6) were also attached to the chest after cleaning the skin with a sterile wipe as described below in figure 5.5.

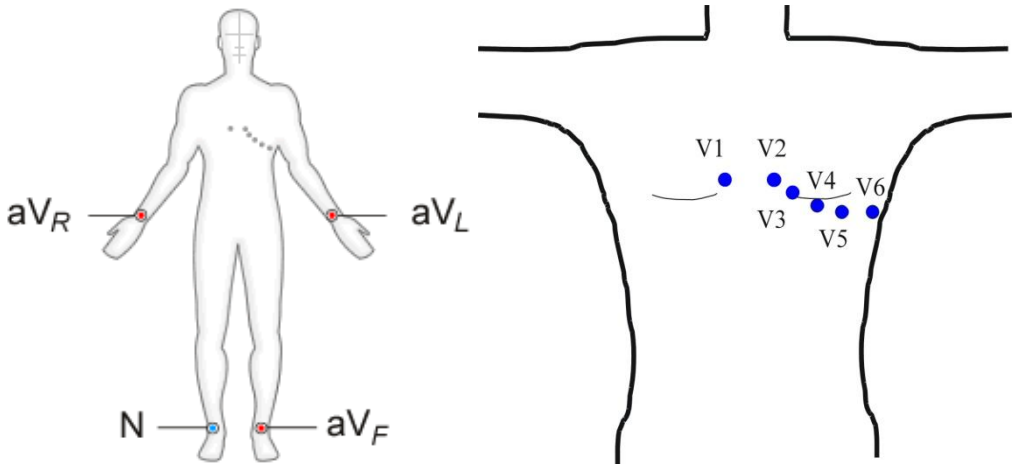


Figure 5.5: Position of ECG chest and limb leads

Limb leads:

aVL: Outer aspect of left wrist.

aVR: Outer aspect of right wrist.

aVF: Outer aspect of left ankle.

N: Outer aspect of right ankle.

Chest leads:

V1 - Right sternal margin in the 4th intercostal space.

V2 - Left sternal margin in the 4th intercostal space.

V3 - Midway between V2 and V4.

V4 - Left midclavicular line in the 5th intercostal space.

V5 - Left anterior axillary line V4 level

V6 - Left midaxillary line V4 level

Finally 12 lead ECG was recorded automatically by machine once the electrodes were attached to the machine. A paper copy of the ECG was stored in participant's file and was also electronically transmitted to the ECG Core Laboratory in Glasgow Royal Infirmary for automated Minnesota Coding .

Clinically significant arrhythmia (such as AF) and specific types of heart block were reported to the General practitioner according to the study protocol. (Appendix 5)

5.7 Measurement of NT-proBNP (N-terminal pro-brain natriuretic peptide)

Venous blood samples for plasma NT-proBNP assay were taken during Newcastle 85+ study core assessment and transported to laboratory (Royal Victoria Infirmary, Newcastle upon Tyne) by trained research nurses according to the study protocol.

Plasma NT-proBNP was measured by electrochemiluminescence immunoassay 'ECLIA' using the Elecsys NT-proBNP II assay (Elecsys® proBNP II, Roche Diagnostics, Indianapolis, IN, USA) performed on a Roche Elecys E170 analyzer. This assay has a measuring range from 5 – 35,000 pg/ml.

This assay contains two monoclonal antibodies which recognize epitopes located in the N-terminal part of the proBNP. This is a two-step sandwich assay. During the first incubation an antigen in the sample, a biotinylated monoclonal NT-proBNP-specific antibody, and a monoclonal NT-proBNP-specific antibody labeled with ruthenium complex form a sandwich complex. During the second incubation, after the addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin. Subsequently this reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are removed with proCell. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier. Results are determined via a calibration curve with a measuring range of 5-35,000 pg/ml.

5.8 New York Heart Association (NYHA) functional severity grading

A dyspnoea questionnaire (Appendix 7) was administered during phase 2 and 3 of the core study and participants were assigned to New York Heart Association (NYHA) functional severity classes: NYHA grade I (asymptomatic), II (mild limitation), III (moderate limitation), or IV (severe limitation).

Participants were assigned NYHA grade using following scheme.

NYHA grade 1: If questions 1, 3 and 5 ALL = 'no' or 'limited for reason unrelated to shortness of breath'.
NYHA grade 2: If (q1 = 'no' and q3 = 'yes') and (q4 = 'a bit' OR 'a lot') or (q1 = 'no' and q3 = 'no' and q5 = 'yes').
NYHA grade 3: If (q1 = 'yes') and (q2 = 'a bit' OR 'a lot') or (q1 = 'no' and q3 = 'yes' and q4 = 'completely unable to walk outdoors').
NYHA grade 4: If (q1 = 'yes' and q2 = 'completely unable to move around the home').

5.9 Data Storage And Data Cleaning

All the electronic data from the cardiac measurements was backed up onto DVDs and was stored according to Newcastle 85+ study policy. Data was also stored on the main Newcastle 85+ study database. All datasets were matched against the PIDs (participant's unique 8 digit study ID), date of birth and gender of the participants. All the datasets were cleaned by performing logic and range checks by the study data manager.

5.10 Reporting Results to General Practitioner

According to our study protocol (Appendix 5) the following abnormal results found on echocardiograms were reported back to GPs.

- Significant impairment of LV function (ejection fraction less than 35%)
- Significant valvular heart disease defined as:
    - Severe Aortic stenosis/regurgitation
    - Severe Mitral stenosis/regurgitation
    - Severe Tricuspid stenosis/regurgitation

- Significant other findings such as hypertrophic obstructive cardiomyopathy (HOCM), and atrial myxoma

Results for carotid intima media thickness (CIMT), pulse wave velocity and pulse wave analysis, which help us to assess the vascular stiffness and extent of atherosclerosis were not fed back to GPs as at present all these parameters are not used in routine clinical practice.

Clinically significant arrhythmias and heart block found on 12 lead ECG were also fed back to GPs as per study protocol (Appendix 6).

5.11 Statistical Methods

Normally distributed data are presented as means and standard deviations and non-normally distributed data as medians and interquartile ranges. Differences between groups were assessed by t-tests (normally distributed continuous data), Wilcoxon-Mann-Whitney U tests (non-normally distributed continuous data) or $\chi 2$ tests (categorical data). Differences in levels of particular variables (for example, left ventricular dysfunction, which could be graded absent, mild, moderate or severe) were assessed by logistic regression and are presented as odds ratios with 95% confidence intervals. All p-values are two-sided with Bonferroni correction where appropriate to account for multiple testing. Missing values were excluded from the analysis (though numbers of participants with missing data are reported throughout) and I therefore present data based on the number of valid responses. With respect to the analyses of symptomatic left ventricular dysfunction, I considered the possibility that dyspnoea may have been due to respiratory disease rather than heart failure. Accordingly, I conducted a sensitivity analysis excluding participants with significant intrinsic lung disease identified using spirometric criteria of a forced expiratory volume in one second of less than 60% of the predicted value (for age, sex and height) or a forced vital capacity less than 70% of the predicted value. The above analyses were performed using Stata 11.0 (StataCorp. 2011. Statistical Software: Release 11.0. College Station, TX: Stata Corporation); and I was assisted in these by Mr. Andrew Kingston, the 85+ study statistician.

The diagnostic performance of NT-proBNP in the identification of left ventricular systolic and diastolic dysfunction was evaluated by receiver-operating characteristic (ROC) curve analysis, described by DeLong et al.[273] The optimal discriminatory value for each assay was estimated by the point along the ROC curve that provided the minimum Euclidean distance between that of a perfect assay with 100% sensitivity and specificity. The positive predictive value and negative predictive values were calculated for the optimal discriminatory values. Statistical significance was accepted at $p \leq 0.05$.

5.12 Power Calculation

The Newcastle 85+ cardiac study aimed to recruit 400 participants. Sample size was determined by the requirements of planned longitudinal analyses i.e. detecting associations by logistic regression between cardiovascular phenotypes and subsequent non-fatal cardiovascular events over 18 month follow-up; under the assumption that a 25% baseline prevalence of diastolic dysfunction (as in our pilot data) in 400 participants would have 80% power at a 5% significance level of detecting an odds ratio of at least 2.0 with an event rate among those without diastolic dysfunction of 25-30%.

5.13 Funding

This study was supported by the British Heart Foundation (grant reference PG/08/026/24712). The core Newcastle 85+ Study was supported by the UK Medical Research Council and the Biotechnology and Biological Sciences Research Council (grant reference G0500997), the Dunhill Medical Trust (grant reference R124/0509), and NHS North of Tyne (Newcastle Primary Care Trust).

Section III

Results

Chapter 6: Cohort Demographics; Feasibility and Reproducibility of Assessments

6.1 Recruitment

Of the 854 people who participated in the baseline Newcastle 85+ Study 631 were re-assessed in phase 2, of whom 484 were seen again in phase 3. It was initially planned to conduct the cardiac sub-study on a subset (almost 400 people) of phase 2 cohort. However, due to delay in securing the funding, cardiac assessments were delayed and only 316 people were recruited from the phase 2 cohort. The cardiac sub-study was extended to phase 3 and the people at the time who were still alive and had not already been offered the cardiac assessments, were invited to participate. A further 111 people for the cardiac substudy were recruited from phase 3 cohort. Figures 3.1 and 3.2 explain the recruitment of cardiac sub-study cohort. Five hundred and seventy one participants (phase 2 = 405, phase 3 =166) were invited to undergo cardiovascular assessments. Four hundred and twenty seven participants (74.8%) took part in cardiac sub-study.

Of the 461 people who were mailed out for both phase 2 and cardiac sub-study, 87.8% (405/461) agreed to take part in phase 2. Further 87.6% (355/405) people, who consented for phase 2 assessments also agreed to take part in cardiac sub-study. Cardiac assessments were performed in 89 % of the people (316/355), who consented for cardiac sub-study. Of the 36 people in whom cardiac visit could not be completed 13 people passed away, 6 were too ill to participate and 9 people did not give any reason for refusal. In on case cardiac tests were declined by the consultee of patient due to fear of distress.

Of the 200 people who were mailed out for both phase 3 and cardiac sub-study, 87.5% (175/200) agreed to take part in phase 3. Nine of the 175 phase 3 participants also received invitation for cardiac sub-study in phase 2 so leaving 166 phase 3 participants,

who were asked to participate in cardiac sub-study. 150 people from invited cohort (90.4%, 150/166) agreed to take part in cardiac substudy. In 29 people cardiac substudy invitation was withdrawn as the target for cardiac substudy was achieved. Cardiac assessments were performed in 91.7 % of the people (111/121), who consented for cardiac sub-study. (Figure 6.1 & 6.2)

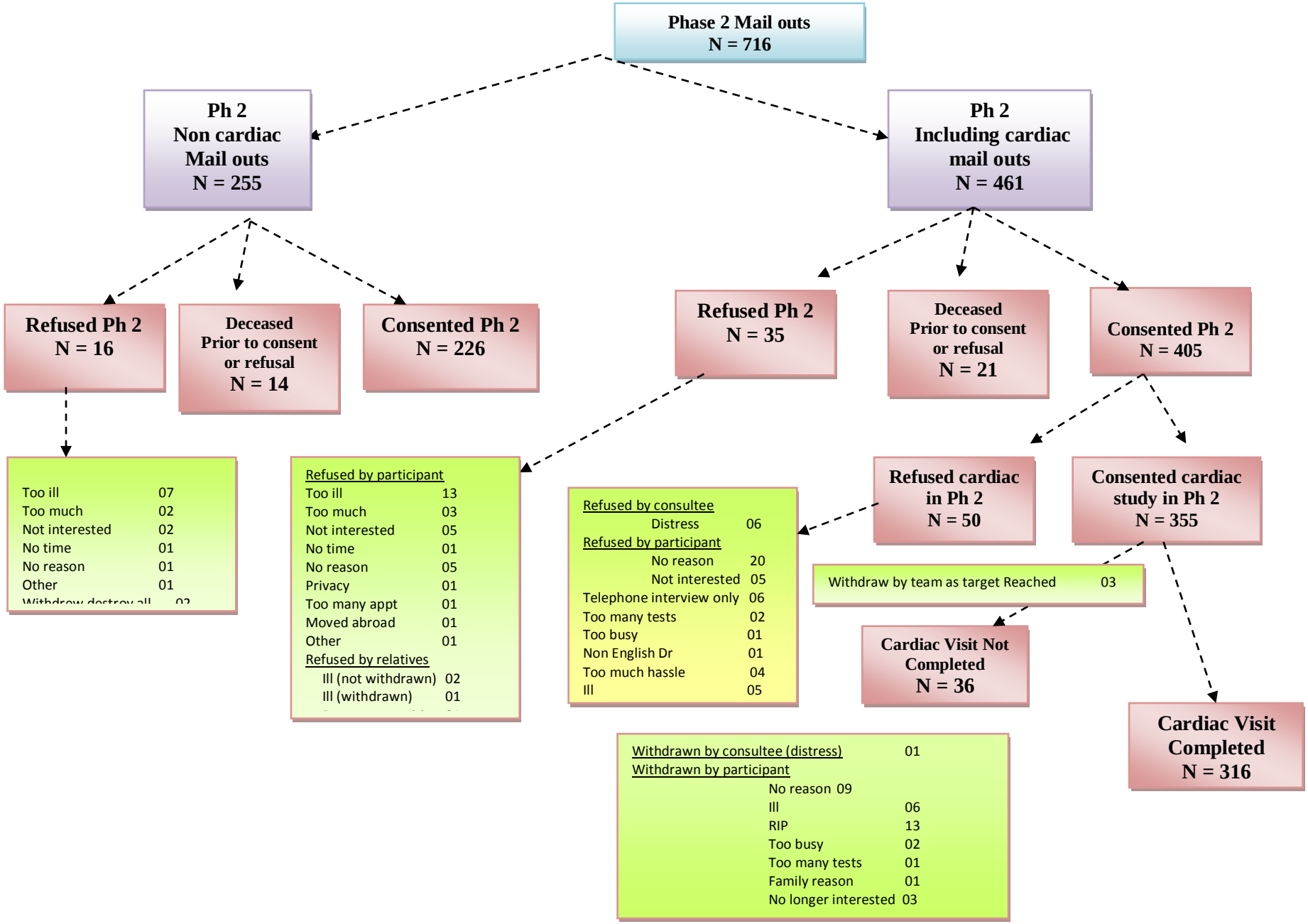


Figure 6.1: Cardiac Sub-study recruitment profile from Phase 2

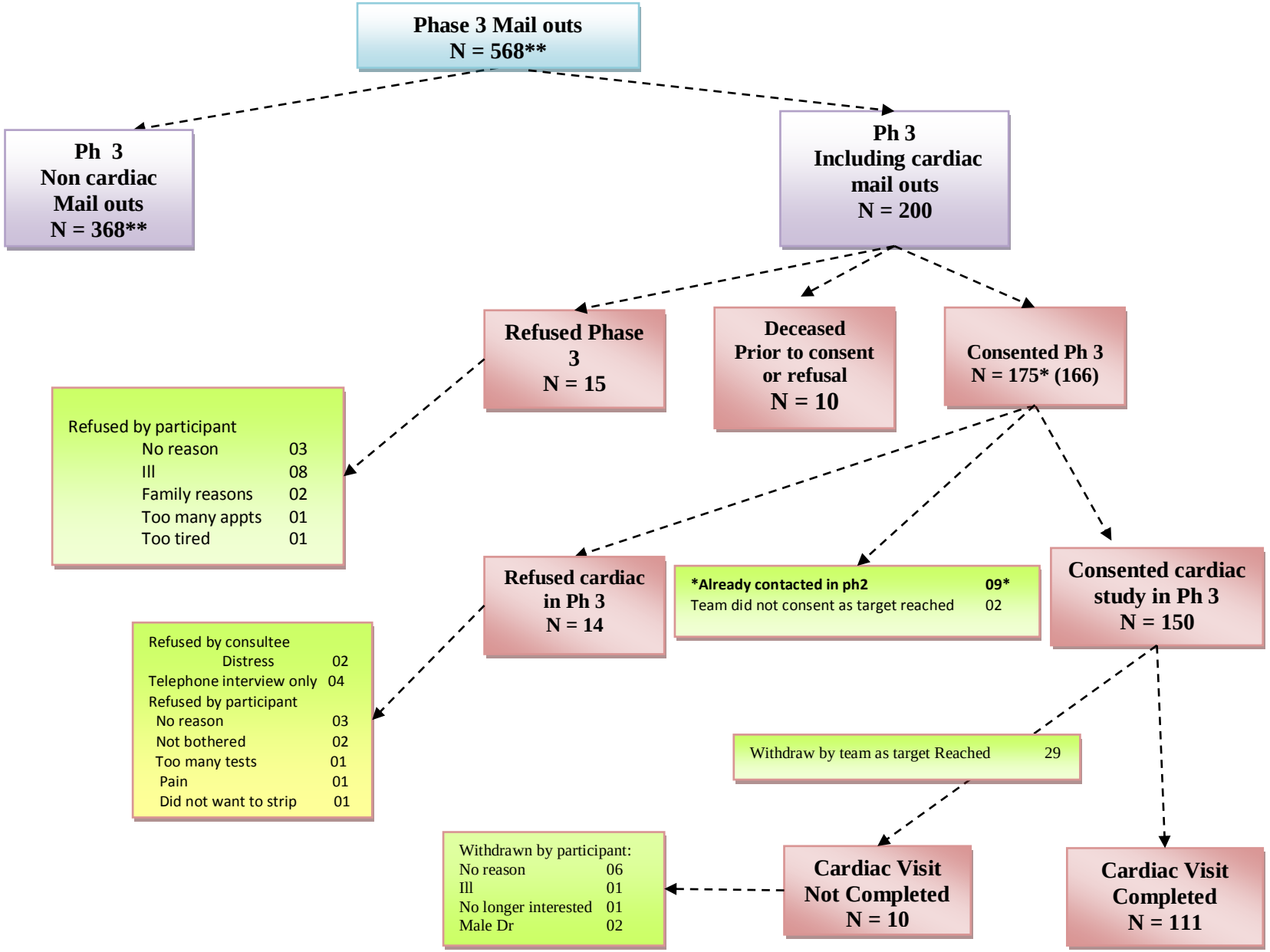


Figure 6.2: Cardiac Sub-study recruitment profile from Phase 3

** Phase 3 non cardiac mail out were still on going even after recruitments for cardiac substudy stopped

6.2 Characteristics and Representative Nature of Cardiac Cohort

Characteristics of 427 cardiac sub-study and 631 phase 2 (core 85+ study) participants are presented in Table 6.1. It also shows the characteristics of cardiac substudy participants assessed in the phase 2 (P2) and phase 3 (P3) of core 85+ study. Mean age of cardiac sub-study cohort was 87.9 years, 60.9% (260/427) were females, 99.3% (424/427) were white ethnic origin, and 5.4% (24/427) lived in an institution. Mean ages of cardiac P2 and P3 participants were 87.9 years and 88.3 years respectively. 81.3% of cardiac substudy and 77.5% of phase 2 core 85+ study rated their health good or above. Disability score was slightly higher in core 85+ phase 2 participants (6.2 ± 4.9) than cardiac sub-study cohort (5.6 ± 4.5). Hypertension (56.9%, 243/427), Ischaemic heart disease (32.3%, 138/427) and cerebrovascular disease (19.0%, 81/427) were common in cardiac sub-study participants. Core 85+ phase participants also had similar prevalence of hypertension (57.9%), ischaemic heart disease (32.1%) and cerebrovascular disease (19.8%). Cardiac P3 participants also had similar prevalence of hypertension (61.0%), ischaemic heart disease (31.7%) but less cerebrovascular disease (14.6%). Majority of both cardiac sub-study (62.2%) and core 85+ phase 2 (61.2%) participants were either current or former regular smokers. (Table 6.1)

Table 6.1 Characteristics and representative nature of cardiac cohort

	Phase2 "core 85+ cohort"	Phase2 cardiac	phase3 cardiac	Phase2/phase3 cardiac
	n=631	n=316	n=111	n=427
Sociodemographics				
Age years (mean ± sd)	87.9 ± 0.44	87.9 ± 0.40	88.3 ± 0.33	87.9 ± 0.44
Gender (females %, n)	62.9 % (397)	60.20%	62.60%	60.9 % (260)
Ethnicity (whites %)	99.5 % (628)	99.30%	99.20%	99.3 % (424)
Housing (institutionalized %, n)	9.2 % (58)	7.20%	1.60%	5.6 % (24)
Non cardiac health characteristics				
Disease count (mean ± sd)	4.6 ± 1.8	4.7 ± 1.8	4.2 ± 1.5	4.5 ± 1.7
Disability score (mean ± sd)	6.2 ± 4.9	5.8 ± 4.7	5.1 ± 3.9	5.6 ± 4.5
MMSE (mean ± sd)	26.6 ± 4.3	26.8 ± 3.9	27.7 ± 2.3	27.0 ± 3.6
Self rated health (good or above) %, n	77.5 % (475)	79.40%	86.40%	81.3 % (347)
Depression (severe) %, n	7.9 % (48)	6.00%	6.50%	6.1 % (26)
Cardiac risk factors				
Smokers or ex smokers %	61.20%	63.80%	58.20%	62.20%
BMI (mean ± sd)	24.7 ± 4.4	24.9 ± 4.5	25.0 ± 3.9	24.9 ± 4.3
Waist hip ratio (mean ± sd)	0.88 ± 0.08	0.88 ± 0.08	0.88 ± 0.07	0.88 ± 0.08
Diabetics %	12.70%	15.10%	7.30%	12.90%
Total cholesterol mmol/l (mean ± sd)	4.2 ± 1.2	5.0 ± 1.2	5.0 ± 1.3	5.0 ± 1.2
HDL mmol/l (mean ± sd)	1.4 ± 0.4	1.5 ± 0.4	1.5 ± 0.4	1.5 ± 0.4
Pre-existing diagnosis				
Myocardial infarction % (n)	14.6 % (92)	14.10%	13.80%	14.1 % (60)
Angina % (n)	29.8 % (188)	30.30%	30.10%	30.2 % (129)
Ischaemic heart disease - IHD % (n)	32.1 % (202)	32.60%	31.70%	32.3 % (138)
Hypertension % (n)	57.9 % (365)	55.30%	61.00%	56.9 % (243)
Heart failure % (n)	9.5 % (60)	10.50%	4.90%	8.9 % (38)
Peripheral vascular disease - PVD % (n)	6.5 % (41)	6.30%	4.10%	5.6 % (24)
Cerebrovascular disease - CVD % (n)	19.8 % (125)	20.70%	14.60%	19.0 % (81)
Any atherosclerotic disease (IHD/PVD/CVD)	47.3 % (298)	47.70%	43.10%	46.4 % (198)

6.3 Feasibility of Domiciliary Cardiovascular Assessments

6.3.1 Feasibility of Domiciliary Echocardiography

Echocardiography could be performed in 419 of 427 participants of which 5.6% (24) were institutionalized. Three people refused to have the echo performed while only five were too frail to attempt measurement. A full study was possible in 87% (n =367) of participants. In 12.4% participants partial study was possible due to lack of either parasternal (PS) or apical views (AP). Mostly it was due to poor echo windows (n= 39). In 12 individuals either of PS or AP view was missing because participant could not be positioned appropriately. (Figure 6.3)

6.3.2 Feasibility Of Domiciliary Ankle Brachial Index (ABI) Assessment

114 (26.7%) participants were excluded from ABI assessment due to presence of atrial fibrillation (20.8%, n=89), paroxysmal atrial fibrillation (4.7%, n=20) or frequent multiple ectopics (1.2%, n=5). Out of remaining 313 eligible participants ABI measurement was available in 84.0% of participants (n=263). 20 participants refused to have ABI assessment done predominantly (n=15) because they didn't like BP cuffs. In 30 participants ABI assessment was not performed as it was difficult to position them appropriately (n=11) or legs were too swollen due to peripheral oedema (n=9). (Figure 6.4)

6.3.3 Feasibility Of Domiciliary Pulse Wave Analysis (PWA)

81 (19.0%) participants were excluded from PWA measurement due to presence of atrial fibrillation (16.4%, n=70), paroxysmal atrial fibrillation (2.6%, n=11). 28

participants with atrial fibrillation / paroxysmal atrial fibrillation (19,9) and operator index above 80 were also included in the PWA analysis as per manufacturer's recommendation (Personal communication with Miss Sandrine Millasseau, Clinical Manager for Europe, Atcor Medical)

Out of remaining 346 eligible participants PWA measurement was available in 86.1% of participants (n=298). 15 participants refused to have PWA measurement done because they didn't like BP cuffs. In 11 participants PWA measurement was not performed as it was difficult to position them appropriately and in 7 participants PWA measurements were discarded because of low operator index (<80). (Figure 6.5)

6.3.4 Feasibility Of Domiciliary Pulse Wave Velocity (PWV) Measurement

114 (26.7%) participants were excluded from ABI assessment due to presence of atrial fibrillation (20.8%, n=89), paroxysmal atrial fibrillation (4.7%, n=20) or frequent multiple ectopics (1.2%, n=5). Out of remaining 313 eligible participants PWV measurement was available in 76.7% of participants (n=240). 15 participants refused to have PWV assessment done because they didn't like BP cuffs. In 26 participants PWV wasn't measured because participants had termers (shakes) in limbs or neck, a main cause of artefacts in PWV measurement. In 11 participants PWV measurements were unavailable because of difficulty in lying flat. (Figure 6.6)

6.3.5 Feasibility Of Domiciliary Carotid Intima Media Thickness (CIMT) Measurement

In 96.7% (n=413) participants CIMT measurement were available. Only two people refused this assessment. In 9 (2.1%) participants CIMT measurement was not available because of difficulty to obtain common carotid artery images. (Figure 6.7)

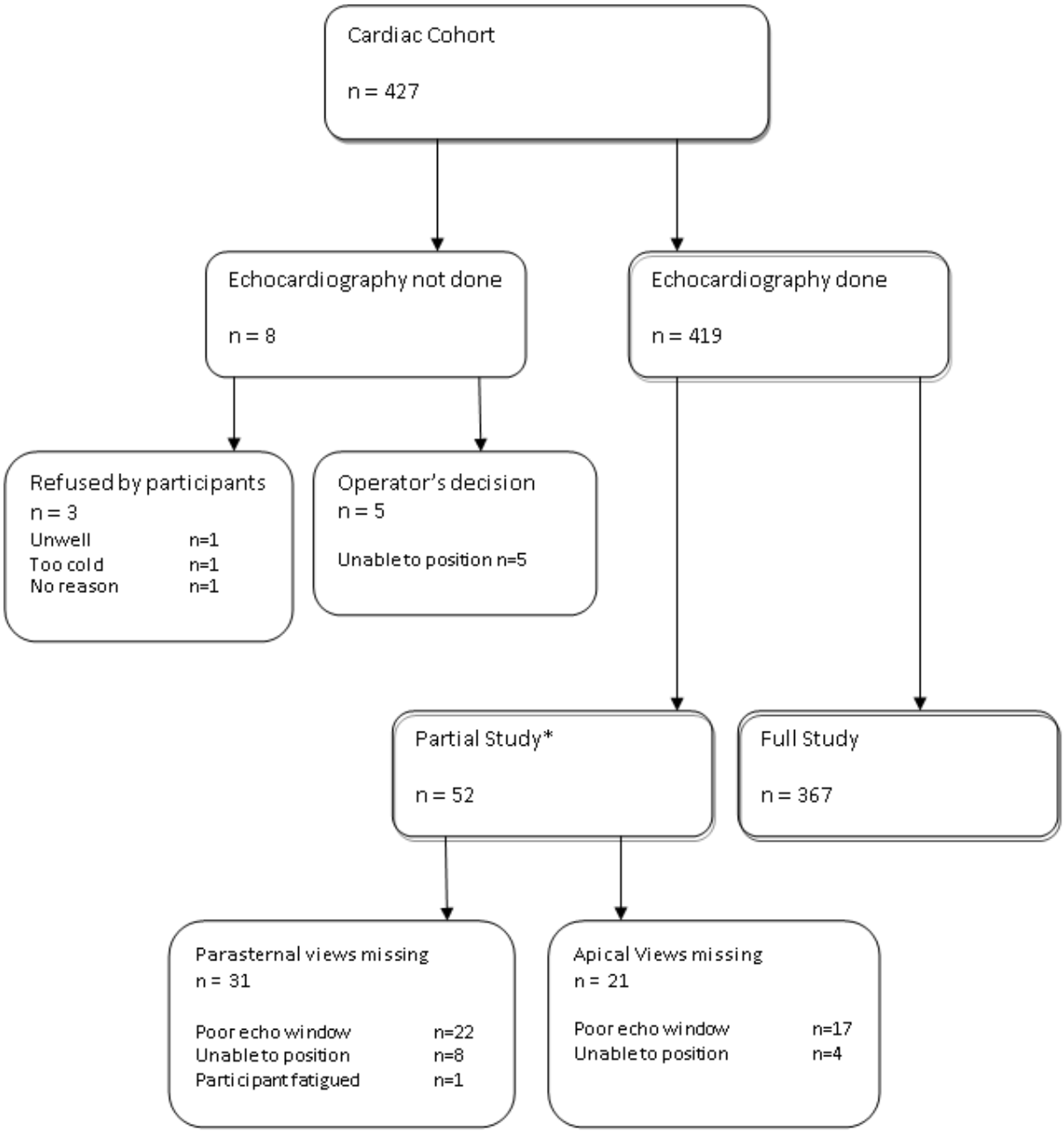


Figure 6.3 Feasibility of domiciliary Echocardiography

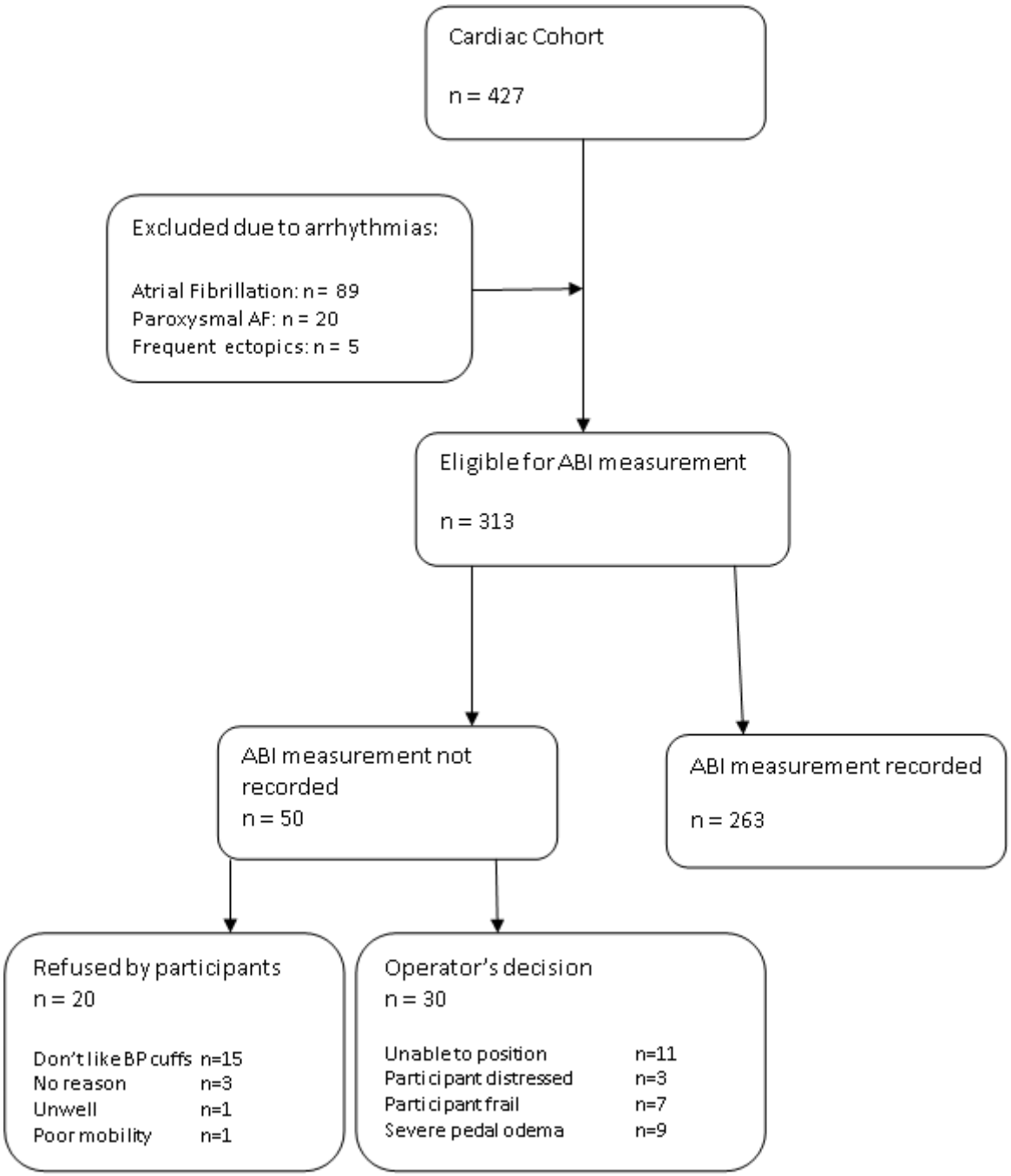


Figure 6.4 Feasibility of domiciliary Ankle Brachial Index (ABI) assessment

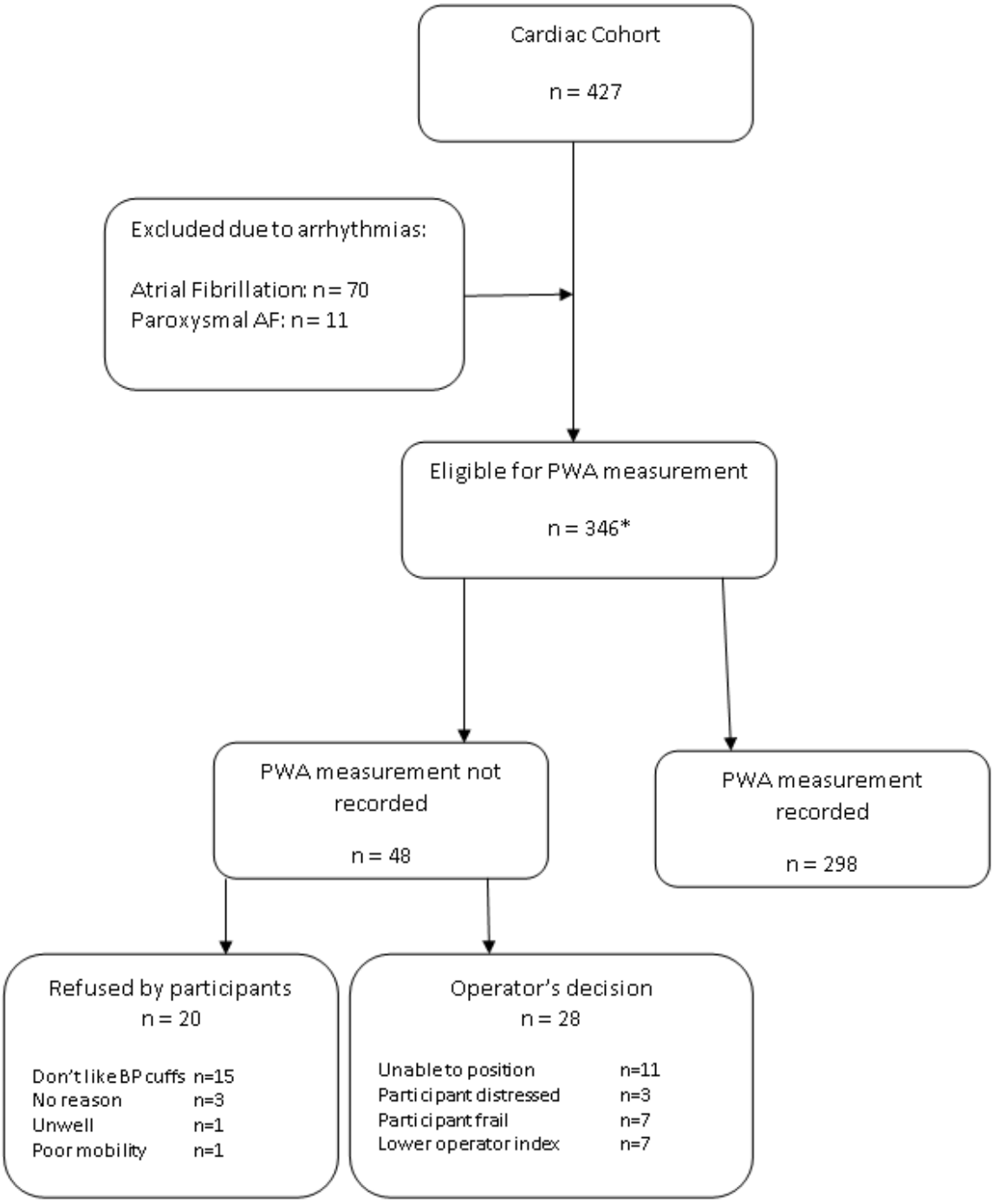


Figure 6.5 Feasibility of domiciliary Pulse Wave Analysis (PWA)

*28 participants with AF/PAF (19,9) with operator index above 80 were also included in the PWA analysis

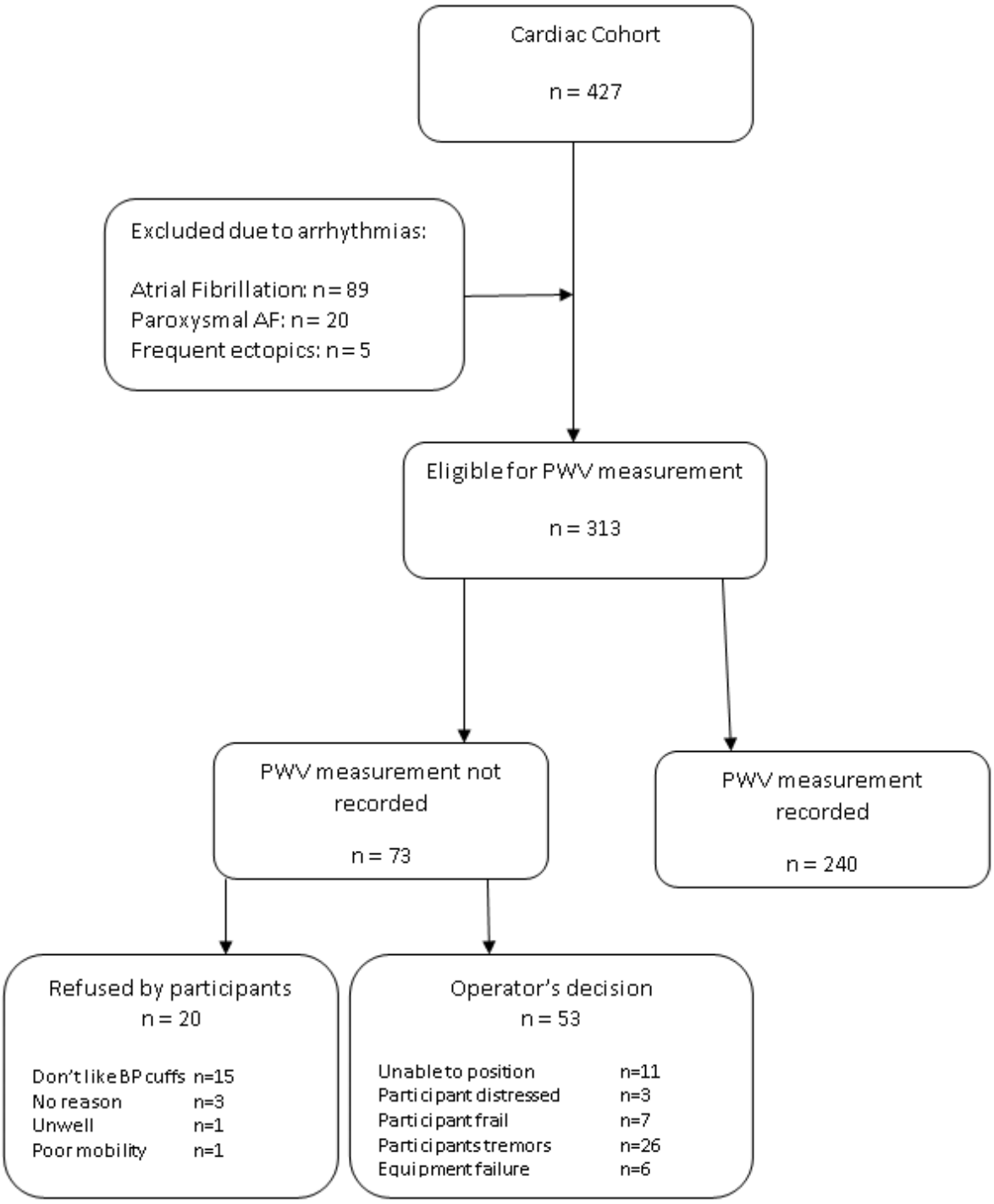


Figure 6.6 Feasibility of domiciliary Pulse wave velocity (PWV) measurement

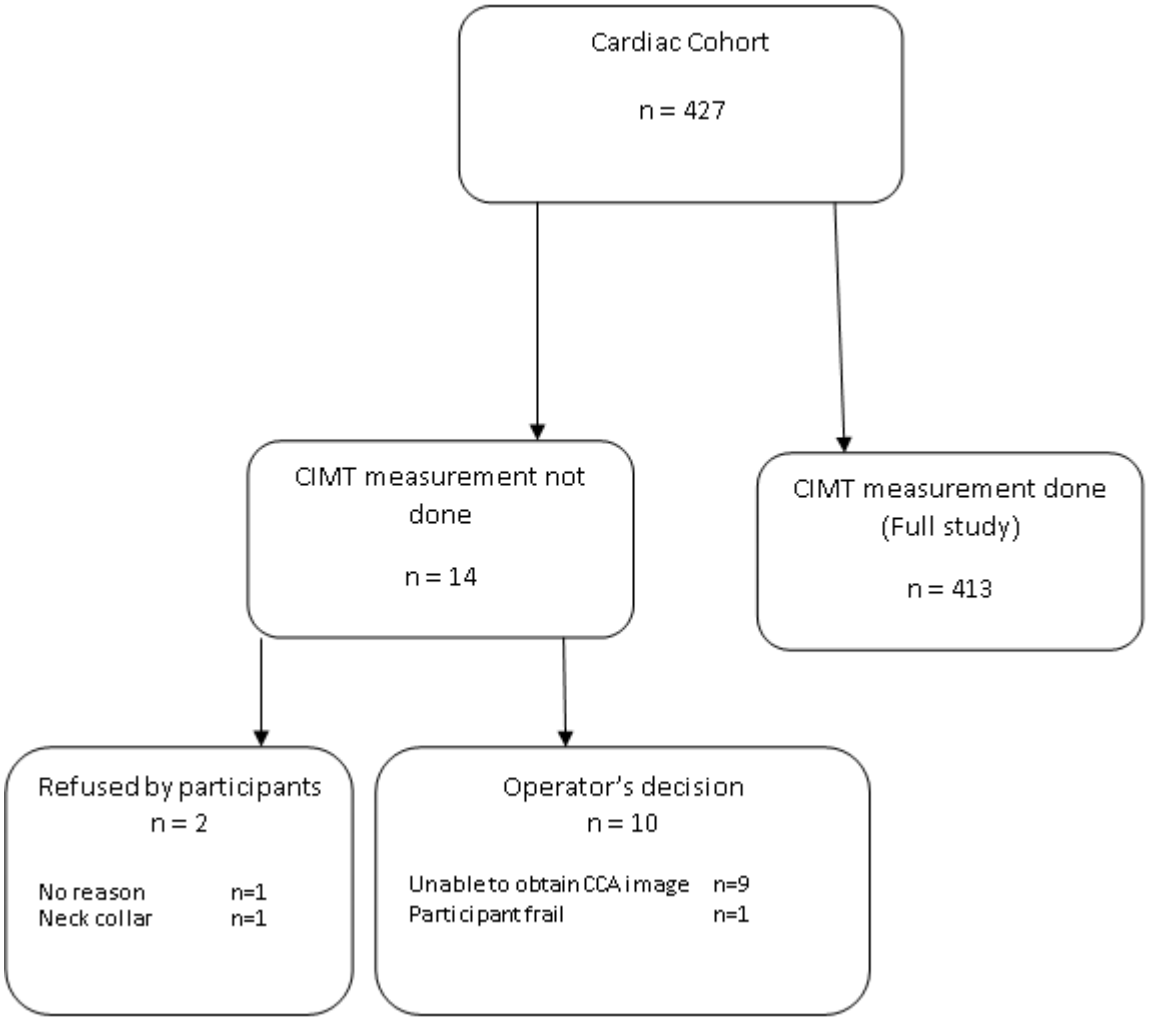


Figure 6.7 Feasibility of domiciliary Carotid intima media thickness (CIMT) measurement

6.4 Prevalence Of Cardiac And Non-Cardiac Health Characteristics

Table 6.2 and 6.3 represent the cardiac and non-cardiac health characteristics of the study cohort. NYHA functional classification was assigned to 281 participants. Most participants exhibited NYHA class I (n=119, 42.4%) and NYHA II, 120 (42.7%). Only 42 (14.9%) participants were assigned NYHA III. None of the participants exhibited NYHA class IV. The majority of the males (51.4%, 57/111) exhibited no symptoms of breathlessness (NYHA I) while 36.5% females were assigned NHYA class I. 63.5 % (n=108) females exhibited either NYHA class II or III. Only 10.4% (n=34) participants mentioned presence of chest pains which were exertional in nature in nearly half of the cases. Some degree of ankle odema was also present in 22.8% (n=72) people. However, it was severe only in 5.7% (n=18) participants.

Table 6.2 Prevalence of cardiac health characteristics

	Men (n, %)	Women (n, %)	Total (n, %)
Shortness of breath (352)*			
NYHA I	57 (51.4)	62 (36.5)	119 (42.4)
NYHA II	39 (35.1)	81 (47.6)	120 (42.7)
NYHA III	15 (13.5)	27 (15.9)	42 (14.9)
NYHA IV	0 (0)	0 (0)	0
NYHA I/II	25 (18.4)	46 (21.3)	71(20.2)
Chest pains (315)ǂ			
Present	13 (38.2)	21 (61.8)	34 (10.8)
Exertional nature	5 (27.8)	13 (72.2)	18 (5.7)
Limits function	3 (21.4)	11 (78.6)	14 (4.4)
Ankle odema (316)ǂ			
Present	20 (27.8)	52 (72.2)	72 (22.8)
Severe	4 (22.2)	14 (77.8)	18 (5.7)

* Based on phase2 and 3 questionnaire
ǂ Baseline symptoms

Table 6.3 Prevalence of non-cardiac health characteristics

Variables		Men (n, %)	Women (n, %)	Total (n, %)
Categorised MMSE				
	26-30 (normal)	136 (39.8%)	206 (60.2%)	342 (80.1%)
	22-25 (mild)	24 (41.4%)	34 (58.6%)	58 (13.6%)
	18-21 (moderate)	2 (13.3%)	13 (86.7%)	15 (3.5%)
	0-17 (severe)	5 (41.7%)	7 (58.3%)	12 (2.8%)
Categorised GDS				
	No Depression	149 (42.1%)	205 (57.9%)	354 (82.9%)
	Mild Depression	10 (23.8%)	32 (76.2%)	42 (9.8%)
	Moderate Depression	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Severe Depression	6 (24.0%)	19 (76.0%)	25 (5.9%)
Categorised Disability				
	None	58 (56.3%)	45 (43.7%)	103 (24.1%)
	1-6	88 (36.2%)	155 (63.8%)	243 (56.9%)
	7-12	14 (21.2%)	52 (78.8%)	66 (15.5%)
	13-17	7 (46.7%)	8 (53.3%)	15 (3.5%)
Self Rated Health				
	Excellent	21 (43.8%)	27 (56.3%)	48 (11.2%)
	Very Good	66 (46.2%)	77 (53.8%)	143 (33.5%)
	Good	59 (36.9%)	101 (63.1%)	160 (37.5%)
	Fair	19 (28.8%)	47 (71.2%)	66 (15.5%)
	Poor	0 (0.0%)	6 (100.0%)	6 (1.4%)
Housing				
	Standard	150 (41.7%)	210 (58.3%)	360 (84.3%)
	Sheltered	13 (24.1%)	41 (75.9%)	54 (12.6%)
	Institutional	4 (30.8%)	9 (69.2%)	13 (3.0%)

The majority of participants had either normal cognitive function (80.1%, n=342) or only mild cognitive impairment (13.6%, n=58). Only 6.2 % (27/427) had moderate or severe cognitive impairment. The majority of participants had either no (82.9%, n=354) or only mild depression (9.8%, n=42). Only 5.9% (25/427) had moderate or severe cognitive impairment.

6.5 Reproducibility 0f Echocardiography Assessments

LV systolic function was assessed by calculation of LVEF by three different methods including m-mode, eyeball assessment and wall motion score index (WMSI) by both reviewers (FY and JS). LV diastolic function was assessed by calculating E/e´ ratio. Table 3.4 shows a very strong correlation between measurements of LV systolic function and diastolic function performed by both reviewers. Correlation coefficient (r) for LVEF (m-mode), LVEF (eyeball), LVEF (WMSI) and E/e´ were 0.921, 0.978, 0.935 and 0.989 respectively. (Table 6.4)

Table 6.4: Means and co-relational analysis for LV systolic and diastolic function

		FY		JS			
Variable	n	Mean	St Dev	Mean	St Dev	r	p value
LVEF(m-mode)	25	71.28	12.77	70.3	11.21	0.921	<0.0001
LVEF(Eye Ball)	24	53.5	9.57	54.48	8.27	0.978	<0.0001
LVEF(WMSI)	24	55.65	8.16	55.03	7.69	0.935	<0.0001
E/e´ ratio	25	12.098	4.83	12.213	4.858	0.989	<0.0001

Figure 3.8 (a-d) shows Bland Altman plots considering the agreements between both reviewers for assessing LV systolic function (LVEF) by m-mode (a), eyeball method (b) and WMSI (c) method and LV diastolic function by E/e´ (d). Mean difference or bias between both reviewers for LVEF (m-mode), LVEF (eyeball method), LVEF (WMSI) and E/e´ was -0.98, -0.10, -0.62 and 0.11 respectively. Limits of agreement between both reviewers for LVEF (m-mode), LVEF (eyeball method), LVEF (WMSI) and E/e´ was quite tight (-6.7% to 4.7%, 6.5% to 6.3%, -6.3% to 5.1% and -1.3 to 1.5 respectively). Mean bias of less than 1.0% and tight limits of agreement suggest good agreement between both reviewers. It is also important to note that limits of agreement between reviewers remains similar for both low and high values of LVEF and E/e´.

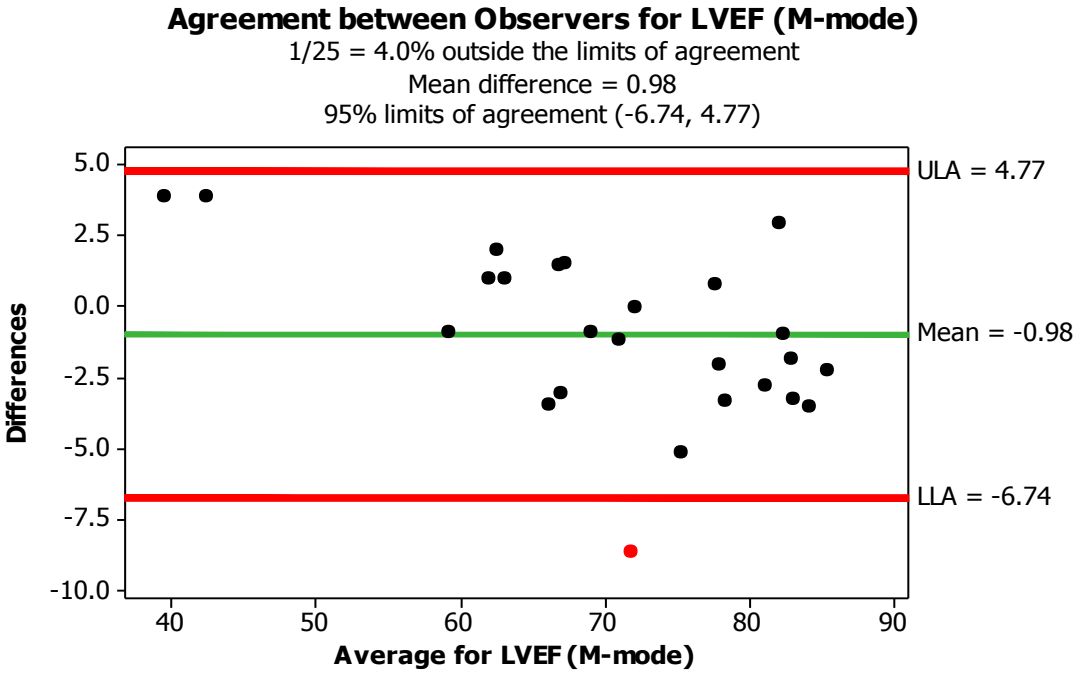


Figure 6.8 (a): Bland–Altman plots showing the mean difference (green lines) and the limits of agreement (red lines) between observers for LVEF (m-mode)

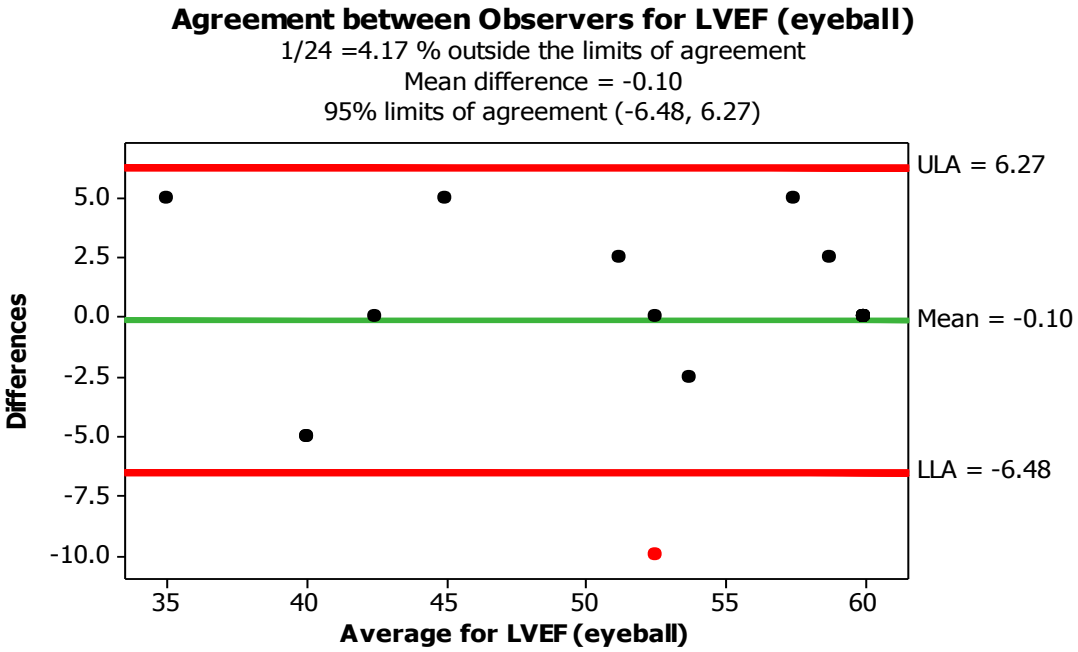


Figure 6.8 (b): Bland–Altman plots showing the mean difference (green lines) and the limits of agreement (red lines) between observers for LVEF (eyeball)

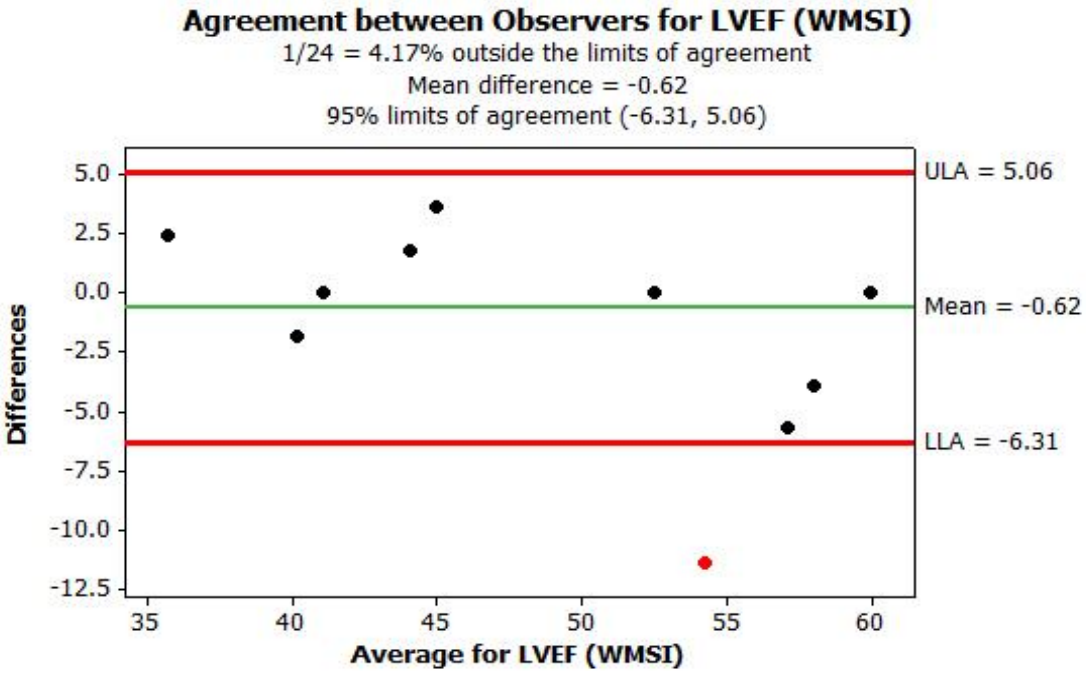


Figure 6.8 (c): Bland–Altman plots showing the mean difference (green lines) and the limits of agreement (red lines) between observers for LVEF (WMSI)

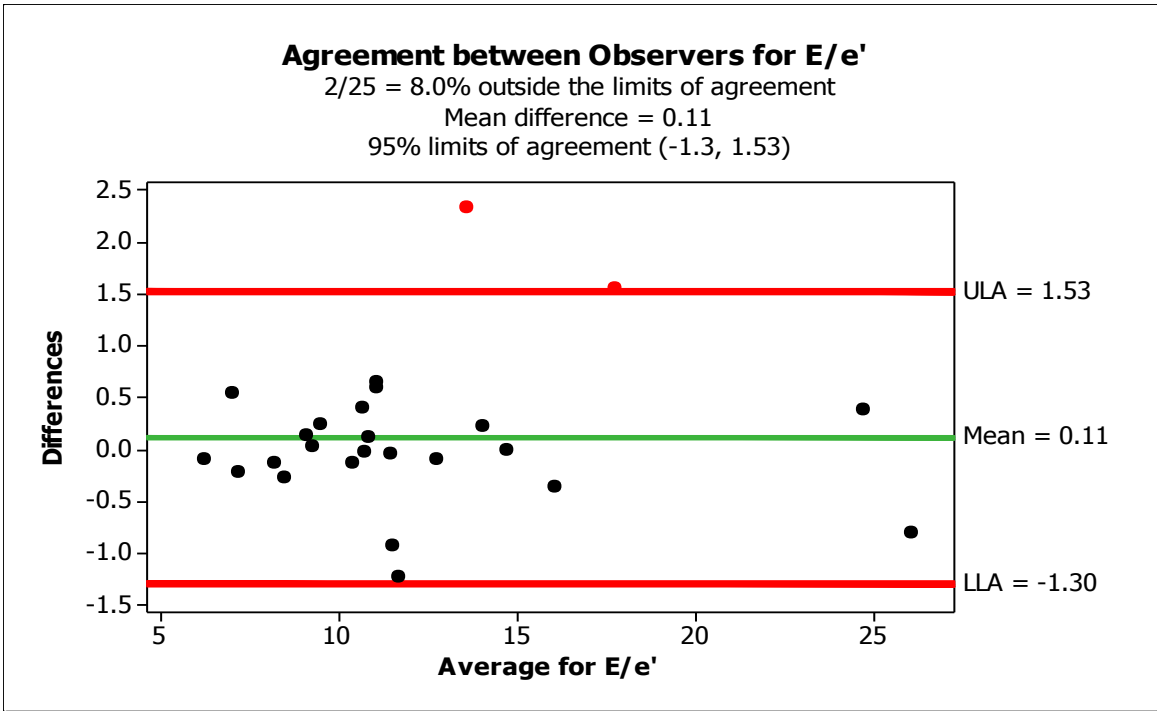


Figure 6.8 (d): Bland–Altman plots showing the mean difference (green lines) and the limits of agreement (red lines) between observers for E/e´

We used Cohen's kappa (κ) statistic to measure agreement between two reviewers on grading RV structure and function. We found both reviewers have substantial agreement ($\kappa = 0.78$) in grading RV structure and almost perfect agreement ($\kappa = 1.00$) in grading RV function.

6.6 Agreement Between Various Methods of LVEF Assessment

Left ventricular systolic function could be assessed in 86% of participants using M-mode measurements, 94% of participants by eyeball, 81% of participants by wall motion score index (WMSI) and 64% by biplane volumetric method.

All three methods for assessment of LVSF by calculating EF including eyeball, biplane and WMSI showed quite substantial agreement ($\kappa > 0.71$) with each other, except m-mode method. LVEF by eyeball assessment method will be used in further analyses in this thesis because it was available in most participants and showed good agreement with other methods of LVEF assessments methods (Table 6.5). Cumulative distribution of LV systolic function as assessed by four methods is displayed in figure 6.9 and convincingly demonstrates a good agreement between various methods throughout the range of LVEF.

	Eyeball	Biplane	WMSI	M-mode
Eyeball	-	0.72	0.75	0.22
Biplane	0.72	-	0.73	0.29
WMSI	0.75	0.73	-	0.27
M-mode	0.22	0.29	0.27	-

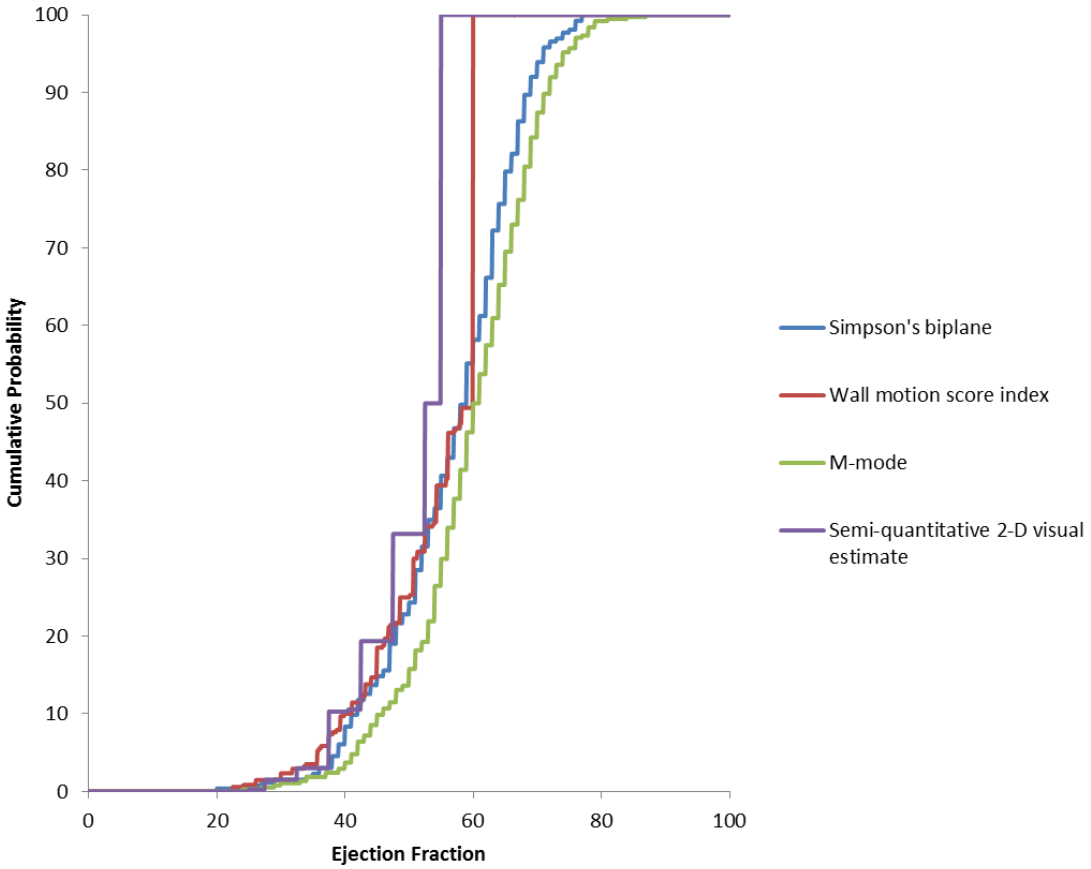


Figure 6.9: Cumulative distribution plot of left ventricular ejection fraction measured by Simpson's biplane volumetric method, 16-segment wall motion score index, M-mode, and semi-quantitative 2-D visual estimate

(Note: The maximum possible LV ejection fraction by wall motion score index was 60% and by semi-quantitative 2-D visual estimate greater than 55%. M-mode and Simpson's biplane are quantitative throughout the range of LV ejection fraction.)

Chapter 7: Prevalence, Diagnosis and Associations of Left Ventricular Dysfunction In the 85+ Cohort

7.1 Prevalence of Left Ventricular Dysfunction

LV systolic (LVSF) and diastolic (LVDF) function were available for 398 and 386 participants respectively. In 376 participants both LVSF and LVDF were available. Nearly half (50.5%, 201/398) of participants had normal LV systolic function (LVEF more than 55%). More females tended to have normal LV systolic function (56.0%, 135/241) as compared to men (42.0%, 66/157). Whereas, moderate to severe LV systolic dysfunction (LVSD) was more prevalent in male (27.4%, 343/157) compared to females (14.5%, 35/241). Overall, 19.6% (78/398) participants had moderate to severe LVSD.

Almost three quarters (72.1%, 106/147) of male participants had either normal or mild diastolic dysfunction while 67.4% (161/239) females had normal or mildly impaired diastolic function. Overall, moderate or severe diastolic dysfunction was present in 30.8% (119/386) participants. Nearly half (n=65) of those with moderate or severe diastolic dysfunction also had some degree of systolic dysfunction. Isolated moderate or severe diastolic dysfunction (IDD) was prevalent in 14.4% (54/376) of participants. In female participants prevalence of IDD was 15.5% while in males it was 12.6%. Slightly more than half (55.2%) of the male participants had some degree of LVSD whereas only 44.2% females had some degree of LVSD (Table 3.6).

Participants (29, 6.8%), in whom LV systolic function was not available were similar to the rest of the cohort in terms of major cardiovascular risk factors for heart disease (Table 7.2). Participants (41, 10.6%), in whom LV diastolic function was not available were also similar to the rest of cohort in terms of major cardiovascular risk factors

except renal disease and ischaemic heart disease (IHD). People with missing LV diastolic function had significantly more prevalence of moderate/severe renal impairment (p=0.001) and IHD (p=0.02). (Table 7.1)

Table 7.1: Prevalence of cardiac dysfunction in 85+ years old

Variables	Male (n, %)	Female (n, %)	Total (n, %)
SYSTOLIC FUNCTION			
Normal LVEF	66 (42.0)	135 (56.0)	201 (50.5)
Mild LVSD	48 (30.6)	71 (29.5)	119 (29.9)
Moderate LVSD	34 (21.7)	32 (13.3)	66 (16.6)
Severe LVSD	9 (0.57)	3 (0.01)	12 (3.0)
	157 (39.5)	241 (61.5)	398 (100)
DIASTOLIC FUNCTION			
Normal diastolic function	25 (17.0)	19 (8.0)	44 (11.4)
Mild diastolic dysfunction	81 (55.1)	142 (6)	223 (57.8)
Moderate diastolic dysfunction	31 (21.1)	65 (67.7)	96 (24.9)
Severe diastolic dysfunction	10 (6.80)	13 (56.5)	23 (5.9)
	147 (38.1)	239 (61.9)	386 (100)
COMBINED			
Normal	46 (32.9)	94 (67.1)	140 (37.2)
Isolated diastolic dysfunction	18 (33.3)	36 (66.7)	54 (14.4)
Systolic dysfunction	79 (43.4)	103 (56.6)	182 (48.4)
	143 (38.0)	233 (62.0)	376 (100)

Table 7.2 Characteristics of participants with & without measurements of systolic function (LVEF)

Variables		Systolic Function Available (n, %)	Systolic Function Unavailable (n, %)	p Value
Gender	n= (398, 29)	-	-	0.60
Male	-	157 (39.4)	10 (34.5)	
Female	-	241 (60.6)	19 (65.5)	
Smoking (smokers/Ex)	n= (397, 29)	243 (61.2)	22 (75.8)	0.13
OBESE (BMI) obese/above	n= (391, 24)	40 (10.2)	4 (16.7)	0.08
Diabetes	n= (398, 26)	52 (13.1)	3 (10.3)	0.67
Hypertension	n= (398, 29)	227 (57.0)	16 (55.3)	0.84
Renal Impairment - MDRD (moderate/above)	n= (389, 28)	231(59.4)	22 (78.6)	0.28
Ischemic Heart Disease	n= (398, 29)	125 (31.4)	13 (44.8)	0.14
Cerebrovascular Disease	n= (398, 29)	74 (18.6)	7 (24.1)	0.46
Atherosclerotic disease	n= (398, 29)	180 (45.2)	18 (62.1)	0.08

Table 7.3: Characteristics of participants with & without measurements of diastolic function

Variables		Diastolic Function Available	Diastolic Function Unavailable	p Value
		(n, %)	(n, %)	
Gender	n= (386/41)			0.18
Male		147 (38.1)	20 (48.8)	
Female		239 (61.9)	21 (51.2)	
Smoking (smokers/Ex)	n= (385/41)	239 (62.1)	26 (63.4)	0.66
OBESE (BMI) obese/above	n= (378/37)	38 (10.0)	6 (16.2)	0.27
Diabetes	n= (386/41)	46 (11.9)	9 (22.0)	0.07
Hypertension	n= (386/41)	221 (57.3)	22 (53.7)	0.66
Renal Impairment - MDRD (moderate/above)	n= (377/40)	220 (58.4)	33 (82.5)	0.001*
Ischemic Heart Disease	n= (386/41)	118 (30.6)	20 (48.8)	0.02*
Cerebrovascular Disease	n= (386/41)	73 (18.9)	8 (19.5)	0.93
Atherosclerotic disease	n= (386/41)	174 (45.1)	24 (58.5)	0.10

7.2 Prevalence of Symptomatic Left Ventricular Dysfunction (SLVD)

73.9% (278/376) participants had data on NYHA functional grading and both LV systolic and diastolic function. NYHA functional grading was not available in 98 (26.1%) participants mainly because limitation of activity was reported by causes other than breathlessness. Participants in whom NYHA grading was not available were similar to the rest of cohort in terms of presence of systolic or diastolic dysfunction or other chronic disease including COPD, IHD and anaemia. (Table 7.4)

Symptomatic left ventricular dysfunction (SLVD) was defined as presence of NYHA class 2 or above in the presence of underlying systolic (mild/moderate/severe) or diastolic dysfunction (moderate/severe).

Prevalence of any SLVD was 37.4% (104/278), in which systolic SLVD was 29.5% (82/278) being more prevalent than isolated diastolic SLVD (7.9%, 22/278).

Symptomatic systolic dysfunction was more prevalent in females than males [OR (95% CI)] 2.52 (1.15-5.54), p =0.01. Symptomatic diastolic dysfunction was also more prevalent in females than males [OR (95% CI)] 6.16 (1.13-36.4), p =0.02. Further 23.0 % (64/278) participants (64/278) had evidence of systolic or diastolic dysfunction but no symptoms of breathlessness (NYHA I), consistent with preclinical heart failure. (Table 7.5)

Table 7.4 Characteristics of participants with & without NYHA grading

Variables		NYHA grading available	NYHA grading not available	p value
Gender	Male	83	84	0.16
	Female	111	149	
Systolic dysfunction	Yes	93	104	0.56
	No	89	112	
Diastolic dysfunction	Yes	62	57	0.87
	No	114	153	
Isolated diastolic dysfunction	Yes	24	30	0.94
	No	146	174	
COPD	Yes	29	38	0.70
	No	165	95	
IHD	Yes	55	83	0.11
	No	139	150	
Anaemia	Yes	42	49	0.79
	No	140	174	

Table 7.5: Prevalence of Symptomatic LV Dysfunction (SLVD) in 85+ year Olds

	NORMAL			ISOLATED DIASTOLIC DYSFUNCTION			SYSTOLIC DYSFUNCTION			TOTAL
	Male	Female	Total	Male	Female	Total	Male	Female	Total	
NYHA 1	18 (48.6)	36 (49.3)	54 (49.1)	9 (64.3)	5 (9.8)	14 (38.9)	29 (50.0)	21 (28.4)	50 (29.9)	118 (34.0)
NYHA 2	15 (40.5)	32 (43.8)	47 (42.7)	**3 (21.4)***	**10 (19.6)**	**13 (36.1)**	**20 (34.5)**	**38 (51.4)**	**58 (34.7)**	118 (34.0)
NYHA 3	4 (10.8)	5 (6.8)	9 (8.2)	**2 (3.9)**	**7 (13.7)**	**9 (25.0)**	**9 (15.5)**	**15 (20.3)**	**24 (14.4)**	42 (12.1)
NYHA 4	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	0 (0.0)
Total	37 (33.6)	73 (66.3)	110 (39.6)	14 (33.3)	22 (66.7)	36 (12.9)	58 (43.9)	74 (56.1)	132 (47.5)	278 (100)

* SLVD figures are shown in bold font.

7.3 Extent of Undiagnosed Symptomatic Left Ventricular Dysfunction (SLVD)

37.4% participants (n=104; 32.7% men & 67.3% women) who had no formal diagnosis of heart failure were symptomatic with NYHA class II or above and had underlying isolated diastolic dysfunction (7.9%, n=22) or systolic dysfunction (29.5%, n=82). Five participants with known diagnosis of HF (23.8%, 5/21) had no echocardiographic evidence of underling systolic or diastolic dysfunction. (Table 7.6)

Table 7.6: Extent of Un-Diagnosed and Mis-Diagnosed Symptomatic Left Ventricular Dysfunction (SLVD)

NO PRE-EXISTING HEART FAILURE DIAGNOSIS										
	Normal			**Isolated Diastolic Dysfunction**			**Systolic Dysfunction**			**Total**
	Male	Female	Total	Male	Female	Total	Male	Female	Total	
NYHA 1	18 (50.0)	34 (49.3)	52 (49.5)	9 (64.3)	5 (22.7)	14 (38.9)	26 (49.1)	20 (31.7)	46 (39.7)	112 (43.6)
NYHA 2	14 (38.9)	31 (44.9)	45 (42.9)	**3 (21.4)**	**10 (45.4)**	**13 (36.1)**	**19 (35.8)**	**34 (54.0)**	**53 (45.7)**	111 (43.2)
NYHA 3	4 (11.1)	4 (5.8)	8 (7.6)	**2 (14.3)**	**7 (32.8)**	**9 (25.0)**	**8 (15.1)**	**9 (14.3)**	**17 (14.6)**	34 (13.2)
NYHA 4	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	0 (0.0)
	36 (34.3)	69 (65.7)	105 (40.9)	14 (38.9)	22 (61.1)	36 (14.0)	53 (45.7)	63 (54.3)	116 (45.1)	257 (100)
PRE-EXISTING HEART FAILURE DIAGNOSIS										
	Normal			**Isolated Diastolic Dysfunction**			**Systolic Dysfunction**			**Total**
	Male	Female	Total	Male	Female	Total	Male	Female	Total	
NYHA 1	0 (0.0)	2 (50.0)	2 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (60.0)	1 (9.1)	4 (25.0)	6 (28.5)
NYHA 2	1 (100.0)	1 (25.0)	2 (40.0)	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (20.0)**	**4 (36.4)**	**5 (31.2)**	7 (33.3)
NYHA 3	0 (0.0)	1 (25.0)	1 (20.0)	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (20.0)**	**6 (54.5)**	**7 (43.8)**	8 (38.1)
NYHA 4	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	0 (0.0)
	1 (20.0)	4 (80.0)	5 (23.8)	0(0.0)	0 (0.0)	0 (0.0)	5 (31.2)	11 (68.8)	16 (76.2)	21 (100)

*SLVD figures are shown in bold font

7.4 Prevalence of Valvular Heart Disease and Echocardiographic Characteristics of 85+ Years Old

Valvular heart disease was not very common in 85+ year olds. Moderate and severe aortic stenosis (AS) were present in 1.8% (7/382) and 0.3% (1/382) of participants respectively. Moderate aortic regurgitation (AR) was present in 5.5% (21/382) participants. Moderate and severe mitral stenosis (MS) was very rare and present in 0.3% (1/376) participants. Moderate mitral regurgitation was present in 6.6% (25/378) participants. Moderate tricuspid regurgitation (TR) was the most common valvular pathology in 85+ year olds. Moderate TR was present in 17.6% (65/369) participants. Severe TR was present in 0.8% (3/369) participants. (Table 7.7)

Table 7.8 shows the echocardiographic characteristics of 85+ year olds. Majority of the participants (90.1%, 337/374) had normal sized left ventricular size (LVIDd). Left ventricle (LV) was moderately or severely dilated in 3.5% (13/374) and 0.3% (1/374) participants respectively. LV systolic function was moderately or severely impaired in 16.8% (66/398) and 2.8% (11/398) participants respectively. 9.6% (26/270) and 33.0% (89/370) participants exhibit moderate and severe LV hypertrophy (LV mass) respectively. Right ventricular (RV) structure and function was normal in majority of participants. Only 2.3 % (6/266) participants had moderate or severely dilated RV, whereas 93.7% (325/347) participants had normal RV systolic function. 12.8% (42/343) and 11.3% (29/257) had moderate or severely dilated left atrium (LA) and right atrium (RA) respectively.

Table 7.7 Prevalence of Valvular Heart Disease in 85+ year olds.

		Men (n, %)	Women (n, %)	Total (n, %)
Aortic Stenosis (AS)				
	no AS	132 (38.3)	213 (61.7)	345 (90.3)
	mild AS	11 (37.9)	18 (62.1)	29 (7.6)
	moderate AS	3 (42.9)	4 (57.1)	7 (1.8)
	severe AS	0 (0.0)	1 (100)	1 (0.3)
		146 (38.2)	236 (61.8)	382 (100)
Aortic Regurgitation (AR)				
	no AR	100 (37.0)	170 (63.0)	270 (70.7)
	mild AR	39 (42.9)	52 (57.1)	91 (23.8)
	moderate AR	6 (28.6)	15 (71.4)	21 (5.5)
	severe AR	0 (0.0)	0 (0.0)	0 (0.0)
		145 (38.0)	237 (62.0)	382 (100)
Mitral Stenosis (MS)				
	no MS	142 (38.4)	228 (61.6)	370 (8.4)
	mild MS	1 (25.0)	3 (75.0)	4 (1.1)
	moderate MS	0 (0.0)	1 (100)	1 (0.3)
	severe MS	1 (100)	0 (0.0)	1 (0.3)
		144 (38.3)	232 (61.7)	376 (100)
Mitral Regurgitation (MR)				
	no MR	89 (42.0)	123 (58.0)	212 (56.1)
	mild MR	48 (34.0)	93 (66.0)	141 (37.3)
	moderate MR	8 (32.0)	17 (68.0)	25 (6.6)
	severe MR	0 (0.0)	0 (0.0)	0 (0.0)
		145 (38.4)	233 (61.6)	378 (100)
Tricuspid Regurgitation (TR)				
	no TR	58 (40.6)	85 (59.4)	143 (38.8)
	mild TR	54 (34.2)	104 (65.8)	158 (42.8)
	moderate TR	26 (40.0)	39 (60.0)	65 (17.6)
	severe TR	0 (0.0)	3 (100)	3 (0.8)
		138 (37.4)	231 (62.6)	369 (100)
Pulmonary Regurgitation (PR)				
	no PR	90 (39.5)	138 (60.5)	228 (83.2)
	mild PR	12 (31.6)	26 (68.4)	38 (13.9)
	moderate PR	4 (50.0)	4 (50.0)	8 (2.9)
	severe PR	0 (0.0)	0 (0.0)	0 (0.0)
		106 (38.7)	168 (61.3)	274 (100)

Table 7.8: Echocardiographic characteristics of 85+ years old

		Men (n, %)	Women (n,%)	Total (n, %)
Right Ventricular Function				
	Normal	120 (36.9)	205 (63.1)	325 (93.7)
	Mild Impairment	11 (61.1)	7 (38.9)	18 (5.2)
	Moderate Impairment	1 (25.0)	3 (75.0)	4 (1.2)
	Severe Impairment	0 (0.0)	0 (0.0)	0 (0.0)
		132 (38.0)	215 (62.0)	347 (100)
Left Ventricular Function				
	Normal	65 (32.8)	133 (67.2)	198 (50.3)
	Mild Impairment	48 (40.3)	71 (59.7)	119 (30.2)
	Moderate Impairment	34 (51.5)	32 (48.5)	66 (16.8)
	Severe Impairment	9 (81.8)	2 (18.2)	11 (2.8)
		156 (39.7)	238 (60.4)	394 (100)
Right Atrial Size				
	Normal	61 (30.0)	142 (70.0)	203 (79.0)
	Mildly dilated	14 (56.0)	11 (44.0)	25 (9.7)
	Moderately dilated	12 (57.0)	9 (43.0)	21 (8.2)
	Severely dilated	4 (50.0)	4 (50.0)	8 (3.1)
		91 (35.4)	166 (64.6)	257 (100)
Left Atrial Size				
	Normal	93 (33.7)	183 (66.3)	276 (80.5)
	Mildly dilated	10 (27.0)	13 (73.0)	23 (6.7)
	Moderately dilated	22 (59.0)	15 (41.0)	37 (10.8)
	Severely dilated	3 (43.0)	4 (57.0)	7 (2.0)
		128 (37.3)	215 (62.7)	343 (100)
Right Ventricular Size				
	Normal	70 (31.7)	151 (69.3)	221 (83.1)
	Mildly dilated	21 (53.8)	18 (46.2)	39 (14.7)
	Moderately dilated	2 (40.0)	3 (60.0)	5 (1.9)
	Severely dilated	1 (100)	0 (0.0)	1 (0.4)
		94 (35.3)	172 (64.7)	266 (100)
Left Ventricular Size (LVIDd)				
	Normal	133 (39.5)	204 (60.5)	337 (90.1)
	Mildly dilated	3 (13.0)	20 (87.0)	23 (6.0)
	Moderately dilated	7 (53.8)	6 (46.2)	13 (3.5)
	Severely dilated	0 (0.0)	1 (100)	1 (0.3)
		143 (38.2)	231 (61.8)	374 (100)
Left Ventricular mass				
	Normal	42 (38.5)	67 (61.5)	109 (40.4)
	Mild	13 (28.3)	33 (71.7)	46 (17.0)
	Moderate	15 (57.7)	11 (42.3)	26 (9.6)
	Severe	29 (32.6)	60 (67.4)	89 (33.0)
		99 (36.7)	171 (63.3)	270 (100)

7.5 Use of Heart Failure Medication In those with Pre-Existing Heart Failure Diagnosis

Of those with a pre-existing diagnosis of heart failure in the general practice medical records: 73.7% (28/38) were taking a diuretic; 71.1% (27/38) an angiotensin converting enzyme inhibitor or angiotensin II receptor blocker; 34.2% (13/38) a beta blocker; 23.7% (9/38) an angiotensin converting enzyme inhibitor/angiotensin II receptor blocker in combination with a beta blocker; and 18.4% (7/38) a cardiac glycoside. No statistically significant gender differences were found in the use of heart failure medication (p values all greater than 0.05).

7.6 Exclusion of Cases With Significant Intrinsic Lung Disease

Spirometric criteria for significant intrinsic lung disease were met by 9.6% (36/376) of participants and an additional 1.3% (5/376) did not have spirometry data. A sensitivity analysis excluding these cases resulted in prevalence rates for LV systolic and diastolic dysfunction and levels of undiagnosed dysfunction which matched to within 2% of the figures reported for the whole sample.

7.7 Cardiac Dysfunction And Arterial Stiffness

Participants with LV systolic dysfunction had higher carotid-femoral PWV (10.77 ± 2.06 m/sec) and LV mass index (113.44 ± 34.3) as compared to people with normal systolic function, but it was not statistically different. CIMT was significantly higher in patients with LV systolic dysfunction ($p = 0.04$). Participants with LV diastolic dysfunction also had stiffer arteries as compared to participants with no diastolic dysfunction with PWV 10.75 ± 1.97 m/sec. Participants with diastolic dysfunction also had higher augmentation index, augmentation pressure and central systolic blood pressure as compared to participants with normal diastolic function, but it was also not statistically significant. (Table 7.9 & 7.10)

Table 7.9	Markers of vascular stiffness and systolic function				
			SYSTOLIC FUNCTION		
Variables	No		Yes		
	Mean	SD	Mean	SD	p Value
Pulse wave velocity (PWV)	10.70	1.84	10.77	2.06	0.79
Ankle brachial index (ABI) Left	1.06	0.21	1.11	0.21	0.12
Ankle brachial index (ABI) Right	1.08	0.20	1.10	0.24	0.37
Peripheral Systolic Blood Pressure (P-SBP)	157.38	18.65	156.13	20.07	0.59
Peripheral Diastolic Blood Pressure (P-DBP)	72.22	10.35	74.42	11.26	0.09
Augmentation Pressure (AG)	25.90	10.92	24.02	10.56	0.14
Augmentation Pressure @ 75	22.32	8.45	20.33	9.38	0.06
Augmentation Index (AGPH)	34.88	9.44	34.09	10.43	0.72
Augmentation Index @ 75	31.73	9.19	30.44	10.37	0.16
Central Systolic Blood Pressure (C-SBP)	145.28	19.31	143.80	19.80	0.54
Central Diastolic Blood Pressure (C-DBP)	73.31	10.66	75.39	11.43	0.11
Central Pulse Pressure (C-PH)	71.92	15.85	68.41	16.37	0.06
SEVR	123.73	23.26	134.44	31.31	0.001*
LV Mass Index (BSA)	107.27	29.72	113.44	34.87	0.94
CIMT Mean Left Posterior	0.83	0.18	0.87	0.20	0.04*
CIMT Mean Right Posterior	0.83	0.16	0.82	0.16	0.35

Table 7.10	Markers of vascular stiffness and diastolic function				
	DIASTOLIIC FUNCTION				
Variables	No		Yes		
	Mean	SD	Mean	SD	p Value
Pulse wave velocity (PWV)	10.68	1.90	10.92	2.14	0.42
Ankle brachial index (ABI) Left	1.10	0.21	1.03	0.21	0.10
Ankle brachial index (ABI) Right	1.10	0.22	1.05	0.20	0.10
Peripheral Systolic Blood Pressure (P-SBP)	156.07	19.07	161.07	20.92	0.06
Peripheral Diastolic Blood Pressure (P-DBP)	72.52	10.67	75.33	11.39	0.06
Augmentation Pressure (AG)	24.84	10.31	26.97	11.74	0.14
Augmentation Pressure @ 75	21.46	8.51	22.77	9.75	0.28
Augmentation Index (AGPH)	34.29	9.31	36.15	10.56	0.16
Augmentation Index @ 75	31.16	9.18	32.47	10.44	0.31
Central Systolic Blood Pressure (C-SBP)	143.92	19.39	149.00	20.54	0.06
Central Diastolic Blood Pressure (C-DBP)	73.61	10.97	76.33	11.50	0.07
Central Pulse Pressure (C-PH)	70.31	15.93	72.67	17.32	0.29
SEVR	127.05	22.74	127.64	34.34	0.86
LV Mass Index (BSA)	110.49	31.80	109.49	33.82	0.82
CIMT Mean Left Posterior	0.85	0.20	0.83	0.19	0.38
CIMT Mean Right Posterior	0.99	0.21	1.01	0.18	0.73

7.8 'Normal Value' For Plasma NT-proBNP In 'Healthy 85+ Year Old Community Dwelling Participants

Participants were considered clinically normal when they had no history of ischaemic heart disease (no angina, myocardial infarction, coronary intervention and coronary artery bypass graft), hypertension, or renal disease; had no diabetes; had normal ECG (no definite changes for IHD; had normal echocardiograms for systolic and diastolic function; and were in normal sinus rhythm.

27 participants (9 males, 18 females) were considered 'normal and healthy' 85+ year old community dwelling individuals. Mean (SD) and median (IQR) values of NT-proBNP in 'normal and healthy' 85+ year old cohort are 189±140 pg/mL and 163 (108) pg/mL respectively. There was no significant gender difference in NT-proBNP levels. (Table 7.11)

Table 7.11 'NORMAL VALUE' for Plasma NT-proBNP in 'Healthy' 85+ years old						
All	n	Mean (SD) pg/mL	95% CI mean	Median (IQR) pg/mL	95% CI median	p value (mean,median)*
All	27	189 (140)	133-244	168 (107)	111-200	
Males	9	157 (84)	92-201	180 (125)	65-206	0.42, 0.68
Females	18	204 (161)	124-284	163 (158)	109-239	

*two means were compared with indpendent t test, while medians were compared with Mann-Whitney Test

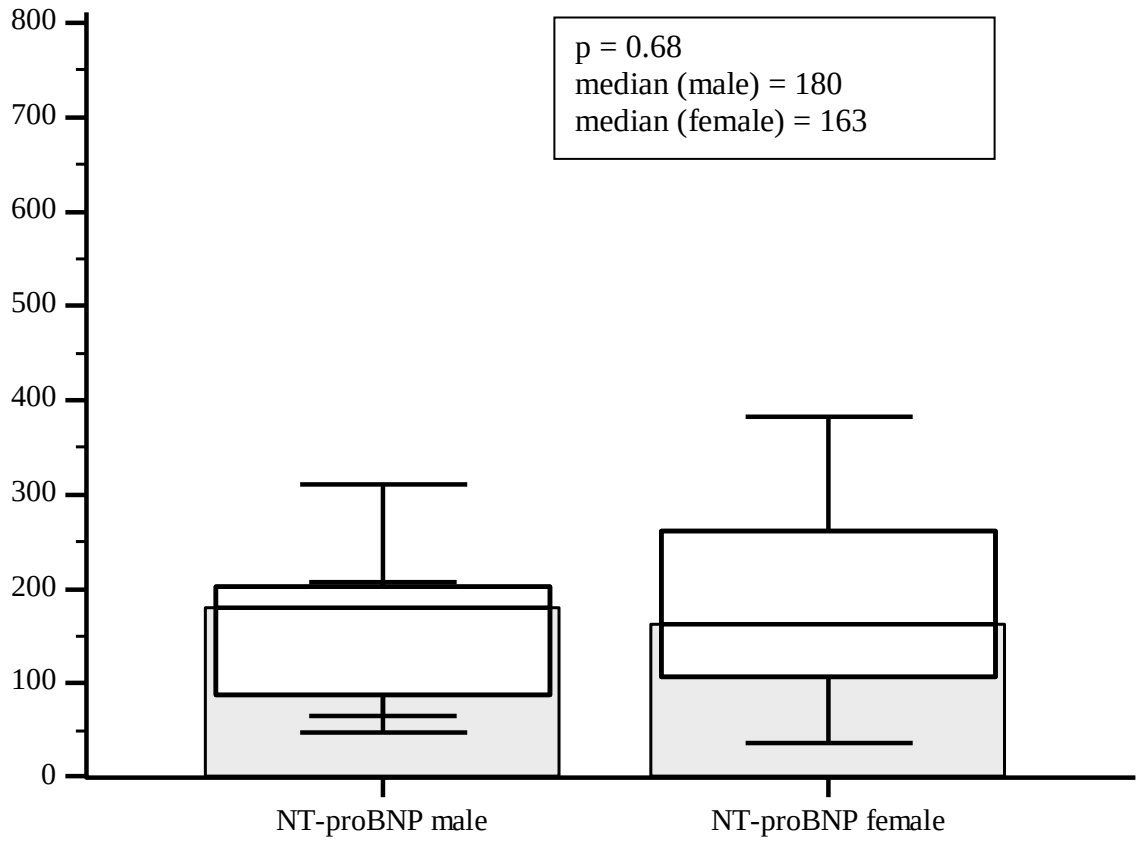


Figure 7.1: Box plot for the comparison of medians for NT-proBNP values in males and females

7.9 Association Between Left Ventricular Function and Plasma NT-ProBNP In 85+ Years Old

Both echocardiographic data on LV systolic function and NT-proBNP levels both were available in 364 participants. We reported mean NT-proBNP levels of 324 ± 275 pg/mL in participants with normal LV systolic function (LVEF ≥55%), which significantly increases with progression of LV systolic dysfunction ($p < 0.00001$). Table 7.12

Both echocardiographic data on LV diastolic function and NT-proBNP levels both were available in 354 participants. We reported mean NT-proBNP levels of 355 ± 333 pg/mL in participants with normal LV diastolic function (LVEF ≥55%), which significantly increases with impairment of LV diastolic function ($p < 0.00001$). Table 7.12

345 participants had echocardiographic data on LV systolic and diastolic function and NT-proBNP level available. Plasma NT-proBNP levels were 280 ± 240 pg/mL in 131 (39.8%) participants in whom no underlying LV systolic and diastolic dysfunction (No SD, No DD) was noted. However, a significant rise in NT-proBNP levels was noted in people with isolated diastolic dysfunction (No SD, Yes DD) and Systolic dysfunction (Yes SD ± DD). Table 7.12

Table 7.12 Association of Left Ventricular Function (LVF) with NT-proBNP in 85+ years old

Systolic Function	n	Mean (pg/mL)	SD	p (ANOVA)
Normal	190	324.1	275.1	<0.00001
Mild impairment	110	487.2	462.1	
Moderate impairment	54	608.0	411.2	
Severe impairment	10	721.6	573.2	

Diastolic Function	n	Mean (pg/mL)	SD	p (ANOVA)
Normal	248	355.3	333.1	<0.00001
Impaired(Moderate/Severe)	106	537.8	451.3	

LV Systolic/Diastolic Function	n	Mean (pg/mL)	SD	p (ANOVA)
No SD, No DD (normal) *	131	281.1	240.2	<0.00001
No SD, Yes DD (isolated DD)	52	415.6	327.7	
Yes SD, No DD	111	452.6	403.1	
Yes SD, Yes DD	51	675.2	528.4	

*SD = Systolic dysfunction, DD = Diastolic dysfunction

7.10 Association Between NT-ProBNP and The Severity of Symptoms Suggestive of Heart Failure

Plasma NT-proBNP levels and NYHA functional status of dysponea both was available in 307 participants. Plasma NT-proBNP levels were 476 ± 676 pg/mL in 124 (40 %) participants with no symptoms of shortness of breath (NYHA I). we reported a significant rise in NT-proBNP levels with worsening NYHA functional status with NT-proBNP levels of 1057 476 ± 1918 pg/mL in people with NHYA function class III. Table 7.13

Table 7.13 Association between NYHA functional status and NT-proBNP in 85+ years old

NYHA functional status	n	Mean (pg/mL)	SD	p (ANOVA)
NYHA I	124	476.0	676.2	
NYHA II	124	527.4	671.6	0.0017
NYHA III	49	1057.1	1918.8	

7.11 Association Between Markers Of Arterial Stiffness And Plasma NT-proBNP in 85+ Year Olds

Plasma NT-proBNP levels and data on pulse wave velocity (PWV) were available in 226. There was no significant correlation between PWV and NT-proBNP levels (Pearson correlation = 0.24, p = 0.72). NT-proBNP levels also didn't change significantly with increasing tertiles of PWV.

Plasma NT-proBNP levels and data on Augmentation Index (AIx) and Augmentation pressure (AP) were available in 278 participants.. There was no significant correlation between AIx levels (Pearson correlation = 0.04, p = 0.42) or AP levels (Pearson correlation = 0.02, p = 0.77) and plasma NT-proBNP. NT-proBNP levels also didn't change significantly with increasing tertiles of AIx or AP. Table 7.14

Table 7.14 Association between arterial Pulse Wave Velocity (PWV) and NT-proBNP in 85+ years old

Pulse Wave Velocity (PWV)	n	Mean (pg/mL)	SD	p (ANOVA)
Lower Tertile	71	378	352	
Middle Tertile	71	360	316	0.74
Upper Tertile	74	403	351	
Augmentation Pressure	**n**	**Mean (pg/mL)**	**SD**	**p (ANOVA)**
Lower Tertile	90	383	350	
Middle Tertile	97	388	361	0.94
Upper Tertile	91	399	332	
Augmentation Index	**n**	**Mean (pg/mL)**	**SD**	**p (ANOVA)**
Lower Tertile	88	361	298	
Middle Tertile	98	407	413	0.62
Upper Tertile	92	391	315	

7.12 Association Between Peripheral Vascular Disease (PVD) and NT-proBNP in 85+ Years Olds

Participants with ankle brachial index (ABI) less than 0.9 were considered to have PVD. ABI assessment and plasma NT-proBNP levels were available in 242 participants. Plasma NT-proBNP levels were significantly higher in participants with PVD (465 ± 334 pg/mL, p value = 0.05) as compared to participants with no PVD .Out of 242 participants 88 participants had no underlying systolic or diastolic dysfunction on echocardiographic assessments. Even in this group levels of plasma NT-proBNP were significantly higher in participants with PVD.

Table 7.15	Association of Peripheral Vascular Disease (PVD) with NT-proBNP in 85+ years old			
Peripheral Vascular Disease	n	Mean (pg/mL)	SD	P value
No PVD	191	362.5	319	0.05
Definite PVD	51	465.1	334	

After adjusting for Systolic and diastolic function

Peripheral Vascular Disease	n	Mean (pg/mL)	SD	p value
No PVD	71	235	174	0.03
Definite PVD	17	344	232	

7.13 Diagnostic Performance of NT-proBNP in Detection of Left Ventricular Dysfunction In 85+ Year Olds

With the aim of evaluating the diagnostic potential of NT-proBNP in 85+ years old population to detect left ventricular functional abnormalities, we classified people in following 4 groups.

A- Left ventricular systolic dysfunction (LVSD)
B- Left ventricular systolic/diastolic dysfunction (LVD – any)
C- Symptomatic Left ventricular systolic dysfunction (SLVD – systolic)
D- Symptomatic Left ventricular / diastolic dysfunction (SLVD – any)

LVSD group had underling LV systolic dysfunction, LVD – (any) group included people with either underlying LV systolic and or moderate-severe diastolic dysfunction, SLVD – systolic group included people with underlying systolic dysfunction with symptom of breathlessness (NYHA II / III) and SLVD – (any) group included people with underling systolic or moderate to severe diastolic dysfunction with symptoms of breathlessness (NYHA II / III). Based on the severity of underlying systolic dysfunction (LVEF <55%, LVEF <45% and LVEF <35%) each group was further sub-divided in to three subgroups and NT-proBNP performance to detect these abnormalities was tested separately for each group. We did not perform separate ROC curve analysis for different gender because there was no statistical difference between normal values of NT-proBNP between them.

NT-proBNP level of 725 pg/mL can detect LVSD (LVEF <55%) with sensitivity 33%, specificity 93% and area under the curve (AUC, 95%CI) is 0.67 (0.64-0.78). However the performance of NT-proBNP to detect LVSD at lower cut-off (LVEF<45%) increases with area under the curve 0.74 (0.68-0.77). For detection of LVSD (LVEF <45%) an NT-proBNP level of 285% has sensitivity 80.5%, specificity 55% and NPV 92%. (Table 7.16, Figure 7.2-7.4)

For detection of any LV dysfunction (LVEF <55% ± moderate-severe diastolic dysfunction), ROC curve analysis provided NT-proBNP cut-off value 386 pg/mL with AUC = 0.68. This level has sensitivity 0f 49.8%, specificity 78%, NPV 47% and PPV 79.9%. However the performance of NT-proBNP to detect LVD at lower cut-off (LVEF<45% ± moderate – severe diastolic dysfunction) increases with area under the curve 0.70 (0.50-0.65). For detection of

LVD (LVEF <45%) an NT-proBNP level of 413 pg/mL has sensitivity 58%, specificity 80% and NPV 69.3%. (Table 7.17, Figure 7.5-7.7)

For detection of symptomatic LV systolic dysfunction (SLVD- systolic; LVEF <55% and NYHA II/III), ROC curve analysis provided NT-proBNP cut-off value 445 pg/mL with AUC = 0.64 (0.56-0.72). This level has sensitivity 0f 50.6%, specificity 80%, NPV 59% and PPV 74%. However the performance of NT-proBNP to detect SLVD (systolic) at lower cut-off (LVEF<45%) increases with area under the curve 0.71 (0.63-0.78). For detection of SLVD-systolic (LVEF <45%) an NT-proBNP level of 399 pg/mL has sensitivity 70%, specificity 70% and NPV 88.4%. (Table 7.18, Figure 7.8-7.10)

For detection of any symptomatic LV dysfunction (SLVD- any; LVEF <55% ± moderate-severe diastolic dysfunction and NYHA II/III), ROC curve analysis provided NT-proBNP cut-off value 442 pg/mL with AUC = 0.68 (0.60-0.75). This level has sensitivity 0f 49%, specificity 88%, NPV 45% and PPV 89.5%. However the performance of NT-proBNP to detect SLVD (systolic) at lower cut-off (LVEF<45%) increases with area under the curve 0.72 (0.64-0.79). For detection of any SLVD (LVEF <45% ± moderate – severe diastolic dysfunction and NYHA II/III) an NT-proBNP level of 389 pg/mL has sensitivity 61%, specificity 78% and NPV 70.1%. (Table 7.19, Figure 7.11-7.13)

Table 7.16 Test Characteristics for NT-proBNP for the detection of Left Ventricular Systolic Dysfunction (LVSD) in 85+ year old population

Population	LVEF cut-off	n	Positive group	AUC (95% CI)	Cut point*	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV
All	<55%	385	192	0.67 (0.64-0.78)	725	32.8 (26.2 - 39.9)	92.8 (88.1 - 96.0)	81.8	58.1
	<45%	**385**	**77**	**0.74 (0.68-0.77)**	**285**	**80.5 (69.9 - 88.7)**	**54.9 (49.1 - 60.5)**	**30.8**	**91.8**
	<35%	385	12	0.69 (0.64-0.73)	830	58.3 (27.7 - 84.8)	83.9 (79.8 - 87.5)	10.4	96.4

*Cut point of NT-proBNP which gives highest accuracy.

†Note the limited number of subjects with LVEF <35% in this subgroup.

AUC = area under curve, PPV = positive predictive value, NPV = negative predictive value

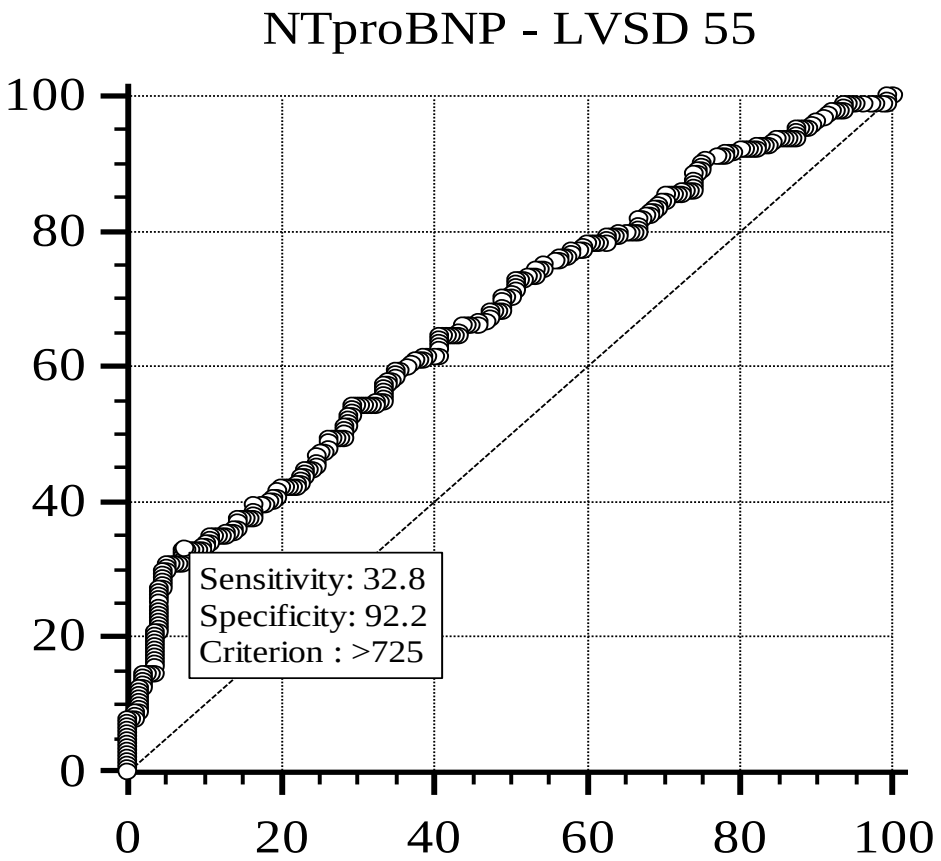


Figure 7.2: The receiver operating characteristic (ROC) curves of NT-proBNP for detecting LVSD (LVEF ≤55%) for entire cohort.

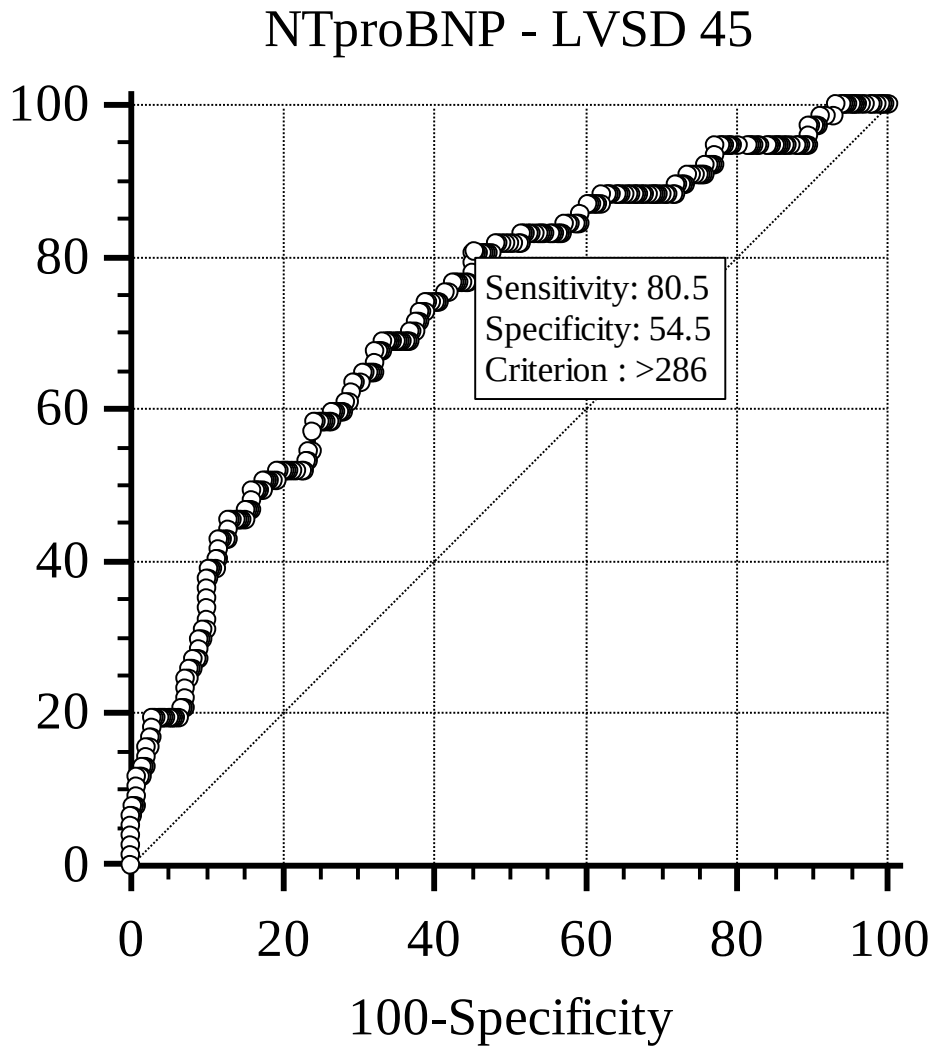


Figure 7.3: The receiver operating characteristic (ROC) curves of NT-proBNP for detecting LVSD (LVEF ≤45%) for entire cohort.

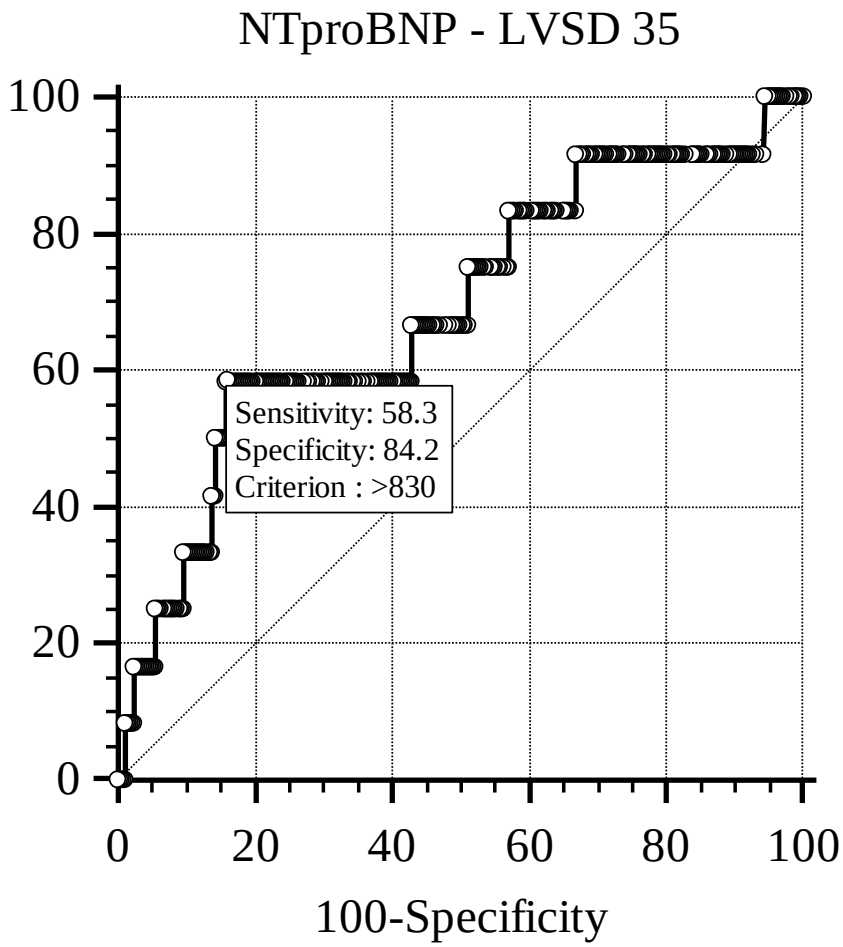


Figure 7.4: The receiver operating characteristic (ROC) curves of NT-proBNP for detecting LVSD (LVEF ≤35%) for entire cohort.

Table 7.17 Test Characteristics for NT-proBNP for the detection of Left Ventricular Systolic/Diastolic Dysfunction (LVD -any) in 85+ year old population

Population	LVEF cut-off	n	Positive group	AUC (95% CI)	Cut point*	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV
All	<55% +/ DD	363	231	0.68 (0.63-0.73)	386	49.8 (43.2 - 56.4)	78.0 (70.0 - 84.8)	79.9	47.0
	<45% +/ DD	**375**	**168**	**0.70 (0.65-0.74)**	**413**	**58.1 (50.2 - 65.7)**	**80.0 (69.6 - 81.6)**	**66.8**	**69.3**
	<35% +/ DD	369	124	0.64 (0.59-0.69)	413	58.4 (45.7 - 63.8)	69.8 (63.6 - 75.5)	47.9	75.3

*Cut point of NT-proBNP which gives highest accuracy.

AUC = area under curve, PPV = positive predictive value, NPV = negative predictive value

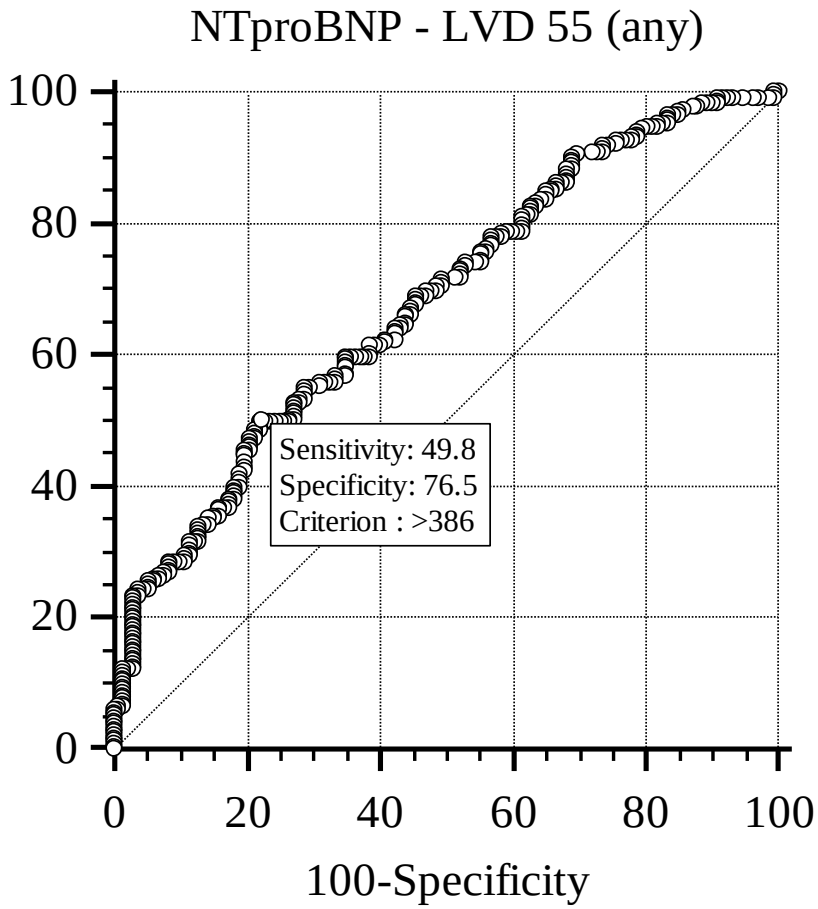


Figure 7.5: The receiver operating characteristic (ROC) curves of NT-proBNP for detecting Left ventricular dysfunction-LVD 55 (LVEF ≤55% & or any moderate-severe diastolic dysfunction) for entire cohort.

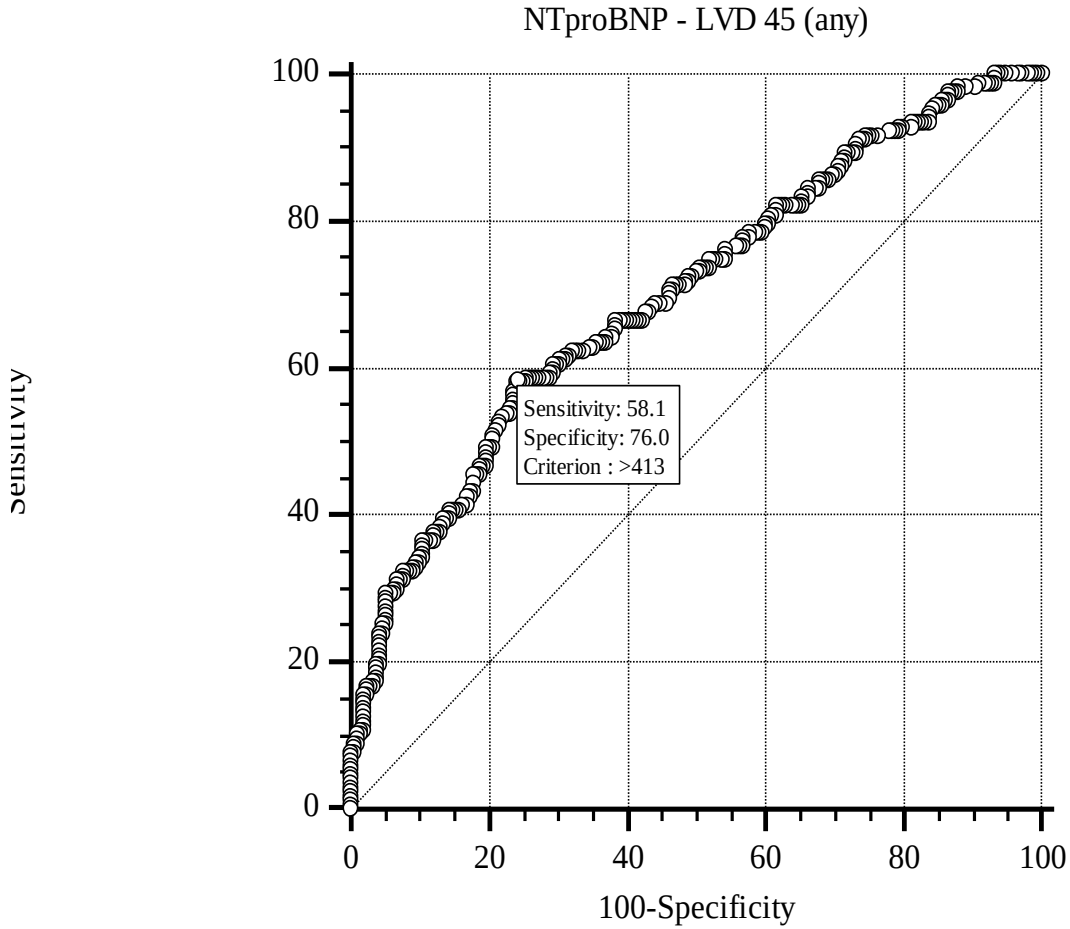


Figure 7.6: The receiver operating characteristic (ROC) curves of NT-proBNP for detecting an Left ventricular dysfunction-LVD 45 (LVEF ≤45% & or any moderate-severe diastolic dysfunction) for entire cohort.

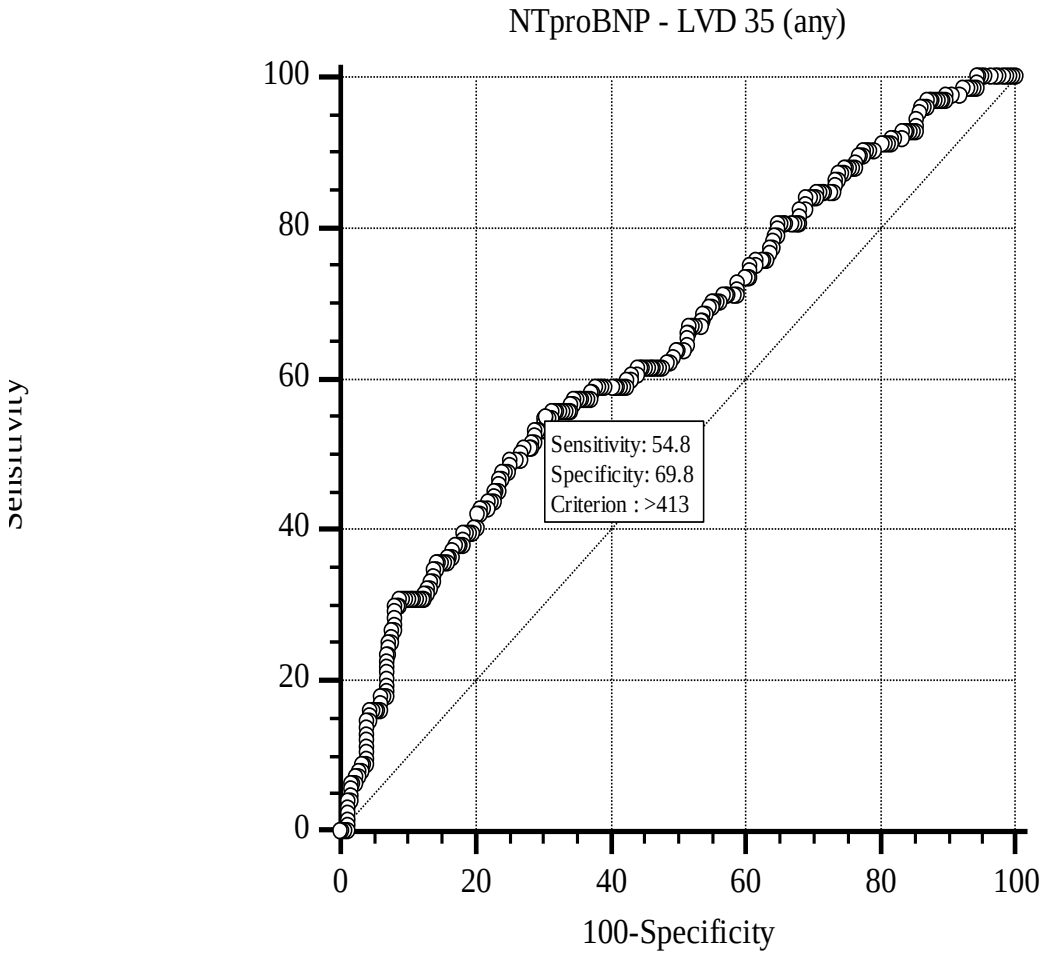


Figure 7.7: The receiver operating characteristic (ROC) curves of NT-proBNP for detecting an Left ventricular dysfunction-LVD 35 (LVEF ≤35% & or any moderate-severe diastolic dysfunction) for entire cohort.

Table 7.18 Test Characteristics for NT-proBNP for the detection of Symptomatic Left Ventricular Systolic Dysfunction (SLVD - Systolic) in 85+ year old population

Population	LVEF cut-off	n	Positive group	AUC (95% CI)	Cut point*	Sensitivity (95%CI)	Specificity (95% CI)	PPV	NPV
All	<55%	156	83	0.64 (0.56-0.72)	445	50.6 (39.4 - 61.8)	79.5 (68.4 - 88.0)	73.7	58.6
	<45%	**156**	**36**	**0.71 (0.63-0.78)**	**399**	**69.4 (51.9 - 83.7)**	**69.4 (60.4 - 77.5)**	**40.3**	**88.4**
	<35%	**156**	**3 †**	**0.71 (0.64-0.78)**	**830**	**66.7 (9.4 - 99.2)**	**82.5 (75.5 - 88.1)**	**6.9**	**99.2**

*Cut point of NT-proBNP which gives highest accuracy.

†Note the limited number of subjects with LVEF <35% in this subgroup.
AUC = area under curve, PPV = positive predictive value, NPV = negative predictive value

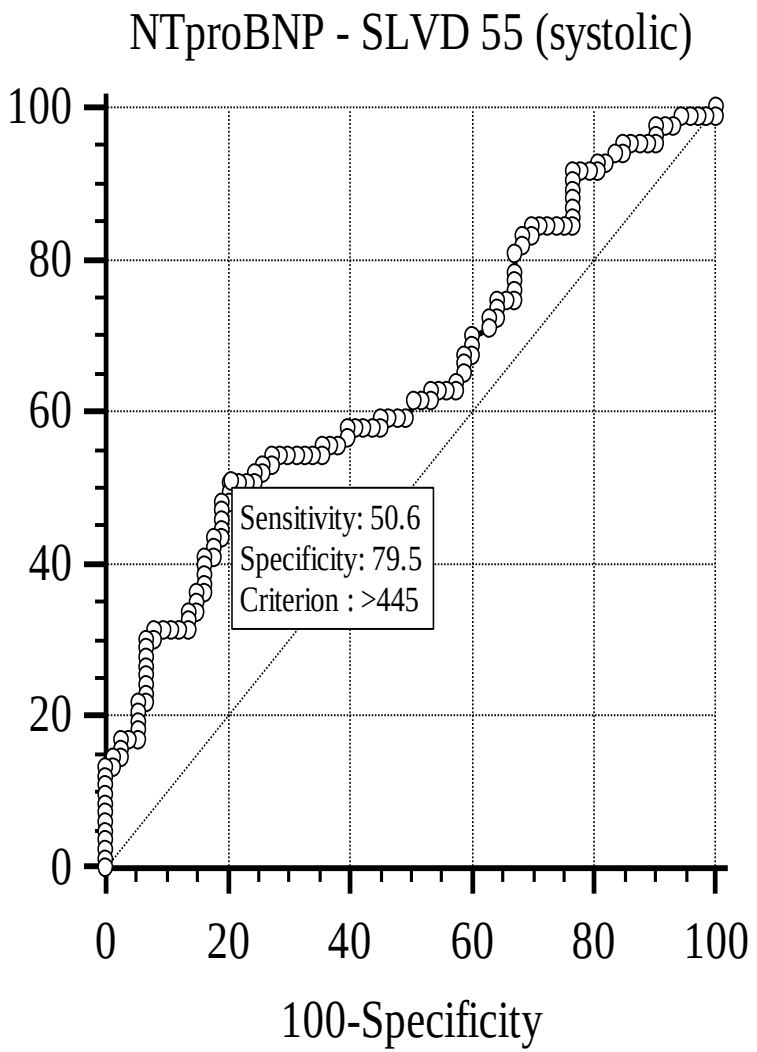


Figure 7.8: The receiver operating characteristic (ROC) curves of NT-proBNP for detecting a Symptomatic Left ventricular systolic dysfunction-SLVD 55 (LVEF ≤55% & NYHA 2/3) for entire cohort.

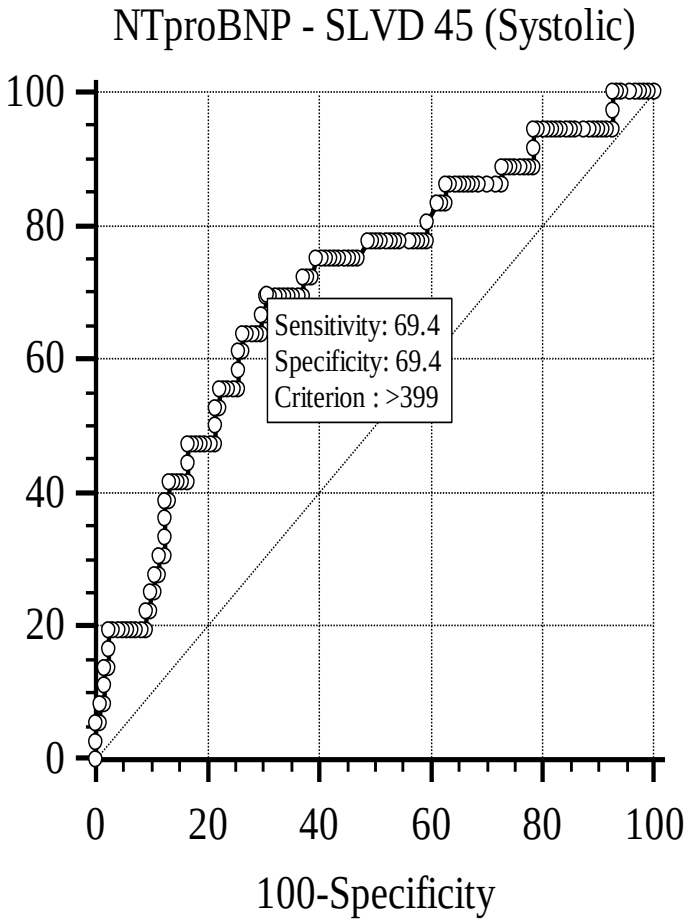


Figure 7.9: The receiver operating characteristic (ROC) curves of NT-proBNP for detecting a Symptomatic Left ventricular systolic dysfunction-SLVD 45 (LVEF ≤45% & NYHA 2/3) for entire cohort.

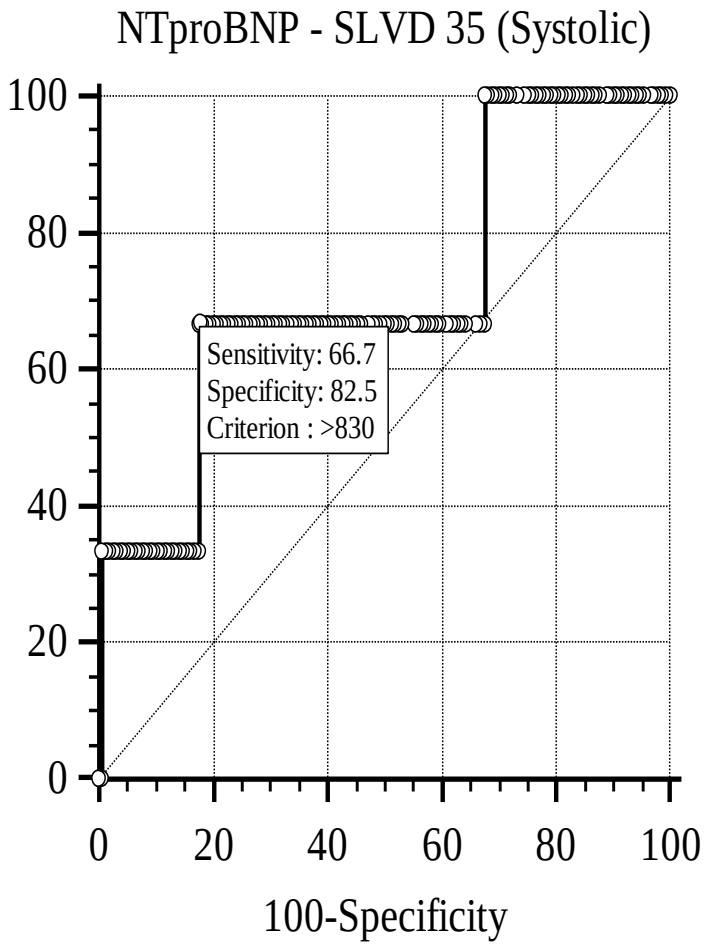


Figure 7.10: The receiver operating characteristic (ROC) curves of NT-proBNP for detecting a Symptomatic Left ventricular systolic dysfunction-SLVD 35 (LVEF ≤35% & NYHA 2/3) for entire cohort.

Table 7.19 Test Characteristics for NT-proBNP for the detection of Symptomatic Left Ventricular Dysfunction ((SLVD – any) 85+ year old population

Population	LVEF cut-off	n	Positive group	AUC (95% CI)	Cut point*	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV
All	<55% +/ DD	155	105	0.68 (0.60-0.75)	442	48.6 (38.7 - 58.5)	88.0 (75.7 - 95.5)	89.5	44.9
	<45% +/ DD	**151**	**70**	**0.72 (0.64-0.79)**	**389**	**61.4 (49.0 - 72.8)**	**77.8 (67.2 - 86.3)**	**70.5**	**70.1**
	<35% +/ DD	150	51	0.68 (0.60-0.75)	389	58.8 (44.2 - 72.4)	69.7 (59.6 - 78.5)	50.0	76.7

*Cut point of NT-proBNP which gives highest accuracy.
†Note the limited number of subjects with LVEF <35% in this subgroup.
AUC = area under curve, PPV = positive predictive value, NPV = negative predictive value

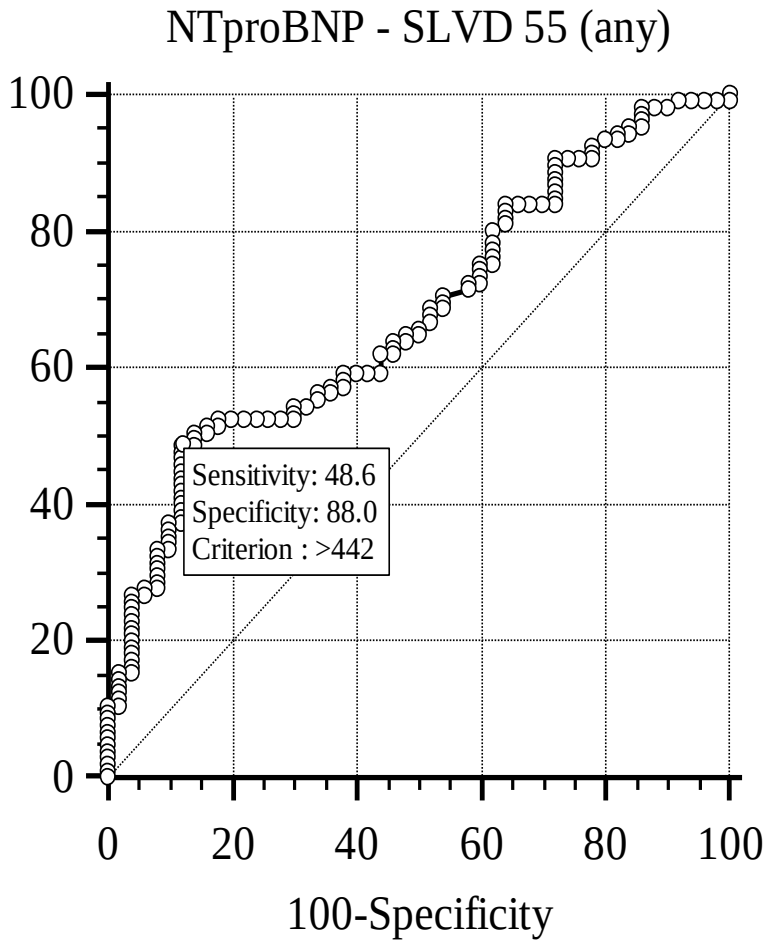


Figure 7.11: The receiver operating characteristic (ROC) curves of NT-proBNP for detecting a any Symptomatic Left ventricular dysfunction-SLVD 55 (LVEF ≤55% & or moderate – severe diastolic dysfunction & NYHA 2/3) for entire cohort.

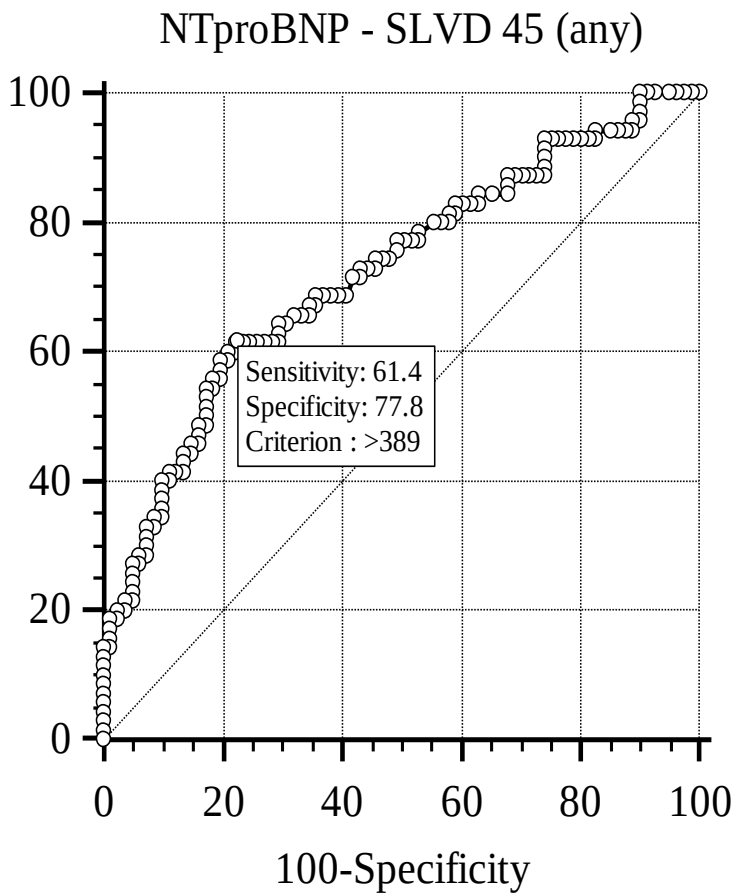


Figure 7.12: The receiver operating characteristic (ROC) curves of NT-proBNP for detecting a any Symptomatic Left ventricular dysfunction-SLVD 45 (LVEF ≤45% & or moderate – severe diastolic dysfunction & NYHA 2/3) for entire cohort.

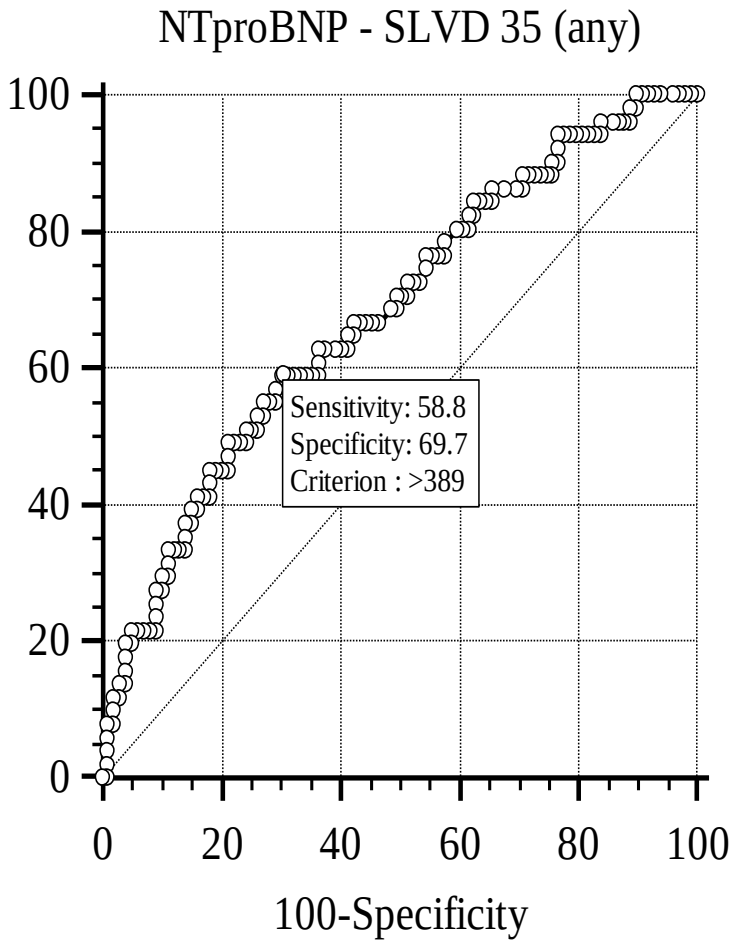


Figure 7.13: The receiver operating characteristic (ROC) curves of NT-proBNP for detecting a any Symptomatic Left ventricular dysfunction-SLVD (LVEF ≤35% & or moderate – severe diastolic dysfunction & NYHA 2/3) for entire cohort.

Chapter 8: Atrial Fibrillation and Peripheral Vascular Disease

8.1 Atrial fibrillation: Prevalence and extent of under-diagnosis

109 participants (25.5%) had atrial fibrillation (AF). 49 participants (49/167 =29.3%) were males and 60 (60/260 = 23.0%) were females. We did not find any significant gender difference in the prevalence of atrial fibrillation/ paroxysmal atrial fibrillation (odds ratio [95% confidence interval] males: females 1.38 [0.87 to 2.20]; p=0.17). 53.2% (58/109 participants) of these participants had no previous GP diagnosis of AF. Atrial fibrillation was significantly more common in participants with heart failure (OR [95%CI]; 2.32 ,[1.11-4.82], p = 0.01), ischaemic heart disease (1.70 [1.06-2.74], p = 0.02) and any atherosclerotic disease (1.77 [1.11-2.81], p = 0.01). There was a suggestion that it was commoner.in people with hyperthyroidism (2.14 [0.58-7.69]), although it was not statistically significant and very few people had hyperthyroidism in our cohort.. (Table 8.1)

Table 8.1 Characteristics of People with Atrial Fibrillation and Sinus Rhythm

Variables		Sinus Rhythm	AF	OR (95% CI)	p- value
Gender					
	Male	118	49	1.38 (0.87-2.20)	0.15
	Female	200	60		
Heart Failure					
	No	296	93	2.32 (1.11-4.82)	*0.01
	Yes	22	16		
Hypertension					
	No	134	50	0.86 (0.54-1.36)	0.49
	Yes	184	59		
Diabetes					
	No	276	95	0.96 (0.48-1.93)	0.92
	Yes	42	14		
IHD					
	No	225	64	1.70 (1.06-2.74)	*0.02
	Yes	93	45		
CVD					
	No	263	83	1.50 (0.85-2.62)	1.13
	Yes	55	26		
Atherosclerotic disease					
	No	182	47	1.77 (1.11-2.81)	*0.01
	Yes	136	62		
Hyperthyroid					
	No	311	104	2.14(0.58-7.69)	0.19
	Yes	7	5		

8.2 Stroke Risk Stratification and Thromboprophylaxis

72.4% (n=80) participants with AF were CHADS2 score 2 or greater. 37 (33.9%) participants were CHADS2 score 3 or more. (Table 8.2) Our entire cohort being above 75 years of age was CHA2DS2-VASc score 2 or above. 87.2% participants (n=95) with AF were CHA2DS2-VASc score 3 or above (Table 8.3). It is obvious that majority of our cohort with AF have higher CHADS2 or CHA2DS2-VASc score and fall in high risk category for thromboembolism or stroke according to NICE guidance for AF management published in 2006. [274]

In our cohort only 13.8% (n=15) participants with CHADS2 score 2 or above were taking warfarin (Table 8.4). In our cohort only 15.6% (n=17) participants with CHA2DS2-VASc score 2 or above were taking warfarin. 84.4% (92) participants with AF, who were not on warfarin, only 42.4% participants (n=39/92) were either on aspirin (n=33) or clopidogrel (n=5). Only one participant was on a combination of aspirin and dipyridamol. (Table 8.5)

Table 8.2 CHADS2 score in patients with Atrial Fibrillation (AF)

CHADS2 score	1	2	3	4	5	6	
Male (n)	16	19	5	6	3	0	49
Female (n)	13	24	13	9	1	0	60
	29	43	18	15	4	0	109

Table 8.3 CHA2DS2-VASc Score in patients with Atrial Fibrillation (AF)

CHA2DS2-VASc Score	2	3	4	5	6	7	8	
Male (n)	14	15	10	7	1	2	0	49
Female (n)	0	10	23	14	8	4	1	60
	14	25	33	21	9	6	1	109

Table 8.4 CHADS2 Score and thromboprophylactic medications

CHA2DS2 Score		1	2	3	4	5	6	
Warfarin	Yes (n)	2	8	3	4	0	0	17
	No (n)	30	39	9	13	1	0	92
		32	47	12	17	1	0	109
Aspirin	Yes (n)	7	13	6	8	0	0	34
	No (n)	25	34	6	9	1	0	75
		32	47	12	17	1	0	109
Clopidogrel	Yes (n)	1	3	1	0	0	0	5
	No (n)	31	44	11	17	1	0	104
		32	47	12	17	1	0	109
Dipyridamol	Yes (n)	0	1	0	0	0	0	1
	No (n)	32	46	12	17	1	0	107
		32	47	12	17	1	0	109

Table 8.5 CHA2DS2-VASc Score and thromboprophylactic medications

CHA2DS2-VASc Score		2	3	4	5	6	7	8	
Warfarin	Yes (n)	1	5	5	5	0	1	0	17
	No (n)	14	22	29	16	6	5	0	92
		15	27	34	21	6	6	0	109
Aspirin	Yes (n)	3	5	12	7	4	3	0	34
	No (n)	12	22	22	14	2	3	0	75
		15	27	34	21	6	6	0	109
Clopidogrel	Yes (n)	0	1	3	1	0	0	0	5
	No (n)	15	26	31	20	6	6	0	104
		15	27	34	21	6	6	0	109
Dipyridamol	Yes (n)	0	0	1	0	0	0	0	1
	No (n)	15	27	33	21	6	6	0	108
		15	27	34	21	6	6	0	109

8.3 Prevalence of Peripheral Vascular Disease (PVD) 85+ Study Cohort

ABI was available in 263 (61.6%) participants and had a mean value of 1.083 ± 0.21. It was significantly lower ($p<0.005$) in females (1.05 ± 0.19; n=147) than males (1.12 ± 0.23; n=116). Participants were categorised into the following four categories based on their ABI values.

a. Definite PVD (<0.9)

b. Borderline PVD (>= 0.9 - <1.0)

c. Low normal ABI (>=1.0 - <=1.1)

d. Normal or No PVD (>1.10)

22.1% participants (n=58) had definite PVD. There was no significant gender difference in prevalence of PVD (13.3%, n=35) and males (8.7%, n=23). Odds ratio [95% confidence interval] female: male 1.26 [0.67 to 2.30]; p=0.45. 15.2% (n=40) participants had borderline PVD (Table 8.6).

People, in which ABI assessment was not available, had significantly higher prevalence of risk factors for PVD including hypertension, high BMI and current smokers. This might lead to underestimation of PVD in our cohort. (Table 8.9)

Table 8.6 Prevalence of Peripheral Vascular Disease –based on ABI assessment

	Definite PVD	Borderline PVD	Low normal ABI	No PVD	Total
Male	23 (8.7%)	13 (4.9%)	18 (6.8%)	62 (23.6%)	116 (44.1%)
Female	35 (13.3%)	27 (10.3%)	35 (13.3%)	50 (19.0%)	147 (55.9%)
	58 (22.1%)	40 (15.2%)	53 (20.2%)	112 (42.6%)	263 (100.0%)

Table 8.7 Prevalence of Peripheral Vascular Disease – GPRR

PVD (GPRR)	Male	Female	Total
No	155 (36.2%)	248 (58.1%)	403 (94.4%)
YES	12 (2.8%)	12 (2.8%)	24 (5.6%)
	167 (39.1%)	260 (60.9%)	427 (100%)

Note: GPRR = General practice record review

Table 8.8 Potential determinants of Peripheral Vascular Disease (PVD)

Variables		PVD (ABI<0.9)	No PVD (ABI≥0.9)	Odds ratio (95% CI)	p value
Gender					
	Male	23 (19.8%)	93 (80.2%)	1.26 (0.67-2.39)	0.46
	Female	35 (23.8%)	112 (73.2%)		
Hypertension					
	Yes	33 (23.7%)	106 (76.3%)	1.23 (0.68-2.21)	0.48
	No	25 (20.2%)	99 (79.8%)		
Stroke					
	Yes	9 (37.5%)	15 (62.5%)	2.32 (0.89-6.01)	*0.05
	No	49 (20.5%)	190 (79.5%)		
Dementia					
	Yes	4 (66.7%)	2 (33.3%)	7.51 (1.15-60.9)	*0.02
	No	54 (21.0%)	203 (79.0%)		
Diabetes					
	Yes	6 (18.2%)	27 (81.8%)	0.76 (0.26-2.07)	0.37
	No	52 (22.6%)	178 (77.4%)		
IHD					
	Yes	18 (22.0%)	64 (78.0%)	0.99 (0.50-1.94)	1.00
	No	40 (22.1%)	141 (77.9%)		
CVD					
	Yes	15 (30.6%)	34 (69.4%)	1.75 (0.83-3.70)	0.08
	No	43 (20.1%)	171 (79.9%)		
Smoking					
	Never	16 (18.2%)	72 (81.8%)	1.64 (0.82-3.30)	0.08
	Current/Ex	42 (26.8%)	115 (73.2%)		
Hyperlipidaemia					
	Yes	37 (25.7%)	110 (74.3%)	1.32 (0.58-3.02)	0.30
	No	11 (17.0%)	43 (83.0%)		

IHD= Ischaemic heart disease, CVD = cerebrovascular disease

Table 8.9 Characteristics of participants with & without measurements of ABI

Variables (n, %)	ABI available (n=263)	ABI unavailable (n=164)	P value
Gender			
Male	116 (44.1%)	51 (31.1%)	*0.01
Female	147 (55.9%)	113 (68.9%)	
Hypertension			
Yes	139 (52.9%)	104 (63.4%)	*0.04
No	124 (47.1%)	60 (36.6%)	
Stroke			
Yes	24 (9.1%)	21 (12.8%)	0.29
No	239 (90.9%)	143 (87.2%)	
Diabetes			
Yes	33 (12.5%)	22 (13.4%)	0.90
No	230 (87.5%)	142 (86.6%)	
IHD			
Yes	82 (31.2%)	56 (34.1%)	0.60
No	181 (68.8%)	108 (65.9%)	
CVD			
Yes	49 (18.6%)	32 (19.5%)	0.91
No	214 (81.4%)	132 (80.5%)	
Smoking			
Never	88 (33.5%)	73 (44.5%)	*0.04
Current/Ex	174 (66.1%)	91 (55.5%)	
BMI			
>= 25	108 (41.9%)	85 (54.1%)	*0.02
<25	150 (58.1%)	72 (45.9%)	

8.4 Extent Of Un-Diagnosed and Mis-Diagnosed PVD

24 participants (5.6%) had diagnosis of PVD on GP record review (Table 8.7). 19.0% participants (n=50; 16.4% of males and 21.1% of females) who had no formal GP diagnosis of PVD had definite PVD on the basis of ABI assessment. Five participants with a diagnosis of PVD in the GP record (31.2%) had normal or low normal ABI (Table 8.8). Thus, there was substantial under-diagnosis and misdiagnosis of PVD in our cohort.

Table 8.10 Undiagnosed Peripheral Vascular Disease

	Definite PVD	Borderline PVD	Low Normal ABI	No PVD	Total
No GP diagnosis of PVD	50 (19%)	37 (14.1%)	50 (19%)	110 (41.8%)	247 (93.9%)
GP Diagnosed PVD	8 (3%)	3 (1.1%)	3 (1.1%)	2 (0.8%)	16 (6.1%)
	58 (22.1%)	40 (15.2%)	53 (20.2%)	112 (42.6%)	263 (100%)

Table 8.11 Undiagnosed Peripheral Vascular Disease by Gender

	Men			Female		
	Definite PVD	**Other**	**Total**	**Definite PVD**	**Other**	**Total**
No GP diagnosis of PVD	19 (16.4%)	88 (75.9%)	107 (92.2%)	31 (21.1%)	109 (74.1%)	140 (95.2%)
Diagnosed PVD	4 (3.4%)	5 (4.3%)	9 (7.8%)	4 (2.7%)	3 (2%)	7 (4.8%)
Total	23 (19.8%)	93 (80.2%)	116 (100%)	35 (23.8%)	112 (76.2%)	147 (100%)

8.5 Medications and Peripheral Vascular Disease (PVD)

Only 10 participants (41.7%) with a GP diagnosis of PVD were on lipid lowering treatment and only 12 (50.0%) participants were on any antiplatelet medication (aspirin n=11, clopidogrel n=1) (Table 8.10). 23 participants (39.6%) diagnosed with definite PVD on ABI assessment were on lipid lowering treatment and only 29 (50.0%) participants were on antiplatelet medication (aspirin n=24, clopidogrel n=3 and dipyridamol n=2). 31 (53.4%) participants with definite PVD (ABI) were undiagnosed and were not on any lipid lowering treatment. 28 (48.3%) people with definite PVD (ABI) were undiagnosed and were not on any anti-platelets. (Table 8.11)

Table 8.12 Medications and Peripheral Vascular Disease

		PVD – GPRR (n=427)		PVD – ABI (n=263)	
		PVD (n=24)	No PVD (n=403)	PVD (n=58)	No PVD (n=205)
Statin					
	Yes	10 (41.7%)	127 (31.5%)	23 (39.6%)	71 (34.6%)
	No	14 (58.3%)	276 (68.5%)	35 (60.4%)	134 (65.4%)
Aspirin					
	Yes	11 (45.8%)	123 (30.5%)	24 (41.4%)	66 (32.2%)
	No	13 (54.2%)	280 (69.5%)	34 (58.6%)	139 (67.8%)
Clopidogrel					
	Yes	1 (4.2%)	18 (4.5%)	3 (5.2%)	10 (4.9%)
	No	23 (95.8%)	385 (95.5%)	55 (94.8%)	195 (95.1%)
Dipyridamol					
	Yes	0 (0.0%)	8 (2.0%	2 (3.4%)	5 (2.4%)
	No	24 (100%)	395 (98.0%)	56 (96.6%)	200 (97.6%)

Table 8.13 Undiagnosed PVD and Medications

Statins			
		PVD (GPRR)	No PVD (GPRR)
Yes	PVD - ABI	4 (6.9%)	19 (32.8%)
	No PVD - ABI	3 (1.5%)	68 (33.2%)
No	PVD - ABI	4 (6.9%)	31 (53.4%)
	No PVD - ABI	5 (2.4%)	129 (62.9%)
Antiplatelet			
Yes	PVD - ABI	4 (6.9%)	22 (37.9%)
	No PVD - ABI	5 (2.4%)	71 (34.6%)
No	PVD - ABI	4 (6.9%)	28 (48.3%)
	No PVD - ABI	2(1.0%)	126 (61.5%)

8.6 Summary

Burden of atrial fibrillation and peripheral vascular disease is high in 85+ year old population. Majority of people with atrial fibrillation and peripheral vascular disease were undiagnosed. Majority of people with atrial fibrillation in 85+ year cohort were at high risk of thromboembolism or stroke and despite that very few people were on thromboprophylactic treatment.

Section 4

Final Summary And Discussion

Chapter 9: Final Summary and Discussion

9.1 Statement of Principal Findings

This study provides estimates of the prevalence of both systolic and diastolic cardiac dysfunction, atrial fibrillation and peripheral vascular disease in a large sample of 85+ year old community dwelling people. This study also provides a comprehensive assessment of echocardiographic characteristics including the prevalence of significant valvular heart disease in this age group. We also established the normative range of NT-proBNP in 85+ year old community dwelling 'healthy' cohort and its diagnostic performance to detect LV dysfunction in this age group.

9.1.1 Prevalence of Symptomatic and Asymptomatic Left Ventricular (LV) Dysfunction

We found that almost a half (50%) of participants had systolic dysfunction (LVEF < 55%), and a further 14.5% had moderate or severe diastolic dysfunction in the presence of preserved systolic function. Overall 37.4% of participants had symptoms consistent with heart failure accompanied by significant LV systolic (29.5%) or diastolic dysfunction (7.9%) on echocardiography, but only 11.5% of these people had been diagnosed with heart failure. A pre-existing diagnosis of heart failure was present in only 5.8 % of our participants and in almost 25% of these we found no evidence of significant LV dysfunction on echocardiography. In addition, 18% of participants had asymptomatic LV systolic dysfunction; around 5% of participants had asymptomatic isolated moderate or severe diastolic dysfunction, all of which were undiagnosed. As previously documented by others at younger ages, we also found the diastolic dysfunction was more common in females and hypertensive patients. In contrast systolic dysfunction was commoner in males and patients with ischaemic heart disease.

Valvular heart disease was not very common in 85+ years old. Moderate and severe aortic stenosis was present only in 1.8% and 0.3% participants respectively. Moderate to severe mitral stenosis was also quite rare (0.3%). Majority of the participants had had normal sized left ventricular. In 19.6% participants LV systolic function was moderate (16.8%) or severely (2.8%) impaired. However, right ventricular structure and systolic function was preserved in majority of the participants. 12.8% and 11.3% had moderate or severely dilated left atrium and right atrium respectively.

We did not find and significant association between markers of arterial stiffness including arterial pulse wave velocity (PWV) and augmentation index and LV systolic or diastolic dysfunction. Arterial PWV was higher in patients with systolic and diastolic functions compared with healthy cohort but it was not statistically significant. Overall, participants with diastolic dysfunction had stiffer arteries as compared to participants without diastolic dysfunction with higher augmentation pressure, augmentation index and central systolic blood pressure. However, these differences were not statistically significant. We also noted CIMT (posterior mean) was significantly higher in patients with LV systolic dysfunction ($p = 0.04$).

Previous community-based studies have recruited small numbers of individuals over the age of 85 and echocardiographic assessments were performed in hospital or clinic

settings. We were aware of the challenges of recruitment in this age group could be as people find it difficult to attend research centres and leave their homes [275, 276]. This potentially could create a recruitment bias towards a relatively health cohort. In the Newcastle 85+ pilot study around 50% of the participants said they would have refused to attend hospital setting for assessment. [252] We therefore, recruited participants regardless of cognitive impairment or place of residence, and conducted a domiciliary echocardiographic assessment. This strategy was superior to previous studies with respect to representativeness and likely to show higher estimates of prevalence than in previous studies including the very old.

Direct comparison with previous studies is complicated mainly due to criteria used to define ventricular dysfunction and age group cut-offs. Overall, however, the prevalence of systolic dysfunction in our population was over twice that of previous large population-based studies in those over 75 years of age. In the Olmsted County study, prevalence of LVSD (LVEF of 50% or less) was 12.9 among 298 participants aged 75 years and above. In the Cardiovascular Health Study, among 689 people over 80, prevalence of LVSD (LVEF 45% or less) was 6%. In the Canberra Heart Study, among 118 people 80-86 years old prevalence of LVSD (LVEF 50% or less) was 14%.[277] In the UK ECHOES study, among 66 participants over 85, reported 17% with LVEF <= 50%. In Rotterdam study group only 29 people were aged 85 years and above and 10.3% showed LVSD (fractional shortening <= 25; equivalent to LVEF ~ 50%). In Helsinki Ageing study only 136 participants were 85 years or above and 11.3% among showed LVSD (fractional shortening <= 25; equivalent to LVEF ~ 50%). Our much larger sample along with domiciliary approach of data collection increases the reliability of those previous estimates and provides additional information on the prevalence of less severe systolic dysfunction and diastolic dysfunction of all grades at this age.

With respect to diastolic dysfunction, the prevalence in our study (88% for any diastolic dysfunction, 31% for moderated or severe dysfunction, 61% for isolated mild, moderate or severe dysfunction, and 14.4% for isolated moderate or severe dysfunction) was again substantially higher than previously described by others in less elderly populations and in the few studies of the very old. For example, among those aged 75 and above in the Olmsted County study moderate or severe dysfunction was about half as common as in our sample (18%), and any diastolic dysfunction was

present in 71% of participants; among 80-86 year olds in the Canberra Heart Study moderate or severe dysfunction was present in 14% and any diastolic dysfunction in 64%. There are no studies to date that have reported data on diastolic function in substantial numbers of participants of this age group. In a recent longitudinal study Halley and colleagues have shown increasing mortality with worsening degree of diastolic dysfunction in patients with preserved systolic function.[278] Moderate and severe diastolic dysfunction alone were associated with increased mortality risk (hazard ratio, 1.58; 95% CI, 1.20-2.08; and hazard ratio, 1.84; 1.29-2.62, respectively; P <.001 for each).

We believe the higher prevalence of both systolic and diastolic dysfunction among our study participant is mainly to the older age of our participants and the inclusive nature of our study design, although other differences including the comorbid conditions and their optimal control like hypertension, ischaemic heart disease and renal impairment between our population and previous studies cannot be excluded as causes or contributing factors. For example, higher prevalence of hypertension and ischeamic heart disease in our study cohort and Jerusalem heart study (56.9% and 71.6% respectively) might be contributing to higher systolic and diastolic dysfunction as compared to other studies including the Rotterdam study, the Helsinki Ageing study and the Olmsted county study where prevalence of hypertension is relatively less (36%, 37%, and 39% respectively).

We reported prevalence of symptomatic LV dysfunction 37.4%, in which systolic dysfunction was 29.5% being more prevalent than isolated moderate/sever diastolic dysfunction (7.9%). This is considerably higher than the prevalence of heart failure reported from previous population-based studies including this age group which range between 2 and 18%. However, caution is needed before comparing our prevalence of symptomatic dysfunction to that of heart failure reported by previous studies as the focus of our study was to identify cardiac dysfunction by echocardiography and to determine the proportion that was symptomatic rather than to identify cases of heart failure by the application of clinical criteria.

Asymptomatic LV dysfunction (also termed as preclinical heart failure) that we have reported in our study is higher (23.0%) than previously reported studies of similar/younger age groups. In the Olmsted County study overall prevalence of asymptomatic LV dysfunction (LVEF<= 50% or moderate/severe diastolic

dysfunction) was 11.7%, however its prevalence in high risk population (aged 65+ and Hypertensive or coronary artery disease) is 27.4% which is similar to our finding.

In our study more than 80% participants with symptomatic LV dysfunction were undiagnosed. 25% of the participants with known diagnosis of heart failure had no underling systolic or diastolic dysfunction. Previous reports, in younger populations, cite the percentage of LV systolic dysfunction which is undiagnosed as between 50 and 80% [18, 43, 279]. In UK Poole study of heart failure prevalence in general population, Morgan and colleague reported 52% of the undiagnosed validated heart failure in elderly cohort (mean age 77 years). It is also important to note that Morgan and colleagues only assessed heart failure with underlying systolic dysfunction and only 20 people with age 80 years and above were included in their study, which can be a reason for lower prevalence and fewer undiagnosed cased of heart failure. In Olmsted County study Redfield and colleagues has reported almost 80% of LV systolic dysfunction (LVEF<= 50%) had no validated diagnosis of heart failure however similarly nearly half of participants with moderate-severe systolic dysfunction and severe diastolic dysfunction had no recognised heart failure diagnosis. Mis-diagnosis of heart failure is also common with 34-75% of general practice cases unsubstantiated by echocardiography and/or specialist assessment.[45, 280-282] Our mis-diagnosis rate (25%) is at the lower end of this range which may be due to two factors: first, our inclusion of moderate/severe diastolic dysfunction in the definition of significant dysfunction whereas previous studies have mainly focused on systolic impairment alone; and second, that our study was conducted after the introduction of the National Service Framework (NSF) for Coronary Heart Disease (CHD) and NHS Quality and Outcomes Framework in 2004 which includes an indicator for the proportion of patients with a diagnosis of heart failure confirmed by echocardiogram or specialist assessment.[283]

The diagnosis of heart failure in very elderly patients, particularly in general practice remains very challenging due to the non-specific nature of its clinical findings, multiple comorbidities mimicking the similar symptoms including anaemia, COPD and renal impairment and the limited access of routine echocardiography (in the UK setting). Many studies have shown in the past that nearly half of the patients were incorrectly diagnosed with heart failure when evaluated with more subjective diagnostic tool like echocardiography.[284] Echocardiography remains a very important diagnostic tool to correctly identifying the condition. In 2004 National

Service Framework (NSF) for Coronary Heart Disease (CHD) & NHS Quality and Outcomes Framework set national standards for improving the diagnosis and treatment of heart failure and recommended that of patients with a diagnosis of heart failure should be confirmed by an echocardiogram or specialist assessment. However, the proportion of people undergoing echocardiogram, especially elderly with suspected heart failure remain below the national standards. Majeed and colleagues looked at the records of 26 general practices in south of England and to compare the management of heart failure with the standards set by NSF. They noted, older people with a diagnosis of heart failure made in the community were less likely to have an echocardiogram than younger patients. [285] This possibly explains the higher numbers of mis-diagnosed heart failure in this age group. It also highlights the need for change in our current strategies to manage heart failure especially in elderly population.

Significant valvular heart disease was quite uncommon in our study cohort. Moderate and severe aortic stenosis was present only in 1.8% and 0.3% participants respectively. Moderate and severe mitral stenosis was very rare and present in 0.3% participants. Moderate mitral regurgitation was present in 6.6% participants. Previously reported study in similar age group has reported higher prevalence of significant valvular heart disease.[286] Thomas van Bammel and colleagues have reported prevalence of moderate and severe aortic stenosis 5%and 1% participants respectively. Moderate and severe mitral regurgitation was present in 30 and 15% individuals respectively. It is also important to note only 81 participants in this study had echocardiographic data on valvular heart disease available. That might have caused some uncertainty in their estimates of valvular heart disease.

No treatment has yet been shown to convincingly reduce morbidity and mortality in patients with HF-PSF. Unfortunately, very few large randomised controlled trials have looked at the patients with HF-PSF as compared with HF-RSF and hence, there is insufficient data on mortality benefit of medications used for patients with HF-PSF. [47, 70, 122, 123] It is believed among physicians and researchers that treating co-morbidities might help to improve survival. Therefore, mainstay of treatment remains on diuretics to control the symptoms and adequate control of blood pressure and ventricular rate. [24, 124] Two trials with target to lower blood pressure in patients with HF-PSF have suggested that ARBs (CHARM preserved trial) and ACE

inhibitors (PEP-CHF trial) may reduce the hospitalisation in patients with HF-PSF. [125] Effectiveness of therapies of heart failure due to systolic dysfunction (HF-RSF) are well established, especially pharmacological therapies including ACE inhibitors/ARBs and beta blockers. However, the importance of treating AHA/ACC class B patients (pre-symptomatic but with evidence of LV systolic dysfunction) to prevent progression to overt heart failure is recognised in guideline statements. We have previously identified a high level of undiagnosed hypertension in this age group and a low level with adequate control in those with diagnosed disease. [251] Whether the risk of progression to HF could be ameliorated in the substantial population of 85+ individuals with diastolic dysfunction by more aggressive management of such co-morbid conditions is a question of considerable interest.

Our findings highlight the continuous nature of the increase in prevalence of cardiac dysfunction with age observed by others in the "younger old", with high levels of both systolic and diastolic dysfunction found in community-dwelling very old people. We also found a substantial burden of undiagnosed and potentially treatable LV dysfunction. Whilst no therapy has been proven to be effective in preventing the progression of preclinical diastolic dysfunction to HF-PEF, or indeed in improving outcomes in established HF-PEF, [287-294] effective (and cost-effective[295]) therapies for HF-REF are well established.[183, 289, 292, 296-307] There is additionally an increasing emphasis on identifying asymptomatic LV dysfunction and preventing its progression to heart failure,[298, 308-311] and the importance of treating people with asymptomatic LV systolic dysfunction recognised in guideline statements.[312] Around a quarter of our participants had undiagnosed LV systolic dysfunction potentially amenable to therapies which can prolong survival and enhance quality of life through symptom control and improved functional status.

Co-morbidities, including renal impairment, anaemia and chronic obstructive pulmonary disease, have been reported to influence the progression of asymptomatic cardiac dysfunction to heart failure and/or to act as prognostic factors in established heart failure.[308, 313-315] We have previously reported the high prevalence of such co-morbidities in this study population.[316] Whether more aggressive management of such co-morbid conditions in the very old could ameliorate the risk of progression of asymptomatic dysfunction to heart failure and improve the prognosis in those with established heart failure is a question of considerable interest.

9.1.2 Diagnostic Performance of NT-ProBNP to Detect Left Ventricular Dysfunction In 85+ Year Old Community Dwelling People

We reported normal reference levels of NT-proBNP in 'normal and healthy' 85+ year old community dwelling individuals. Mean (SD) and median (IQR) values of NT-proBNP in 'normal and healthy' 85+ year old cohort were 189±140 pg/mL and 163 (108) pg/mL respectively. There was no significant gender difference in NT-proBNP levels as previously reported by others in people aged 75 years and above. [317] However, many studies in younger age groups have shown slightly higher NT-proBNP levels in females. [229, 232]

No previous studies have reported the normal values of NT-proBNP in a community dwelling 85+ cohorts. Two previous studies by Costello et al [230] and Abhayaratna et al [234] included people above 75 years and over as subgroup or exclusively and used NT-proBNP test. NT-proBNP levels in 'normal patients' were slightly higher in our cohort than reported by Costello-Boerrigter et al in people aged 75 years and above (female, median = 124pg/ml; male, median = 57pg/ml). As levels of NT-proBNP increase with increasing age [229, 232-234, 317], we believe this slightly higher levels of NT-proBNP levels in our cohort are due to our more elderly cohort than Costello-Boerrigter et al study. In the Leiden 85+ study NT-proBNP test was used to detect various echocardiographic abnormalities in community dwelling 85+ cohort but investigators have not reported the normative range of NT-proBNP in this cohort. [318]

We also reported a significant increase in plasma NT-proBNP levels with progression in LV systolic ($p<0.00001$) or diastolic dysfunction ($p<0.00001$) and worsening of NYHA functional status ($p = 0.0017$). However, NT-proBNP levels did not change significantly with increasing arterial stiffness.

Investigators of the Framingham Heart Study have reported significant positive association of BNP and ANP with worsening severity of both systolic and diastolic dysfunction in relatively young participants (mean age = 58±10 years). [319] Tschöpe et al have also reported a significant rise in NT-proBNP levels with worsening severity of overall diastolic dysfunction in younger age group (mean age = 51±9). [241] Similar results were reported by Abhayaratna et al in Canberra Heart Study in older community based people (aged 60-86 years, mean age = 60.4 years).[234] Blonde et al reported a significant increase in plasma BNP levels in people (84.3 ± 7.4

years old, 65–102) with worsening NYHA functional status.[320] Similar correlation has also been reported by others in younger age group (mean age 57 years, 31-80 years). [239, 321, 322] Frankenstein et al reported a significant rise in NT-proBNP levels with worsening NYHA status in both younger (<65 years, mean age = 53±8 years) and older (>65 years, mean age = 73±6) heart failure patients and suggested that NT-proBNP levels equally predict the severity of heart failure symptoms in both younger and older patients. [323] However, we believe no study has so far reported this association in 85+ years old community dwelling participants. Our findings highlight the similar associations of NT-proBNP with systolic, diastolic and NYHA status in community-dwelling very old people as observed by others in the "younger old".

We found NT-proBNP test performed much more poorly to detect LV dysfunction (systolic /+ diastolic) in community-dwelling 85+ years old people than has been previously reported in younger cohorts. Moreover, the diagnostic performance of NT-proBNP did not improve with lower EF and symptomatic patients (NYHA 2 and above) as suggested by others in the "younger old". The performance of NT-proBNP (AUC, 95%CI) for the detection of EF <55%, <45%, <35% and moderate-severe diastolic dysfunction was 0.68 (0.63-0.73), 0.70 (0.65-0.74) and 0.64 (0.59-0.69) respectively. The performance of NT-proBNP (AUC, 95%CI) for the detection of symptomatic EF <55%, <45%, <35% and moderate-severe diastolic dysfunction was 0.68 (0.60-0.75), 0.72 (0.64-0.79) and 0.68 (0.60-0.75) respectively.

Natriuretic peptides have been shown reliably to exclude LVSD, symptomatic isolated diastolic dysfunction and heart failure in younger patients. [241, 324-328] However, in an elderly community dwelling population, its diagnostic performance decreases. Redfield et al have reported BNP as a suboptimal test for screening for asymptomatic LV dysfunction in community dwelling 45 years and above (mean age = 75 years). They found the diagnostic performance of BNP was higher to detect asymptomatic moderate – severe LV systolic dysfunction (AUC = 0.82-0.92) than any systolic dysfunction (AUC = 0.51-0.74), moderate –severe diastolic dysfunction (AUC = 0.74-0.79) or any diastolic dysfunction (AUC = 0.52-0.68). [329] Investigators of the Framingham Heart Study have also reported poor performance of BNP to identify LVSD in a community based sample of the "younger old" with overall AUC less than 0.75, even in a subgroup that were at high risk. [319] Abhayaratna et al also found similar results in cohort aged 75-86 years (n=46). They

found the diagnostic performance of NT-proBNP to detect any degree of LV dysfunction was poor (AUC = 0.56-0.66). In contrast, the performance of NT-proBNP for the detection of EF ≤40% and moderate-severe diastolic dysfunction was much stronger with AUC levels consistently >0.90. [234] In a meta-analysis of natriuretic peptides in the diagnosis of heart failure and screening of LVSD in the community, Ewald et al have reported the age related decrease in the performance of NT-proBNP and BNP. At a given cut point, which would give sensitivity of 85% for BNP to detect underlying LVSD, the associated specificity would decrease from 90% in people aged 55 years to 54% in people aged 85 years. The values for NT-proBNP decrease more steeply. [245] In another systemic review, Vaes et al also found limited evidence of diagnostic utility of natriuretic peptides to detect LVSD and heart failure in community dwelling elderly patients aged 75 and over.[246] Hetmanski et al also have reported the poor ability of BNP to identify LVSD in a large (n= 653) community based elderly population (median = 76 years, IQR = 70-82 years). However, BNP levels in people with LVEF < 40% were significantly higher than people with LVEF > 40%. [330]. Our findings of poor diagnostic performance of NT-proBNP to detect LV dysfunction in 85 years and above community dwelling people confirm the similar findings reported by others in "younger olds".

The exact cause of this poor performance of natriuretic peptides to identify LVSD and heart failure in community dwelling elderly population remains unclear. However, increased prevalence of co-morbidities in the elderly population, including renal impairment, ischaemic heart disease and atrial fibrillation that could influence the circulating levels of natriuretic peptides, may reduce the diagnostic utility of natriuretic peptides. [318, 324, 331] Cardiovascular medications including diuretics, ACE inhibitors, angiotensin receptor blockers (ARBs) and beta blockers have also shown to reduce the circulating levels of natriuretic peptides and probably can affect their diagnostic performance of to identify LVSD and heart failure. [328, 332-335] In our study nearly 33% people were taking diuretics, nearly 28% were taking ACE inhibitor or angiotensin receptor blockers (ARBs) and nearly 28% were taking beta blocker medications.

Prevalence of both asymptomatic and symptomatic LV dysfunction is high in the rapidly growing very old population in the community and is quite difficult to diagnose especially in primary care settings. Therapeutic interventions in both cases have shown to reduce the morbidity. [336-340] In order to maintain independence and

better functioning in this rapidly growing fraction of the ageing population it is important to early detection of under LV dysfunction and initiate therapeutic interventions. Since the role of natriuretic peptides in the diagnostic algorithm of LV dysfunction and heart failure in very old still remains unclear, there is need for newer biomarkers and other strategies to identify LV dysfunction and heart failure in very old fraction of the population. Potential newer biomarkers to detect heart failure, including galectin-C and cystatin-C, are under investigation but this work is still in its early stages. [341-343] Some people have also suggested the role of handheld portable echocardiography to detect LV dysfunction in community. Handheld echocardiography systems have been shown reliably and accurately (including in this study) to detect LV systolic dysfunction in community. Although cost effective, this technique is highly operator dependent and requires a period of training, which may limit its use in primary care setting. [344-348]

9.1.3 Burden of Peripheral Vascular Disease (PVD) and Ankle Brachial Index (ABI) In 85+ Years Old Community Dwelling People

In this large population based study we reported the prevalence of peripheral vascular disease as 22.1% in the entire cohort. It means, on average every fifth person in our study had PVD. We did not find any significant gender difference in the prevalence of PVD in our cohort. (Female: male odd ratio was 1.26 [0.67 – 2.30]; p =0.45). 19.0% of participants (16.4% of males and 21.1% of females) who had no formal GP diagnosis of PVD had definite PVD on the basis of ABI assessment. A pre existing diagnosis of PVD was present only in 5.6% of our participants and 31% of these has normal ankle brachial index assessments (ABI). Thus, there was substantial under-diagnosis and misdiagnosis of PVD in our cohort. 39.6% participants with definite PVD were using lipid lowering treatment and 50% were using antiplatelet medication. Even people with already diagnosed PVD only 41.7% were taking lipid lowering treatment and only half of participants were taking antiplatelet medication. We did not have data on any contraindications or reasons why people were not taking these treatments.

It would be difficult to compare with other studies mainly due the different methods used to ascertain to detect PVD and different cut-off values of ABI used to define PVD. Due to these factors prevalence of PVD in community varies markedly from each other. Also, very few studies selectively were done on people aged 85+ years and above to ascertain prevalence of PVD. I am comparing our findings with those community based studies in ABI value <0.9 was used to define PVD and included people aged 75 and above.

Our findings were almost similar to the results from the Finish study on 90 years old community living people. In this study Suominen et al reported prevalence of PVD as 22% of which 85% people were asymptomatic. They also reported no significant gender difference in the prevalence of PVD. However, it was slightly more prevalent in females confirming the findings from our study. In this study a significant poor survival was reported in people with PVD over one year follow up. Mortality in people with PVD was 25% vs 7% in people with no PVD. Nearly 67% of these deaths were due to cardiovascular disease. [349] Criqui et also reported similar prevalence of

PVD (21%) in people aged 75 years and above (294 aged between 75 years and 82). [350] Our reported prevalence of PVD in people with 85+ year olds was much lower than reported by Diehm et al from the German Epidemiological Trial on Ankle Brachial Index (getABI Study) and by Bergiers et al from the BELFRAIL Study. Diehm et al randomly selected 6821 community living participants from all across the general practices of Germany patients aged 65 years and above to assess prevalence of PVD. Their sample included 150 participants who were 85 years old or above. Reported prevalence of PVD in community dwelling 85+ year olds was 33%.[351] Bergiers et al measured ABI in 80+ year old community dwelling participants (n=175, mean age = 85.0±3.9 years) and reported 40% participants had PVD. [352] In our study people who did not had ABI measurements were significantly higher prevalence of risk factors for PVD including hypertension, high BMI and current smokers, which might mean that actual prevalence of PVD in study might be higher. Furthermore, difference in racial demography and differences in the co-morbidities between cohorts may have lead to difference in the prevalence figures. In BELFRAIL Study prevalence of hypertension, diabetes and people with BMI ≥30 was 74.9%, 20.6% and 40% respectively. [352] In contrast, our cohort in whom ABI measurements were available, prevalence of hypertension [52.9% ($p<0.0001$)], diabetes [12.5% ($p=0.03$)], and people with BMI ≥30 [7.8% ($p<0.0001$)] was significantly less. That can also explain the higher prevalence of PVD in BELFRAIL Study as compared to ours.

In our study we did not collect on the data about symptoms of PVD as focus of the study was more on epidemiological aspects of cardiac dysfunction, atrial fibrillation and PVD. However, we also know that PVD is symptomatic only in small numbers of the patients with PVD (ABI<0.9), nearly 80% remain asymptomatic. [353, 354] Diehm at al reported only 5.6% of people with age 85 years and above were experiencing symptoms of intermittent claudication. Moreover, symptoms of intermittent claudication had sensitivity of 11.0% and specificity of 98.0% in detecting underling PVD. [351] ABI is simple, inexpensive and non-invasive test that can be performed in general practice or even domiciliary (Newcastle 85+ study) settings with high sensitivity (79% to 95%) and a specificity (95% to 100%). [355] ABI value less than 0.9 is considered diagnostic of PVD as recommended in Inter-Society Consensus for the Management of Peripheral Arterial Disease published in 2007.[356] Although, only small fraction of PVD patients are symptomatic but

increased cardiovascular morbidity and mortality associated with low ABI remain similar in both symptomatic and asymptomatic patients. [357] Leng et al looked at a random sample of 1582 people aged between 55-75 from 10 General Practices in Edinburgh, UK and performed ABI assessment along with symptoms assessment. He reported increased and almost equal cardiovascular mortality in people with symptoms of claudication (RR: 2.67, 95% Cl: 1.34–5.29) and asymptomatic people with PVD (RR: 2.08, 95% CI: 1.13–3.83). Similar results were reported later in much larger population based studies of elderly people. [358, 359] In a population based study of 6880 participants of age 65 years and above, Diehm et al reported increase in all cause and cardiovascular mortality in patients with symptomatic PAD and people with asymptomatic PAD picked up on routine screening. In this study all ABI measurements were done by GPs or practice nurse in the GP surgeries. [359] In a meta-analysis and systemic review by Doobay et al, which included 9 population based studies, reported an association of ABI<0.9 and adverse cardiovascular outcome. The specificity of low ABI for coronary heart disease, stroke, and cardiovascular mortality was 92.7%, 92.2%, and 87.9%, respectively.[360] In another meta-analysis by Ankle Brachial Index (ABI) collaboration, which included 16 population based cohort studies, ABI<0.9 was associated with increased cardiovascular mortality. [361] In people with low ABI cardiovascular mortality was 18.4% in males and 12.6% for females whereas in people with normal ABI it was 4.4% for males and 4.1% for females. Authors of ABI collaboration also reported that by adding ABI to existing Framingham Risk Score for cardiovascular risk stratification would have reclassified the risk category and modified treatment strategy in nearly 19% of males and 36% of females. Until recently, screening for PVD was not recommended. Theses findings, especially from Diehm et al and Hooi et al support the idea of ABI assessment in selected patients in primary care practice to identify people with cardiovascular risks. Some studies have previously reported that at very old ages classical cardiovascular risk factors like hypertension may loose power to predict cardiovascular mortality. [362-364] Investigators of Leiden 85+ Study have reported that even Framingham risk score, which is based on the classical cardiac risk factors failed to predict cardiovascular mortality in a cohort of 85+ years olds. [365] Due to growing and strong evidence of worse cardiovascular outcomes in asymptomatic or symptomatic PVD patients, routine screening of people with age 70 years and above has been recommended and some scientist are suggesting that ABI

might be used as a predictor of cardiovascular mortality especially in later ages. [352, 366] The Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease (TASC-II) was published in 2007, which is an international collaboration of various medical and surgical societies across Europe, Northern America, Asia, Africa and Australia. [356] This consensus document clearly lays down the recommendation diagnosis and treatment of PVD. This document also recommends the routine screening of for PVD in people aged 70 years and above irrespective of their cardiovascular risks status (Recommendation 12) and also use of antiplatelet treatment in patients with PAD (Recommendation 6). American College of Cardiology (ACC) and American Heart Association (AHA) also recommend routine screening for PVD in people aged 70 years and above. [367]

According to the recently published SIGN (Scottish Intercollegiate Guidelines Network) guidelines and collaborative report from American Association of Vascular Surgery, Society of Vascular Medicine and Biology, Society of Interventional Radiology and AHA/ACC task force on practice guidelines (2010) people with asymptomatic PVD should be identified with examination or ABI assessment so that treatment should be offered to asymptomatic PVD patients to reduce the increased risk of MI, stroke and death in these patients. They also suggested antiplatelet therapy to even asymptomatic patients. Guidelines also highlighted the importance other risk modification including smoking cessation, optimization of blood pressure, treatment of dyslipidaemia and diabetic control.[356, 367-369] Risk reduction in cardiovascular mortality by use of lipid lowering treatment and antiplatelet therapy in symptomatic PAD patients has been well established.

Due to very central role of platelets in the pathophysiology of atherosclerosis and thrombogenesis, antiplatelet treatments play an important role in treatment of PVD. Role of aspirin and other antiplatelet agents in the cardiovascular risk reduction in both symptomatic and asymptomatic patients of PVD is well established. Antithrombotic Trialists Collaboration conducted a major meta-analysis (>147 randomised trials and >100,000 patients were included) regarding the efficacy of antiplatelet therapy and reported 23% odds reduction in the number of vascular events in PAD patients. These benefits were observed in all age groups and were unrelated to comorbidities including HTN and diabetes [370] Regarding the choice of antiplatelet, data in a bit conflicting. Some people believe clopidogrel is superior to aspirin and

vice versa. Investigators of CAPRIE study (n=19,185) conducted a large multicentre randomised double blind trial to compare aspirin vs clopidogrel and reported, clopidogrel compared with aspirin significantly reduced the annual risk of vascular events by 23.8% (95% CI 8.9 – 36; p=0.003) in PAD. [371] Investigators from CHARISMA trail did not find dual therapy with aspirin and clopidogrel any better than aspirin alone in reducing cardiovascular mortality in PAD patients. [372] In Heart Protection Study simvastatin use in patients with PVD was associated with significant relative risk reduction in vascular events (22%, p<0.0001). [373] Despite the compelling evidence of reduction in cardiovascular morbidity and mortality PVD patients are not aggressively treated with antiplatelet or lipid lowering therapy. In our study we found only 39% and 50% people with PVD were using lipid lowering treatment and antiplatelet treatment respectively. Suominen et al also reported similar findings from the study on 90 years old community living people. They reported only 46% of people with PVD were taking antiplatelet medication while only 44% were on lipid lowering treatment. [349] Similar trends in under treatment of PVD have been reported by others in the past. In 2002 Hirsch et al conducted a large (>6500 people, aged 70 years and above) multi centred study (PARTNERS Study) on community based older adults and found people with CVD were less aggressively treated. In this study only 56% and 54% people with PVD were using lipid lowering and anti platelet treatment respectively. [353] similar results have been reported by Lange et al from 'getABI Study' where only 53% people with PAD were using antiplatelet treatment. [374] Suboptimal use of antithrombotic and lipid lowering medications in PVD patients to lower cardiovascular risk have been reported by others as well. [375-377] It is difficult to comment on the low utilization of risk lowering therapy including antiplatelet medications in our cohort due to lack of data as this study was primarily designed to estimate prevalence of un-diagnose cardiovascular disease burden in this community dwelling population of 85 year and above people. However we can assume that side affect profile, multiple comorbidities, poly pharmacy and cognitive impairment may be playing some role in that. But these might not be the only factors as we have seen similar pattern of under diagnosis and poorly managed cardiovascular risk in relatively younger cohorts as well. Although, many studies included community based cohort of relatively older people (60-80 years old) but very few included people of age 85+ and above, highlighting the need for similar studies in very old cohort.

9.1.4 Burden of Atrial Fibrillation and Thromboprophylaxis In 85+ Years Old Community Dwelling People

In this large population based study we reported the prevalence of atrial fibrillation as 25.5% in the entire cohort. We did not find any statistically significant gender difference in the prevalence of AF (odds ratio [95% confidence interval] males: females 1.38 [0.87 to 2.20]; p=0.17). However, prevalence in males (29.3%) was higher than females (23.0%) as previously documented by other studies. Nearly half (53.2%) of these patients had had no existing GP diagnosis of AF. Majority of our participants with AF were in high risk category for thromboembolism or stroke according to NICE guidance for AF management published in 2006 and evidence based clinical guidelines for antithrombotic therapy in atrial fibrillation published by American College of Chest Physicians (ACCP) in 2008. [274, 378] 72.4% participants with AF had $CHADS_2$ score 2 or greater. 87.2% participants with AF were CHA2DS2-VASc score 3 or above. Only 17 (15.6%) participants with AF were taking warfarin. 84.4% (n=92) participants with AF, who were not on warfarin, only 42.4% participants (n=39) were either on aspirin (n=33) or clopidogrel (n=5).

Direct comparison with previous studies is complicated due to different ways used to detect AF cases and age group cut-offs. However, prevalence of AF in our study is comparable with findings from the Vantaa 85+ Study and the Rotterdam Study. Both of these studies used similar method to detect AF like our study and age group cut-off at 85+ make comparison easier with these studies. The Vantaa 85+ Study was longitudinal prospective community based study and included 553, 85+ year old participants living in Finish town of Vantaa. They looked at the risk of stroke and dementia in this age group. They reported prevalence of AF as 22.1%. AF was detected by 12 lead ECG and GP medical case notes review. [379] Prevalence of hypertension, diabetes mellitus, ischaemic heart disease and heart failure in Vantaa 85+ Study was 25.5%, 20.2%, 14% and 61% respectively. Whereas in our study prevalence of hypertension, diabetes mellitus, ischaemic heart disease and heart failure was 57%, 13%, 32% and 9% (37.4% symptomatic LVSD). Higher prevalence of hypertension and ischaemic heart disease in our study might be one of the factors for slightly higher prevalence of AF in our study. In Rotterdam Study 427 people

were 85 year and above (same number as in our study) and prevalence of AF was 17.6%. [male = 17.9%, female = 17.5%; OR 1.03 (0.54 – 1.9)].[380] To detect cases with AF, all participants had 12 lead ECG along with GP medical case notes review.

In large cross-sectional US study ATRIA prevalence of AF was reported as 10.5% (n= 1891) in people aged 85 year and above. They also reported that 45% of all AF cases were in people aged 75 years and above. AF was more prevalent in males than female in all age groups. In 85+ year cohort prevalence in males was 11.1% and in females 9.1%). [381] In ATRIA Study AF was diagnosed by searching electronic medical case notes, electronic ECG database and hospital discharge database. None of the participant was offered ECG as this survey only involved review of database. AF prevalence in our study was almost double than reported by ATRIA study in 85+ year age group. There are probably many factors that may cause the difference between studies. Many people with AF remain asymptomatic or unaware of the arrhythmia and also majority of the people with AF get treated in community with no contact with hospital. [382, 383] Due to the screening nature of our study every participant was offered an ECG even people with asymptomatic AF might have been picked. Furthermore, difference in racial demography and differences in the co-morbidities between cohorts may have lead to difference in the prevalence figures.

Sudlow et al reported prevalence of AF in people aged 75 year and above as 10.0% in males and 5.6% in females. They detected AF cases by performing limb lead ECG in a sample of 3678 community based people aged 65 year and above registered with a large General Practice in southern part of Northumberland, UK. Participants were invited to attend a clinic for ECG. [384] Prevalence of hypertension, diabetes mellitus, cerebrovascular disease and heart failure was 56%, 9.5%, 23% and 9.3% respectively which was almost similar to our cohort (57%, 13%, 19% and 9% respectively). However in our study mean age of participants was higher and prevalence of significant LVSD (55%) was also much higher than the cohort reported by the Sudlow et al (prevalence of LVSD as defined by fractional shortening <25 was only 3%). This may be one of the possible reasons for difference in prevalence figures between two studies. Another factor that might affect the prevalence figures of all studies is the presence of paroxysmal atrial fibrillation, which would depend on atrial fibrillation being present at the time of the test. The better way to detect the atrial fibrillation or paroxysmal atrial fibrillation would be through frequent repeated ECGs

or Holter monitoring. Neither of these options is feasible for such cohort of elderly people.

We do not know how many of our participants with AF had contraindications for the use of warfarin but only 15.6% participants with AF were taking warfarin. Sudlow et al and others have reported that people with AF especially above 75 years age are under prescribed with warfarin even in the absence of any contraindication. [384, 385] Sudlow et al looked at the prevalence of AF in the community dwelling people aged 75 year and above and also the proportion of people that might benefit from thromboprophylaxis. They assessed the risk factors for stoke and contraindication to warfarin in this high risk population. They reported that most common contraindications to warfarin in people with AF aged 75 year and above were fall, uncontrolled hypertension and poor compliance. 34% of the people with AF aged 75 year and above had contraindications to warfarin. Whereas, 93% of females and 94% of males aged 75 year and above had one or more clinical or echocardiographic risk factors for stroke. Only 16.9% people with AF aged 75 year and above were taking warfarin. In ATRIA Study mean age of participants was 71.7 ± 11.6 years and 65% of the participants with AF had at least one risk factor for stroke other that increasing age (>65 years). Only 17% of these had contraindication to warfarin. Only 55% of participants with AF and no contraindication were using warfarin. Warfarin use was much lower in people aged 85 year and above. Only 35.4% of participants aged 85 year and above with AF and no contraindication were taking warfarin. [386] We cannot compare this figure with our study as we do not know the contraindications to warfarin in our study participants with AF. Results from SCAF Study (Stockholm Cohort-study on Atrial Fibrillation) also reported people with AF and aged 80 years and above were under treated with warfarin even in the absence of any contraindication to warfarin therapy. [387] Investigators of ATRIA study also reported that people aged 85+ years [OR (95% CI); 0.35 (0.31– 0.40)], previous history of intracranial bleed [[OR (95% CI); 0.33 (0.21– 0.52)] and gastrointestinal bleeding [[OR (95% CI); 0.47 (0.40–0.57)] were major factors with low likelihood for using warfarin. Existing studies show that high risk of bleeding, inability of patient to follow dosing or monitoring advice and high risk of falls are major reasons why clinicians consider patients unstable for warfarin. Whereas, fear of bleeding, actual bleeding, difficulties with monitoring and poor understanding of stroke risk/benefit of warfarin therapy were major reasons why patients refuse warfarin therapy.[388-390]

Atrial Fibrillation is associated with increased risk of stroke which increases significantly with increasing age. Risk of thromboembolic stroke is increased up to sevenfold in people with non rheumatic AF. In Framingham Heart Study annual risk of stroke attributed to AF increases from 1.5% in 50-59 years olds to 23.5% in 80-90 year old.[391] Key consideration in the management of AF in elderly is to reduce the risk of thromboembolic events associated with it. Several scoring tools are available to assess the risks of stroke associated with AF. $CHADS_2$ is one of the commonly used tools (**C**ongestive heart failure, **H**ypertension, **A**ge ≥75 years, **D**iabetes mellitus and Previous history of TIA/**S**troke each attract 1 score except Stroke which attracts 2 scores).[392] Results from the National Registry of Atrial Fibrillation reported that the stroke rate per 100 patient-years without warfarin therapy increased by a factor of 1.5 (95% CI, 1.3-1.7) for each 1 score increase in the $CHADS_2$ score. People with AF and $CHADS_2$ score 2 have 5.9 fold higher risk of stroke without antithrombic therapy. The Euro Heart Survey on Atrial Fibrillation later refined the existing scoring system ($CHADS_2$) and suggested another validated scoring tool to assess the risks of stroke associated with AF (CHA2DS2-VASc) which included additional risk factors including peripheral vascular disease and raised the weightage of increasing age as a stronger risk factor by attributing two points for age above 75 years. [393] It is suggested that people with $CHADS_2$ score ≥2 or CHA2DS2-VASc score ≥ 2 are in high risk category of stroke and merit antithrombic (warfarin) therapy (providing no contraindication). [394, 395] Majority of our study participants 72.4% participants with AF had $CHADS_2$ score 2 or greater. 87.2% participants with AF were CHA2DS2-VASc score 3 or above. Only 15.6% participants with AF were taking warfarin. 84.4% participants with AF, who were not on warfarin, only 42.4% participants were either on aspirin or clopidogrel. We do not know how many of our participants had contraindications for the use of warfarin, but probably, at least partially, the low rate is related to attitudes, co-morbidity, concerns of serious adverse events polypharmacy and drug interaction as mentioned in previous studies. Atrial fibrillation is associated with significant burden in especially in elderly due to its association with thromboembolic events including stroke and disability caused by stroke. In Framingham Study, AF was a strong independent predictor of the degree of functional deficit following a stroke. It was reported that ischaemic stroke due to AF was associated with higher mortality than non- AF stroke. [396] Investigators from

ATRIA study have reported a substantial risk reduction of thrombotic stroke in cohort aged 85 years and above with warfarin. Annual stroke rate in those aged 75-84 years and were no taking warfarin was 1.4% compared with 3.3% in aged 85 years and above who were also not taking warfarin. These people had no additional stroke risk factor apart from increasing age and atrial fibrillation. Annual stroke rate in those aged 75-84 years and were taking warfarin was 0.53% compared with 0.86% in aged 85 years and above who were also using warfarin. [386] This indicates a substantial benefit of warfarin in stroke prevention in atrial fibrillation in this age group. Warfarin has also proven superior to aspirin in preventing stroke in people aged 75 years and above with AF. The Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA) was a randomised control trial randomly that compared the efficacy of warfarin verses aspirin in preventing stroke in AF patients aged 75 years and above. [397] 934 participants with AF were recruited from 234 general practices and mean age of participants was 81.5 ± 4.2 years. Primary outcome was fatal and non-fatal disabling stroke (ischaemic and haemorrhagic) and intra-cranial haemorrhage. Participants were randomly assigned warfarin (target INR 2.0- 3.0) and warfarin (75mg OD). Both groups were almost identical in co-morbidities (both had nearly 28% participants with $CHADS_2$ score 3 or above). There were 10 ischaemic strokes, 6 haemorrhagic strokes and 2 other intracranial haemorrhages in group assigned to warfarin compared to 32 ischaemic strokes, 5 haemorrhagic strokes and one other intracranial haemorrhages in group assigned to aspirin. Participants assigned to warfarin had annual stroke risk of 1.8% vs 3.8% in aspirin group (p=0.003). Whereas yearly risk of extracranial was 1.4% in warfarin group vs 1.6% in aspirin group. This study clearly showed that anticoagulation was significantly more effective than aspirin without any difference in major bleeding event. In another randomised prospective study of primary thromboprophylaxis for AF in elderly patients (aged between 80-90 years) comparing aspirin vs warfarin showed that more people discontinued aspirin than warfarin mainly due to gastrointestinal side affects. [398] Despite clearly shown benefits of warfarin in preventing stroke in atrial fibrillation in elderly patients issues associated with INR monitoring including repeated blood tests, cognitive impairment and poor mobility can make its use quite challenging in certain people.[399] However, newer oral anticoagulants including dabigatran can possibly bridge the gap created by under utilization and under prescribing of warfarin due the factor motioned already. In a recently publish trial (Re-LY, Dabigatran versus

warfarin in patients with atrial fibrillation) dabigatran showed similar efficacy at 110 mg BD dose, for preventing stroke/systemic embolism in patients with AF (annual stroke rate 1.53% vs 1.69% for warfarin) and 20% less major bleeds compared to warfarin; the 150mg BD dose had approximately 35% superior efficacy and similar rates of major bleeds to warfarin. Both dabigatran dose arms had significantly less intracranial bleeds or haemorrhagic strokes, compared to warfarin. [400] Dabigatran has advantages over warfarin as it does not need monitoring or loading and has few interactions with diet or other drugs. Hence, it may prove particularly useful in the elderly. NICE guidance on use of dabigatran is currently awaited. Guidelines published by European Society of Cardiology guideline (2010) and from the American College of Cardiology/American Heart Association/Heart Rhythm Society (2011) have mentioned dabigatran as an alternative to warfarin in stroke prevention in patients with atrial fibrillation. [401, 402] However, the Canadian Cardiovascular Society guidelines (2011) state that dabigatran should be used in preference to warfarin, for stroke prevention in patients with atrial fibrillation. [403]

Trials on some other newly available oral antithrombotic agents like Ximelagatran have also shown the better efficacy than warfarin in stroke prevention in AF (SPORTIF V Trial). [404]

Availability of newer antithrombic agents will hopefully improve outcomes and contain costs associated with ischaemic stokes and disability caused by acute ischaemic stroke in the rapidly expanding population of the very old.

9.2 Strengths and Limitations

Strengths of this study include its population-based sample, which included both cognitively impaired and institutionalised participants who have been excluded from many previous studies in this age group[405-408], and the domiciliary echocardiographic approach; we have previously shown that up to 50% of very old people would be unwilling to participate in a study requiring hospital attendance.[409] The Newcastle 85+ Study cohort has been shown to be socio-demographically representative of the local population, including the proportion in care homes.[316] We undertook quantitative echocardiographic assessment of both systolic and diastolic dysfunction using rigorous and heamodynamically validated Doppler criteria. Rather than rely on self-reported diagnoses, which are known to be unreliable at this age, [410, 411] we carried out review of general practice records to ascertain disease diagnoses. In addition we repeated our analysis after removing participants with spirometric evidence of significant intrinsic lung disease and showed that this did not alter our conclusions. Some limitations merit comment. We did not assign or validate heart failure diagnoses using Framingham or other criteria and we cannot therefore consider our category of symptomatic LV dysfunction as entirely overlapping with heart failure. Participants in this study cannot be considered a random sample of the very old population; they had elected to participate in the Newcastle 85+ study and made a subsequent additional commitment to undergo the cardiac assessment. It is therefore possible that study participants were in somewhat better health than the general population of the very old and as a result we may have under-estimated the true population prevalence of LV dysfunction. Our population was of overwhelmingly white ethnicity and although representative of the very old in the UK,[412] may not be typical of people of this age resident in other parts of the world. Although diagnostic performance of natriuretic peptides to detect LV dysfunction in elderly cohort have shown to be poor in some previous studies as well, but some cardiovascular medications could also affect plasma levels of theses peptides and can interfere with the diagnostic performance of natriuretic peptides to detect LV dysfunction (LVD). In our study nearly quarter of participants were on some cardiovascular medication, which could have also affected the diagnostic performance of NT-proBNP to detect LVD. We also lacked the data on contraindications and reasons for of thromboprophylactic medications in AF patients

in our cohort which could partially explain the low rates of thromboprophylactic medications in AF participants.

9.3 Conclusions

LV systolic and diastolic dysfunction was very common in community-dwelling 85+ year olds and the majority of those affected had limiting symptoms of dyspnoea. Despite the NHS Quality and Outcomes Framework[283] initiative to improve the management of heart failure in primary care in England, the majority of very old people with symptomatic LV dysfunction remained undetected. Due to poor performance of NT-proBNP to detect symptomatic or asymptomatic LV dysfunction, its role in the diagnostic algorithm remains unclear in older adults. Accurate and early diagnosis of LV dysfunction and heart failure, followed by the implementation of individually tailored therapy, is needed to improve outcomes and contain costs in the rapidly expanding population of the very old. Further studies are needed to determine the optimal approach to identifying those with, and at risk of, heart failure in this age group.

Peripheral vascular disease (PVD) is also very common in community dwelling 85-89 year olds. Majority of this remain undiagnosed. Undiagnosed PVD and associated other cardiovascular pathologies probably are barrier for effective primary and secondary prevention of atherosclerotic diseases. ABI assessment can be used in primary care setting to screen for PVD and can be used to predict cardiovascular morbidity and mortality. However, there is need for further studies to determine the optimal approach to screen PVD in primary care and optimise cardiovascular risk in older adults.

Atrial fibrillation is very common arrhythmia in community dwelling 85+ year olds. As the population is ageing with rapidly expanding numbers of 85+ year olds, the prevalence of AF will continue to increase. AF is affecting approximately 2.3 million people in United States and 6 million in Europe and these figures are expected to double by year 2050. [381, 413, 414] In order to reduce mortality, morbidity and maintain independent functioning among very old is stroke prevention in patients with atrial fibrillation. Most effective intervention would be to develop strategies to detect atrial fibrillation and offer them appropriate thromboprophylaxis after risk stratification for stroke.

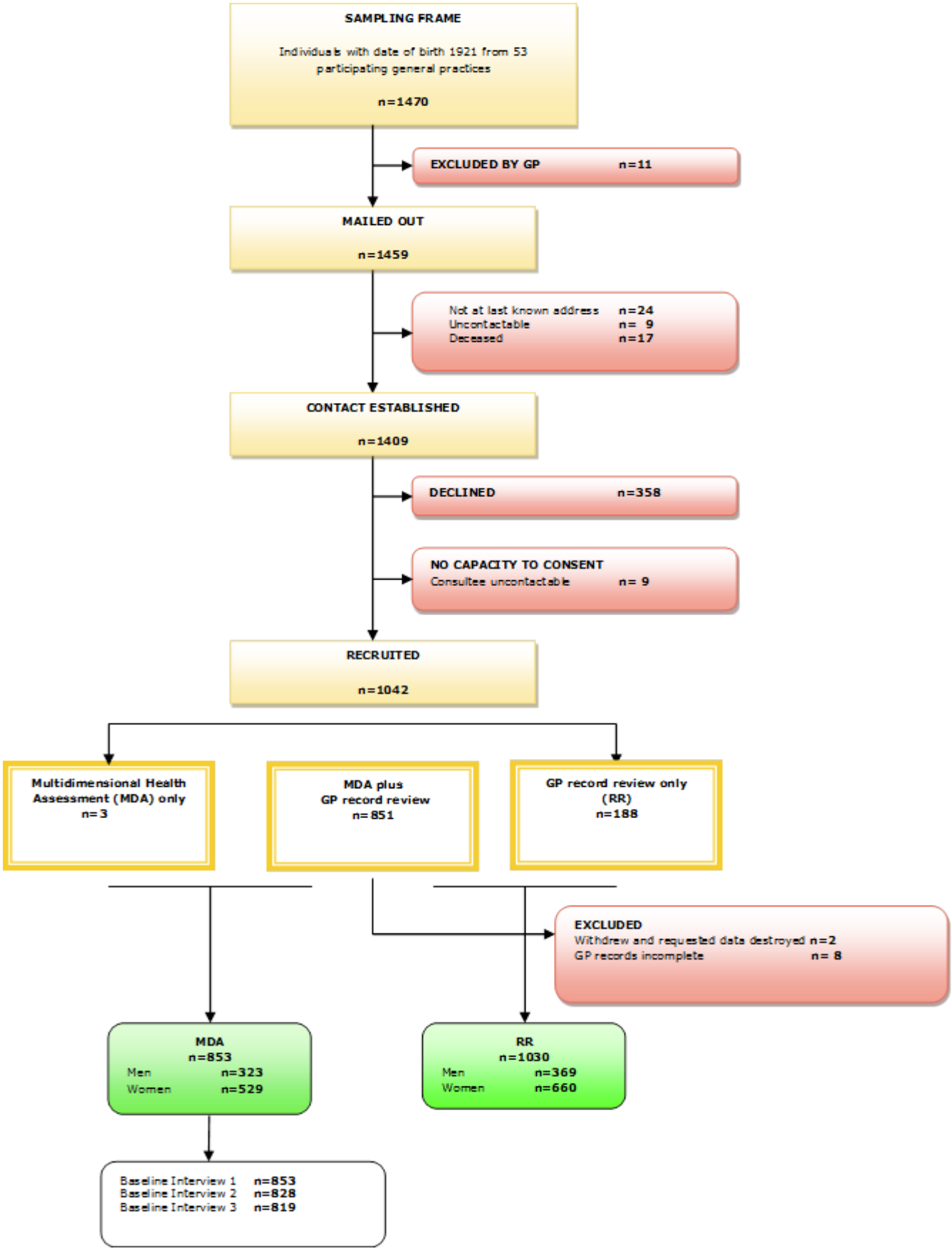
9.4 Further Research Directions

Further research is needed to identify the optimal approach to detecting heart failure or asymptomatic cardiac dysfunction in community-dwelling very old people, particularly in health care systems with limited availability of echocardiography. The UK National Institute for Health and Clinical Excellence 2010 Chronic Heart Failure Guidelines advocate the use of circulating natriuretic peptides in those in whom there is a clinical suspicion of heart failure to either rule out the diagnosis or identify those requiring specialist assessment including echocardiography.[295] Population-based screening of high risk groups, such as the elderly, has been suggested to additionally identify those with asymptomatic dysfunction.[415-418] The role of natriuretic peptides in diagnostic algorithm in the very old remains unclear and requires further investigation[246] as levels rise with age[233, 419, 420] and with co-morbidities[232, 233, 295] prevalent at this age.[316] Should such screening approaches be widely adopted, our finding of the high prevalence of the target condition suggests that substantially increased provision of echocardiography, in accessible settings, will be required for the very old. In this regard, our study has demonstrated the feasibility of a domiciliary approach.

Further studies are needed to determine the optimal approach in identifying those with atrial fibrillation (even asymptomatic AF) and at risk of cerebrovascular disease in this age group. In order to maintain independent functioning and prevent stroke related mortality and morbidity in this age group thromboprophylaxis is important. However, further research is needed to find safer and convenient therapeutic interventions to reduce thromboembolic risk associated with AF in this age group.

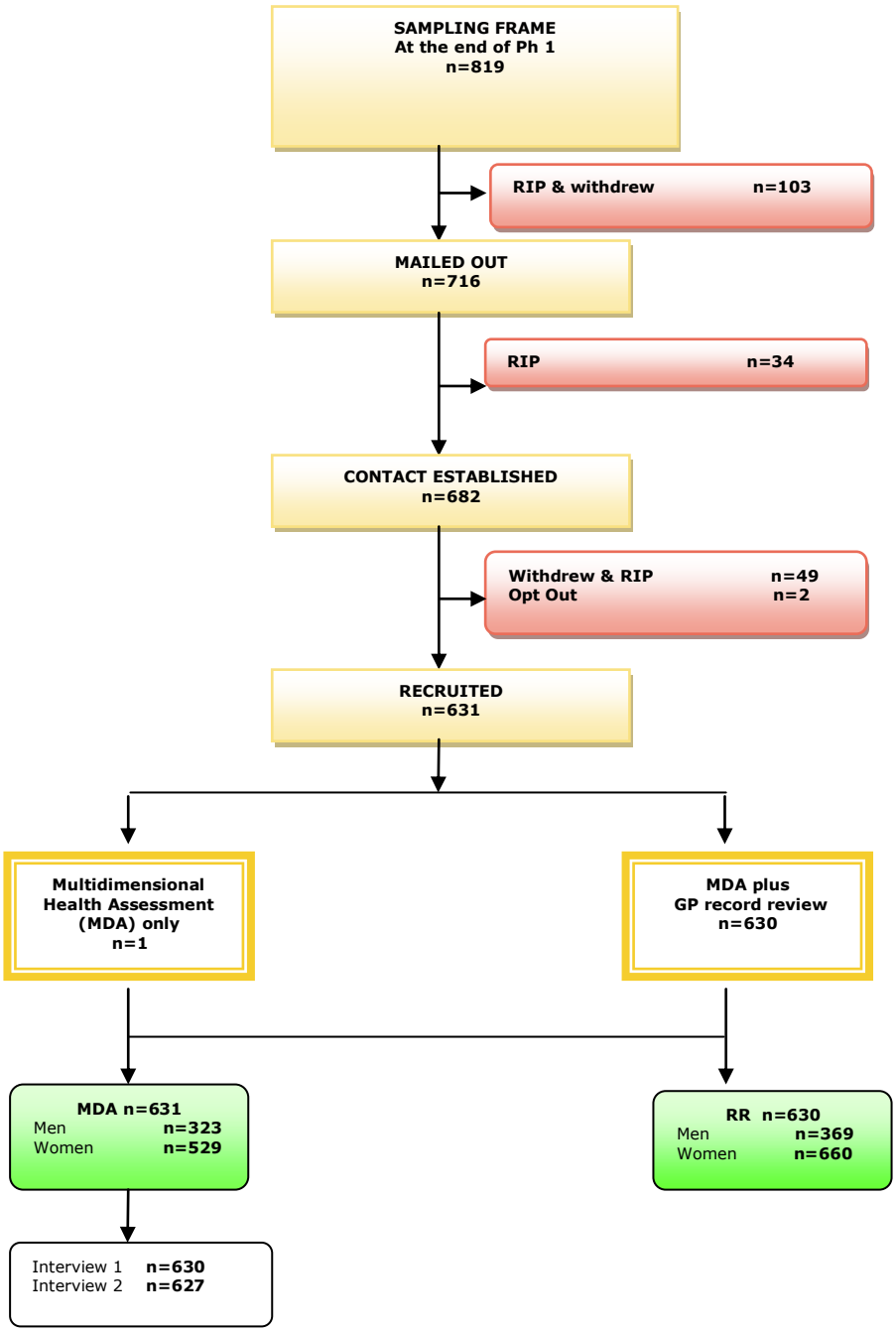
Appendices

Appendix 1



Recruitment Profile to the Newcastle 85+ Study Phase 1

Appendix 2



Recruitment Profile to the Newcastle 85+ Study Phase 2

Appendix 3.

Multidimensional Health Assessments undertaken in Newcastle 85+ Study

MULTIDIMENTINAL HEALTH ASSESSMENT		
Questionnaire	Socio-demographics	Gender, ethnic origin, living arrangements, socioeconomic status
	Family data	Number of siblings and children
	Physical health	Self rated 'global' health status, self reported long standing illness, angina, shortness of breath, joint pain, generalized pain, fractures, falls, vision and hearing, incontinence
	Depression	
	Disability	Aids/appliances, house hold modifications
	Diet	
	Lifestyle	Smoking, alcohol, exercise
	Social support	
	Use of health and social care	
Clinical measurements & Functional tests	Blood pressure	
	Cognitive function	Mini mental state examination and computerised assessment of memory and attention (CDR)
	Hand grip strength	
	Walking test	Timed 'up and go test'
	Anthropometrics	Weight, bio impedance (body composition- fat and water), demi-span, waist and hip circumference
	12 lead ECG	
	Spirometry	Forced expiratory volume in one second (FEV1), Forced vital capacity (FVC),
	Tooth count	
Blood tests	Routine haematology and biochemistry	Full blood count, renal function and electrolytes, liver profile, glucose and glycosylated haemoglobin
	Lipid profile	Cholesterol, triglycerides, high and low density lipoproteins, apolipoproteins A1 and B
	Thyroid function	Free T4, free T3, reverse T3, TSH and TPO antibodies
	Inflammatory markers	High sensitivity CRP, rheumatoid factor, cytokines (TNF –alpha & interleukin 6)
	Nutritional markers	Vitamin B2, B6, B12, C and D, ferritin, folate and homocysteine.
	Biomarkers	DNA repair capacity, telomere length, F2 isoprostane
	Markers of immunosenescence	

Appendix 4

Assessments included in each phase of Newcastle 85+ study

ASSESSMENTS	Phase1	Phase2	Phase3
Application of 7 day activity monitor		X	X
Blood pressure: Sitting	X	X	X
Chair stand test		X	X
Cognition: CDR assessment	X		
Demi-Span	X		
Disability	X	X	X
ECG	X	X	X
Eyesight	X	X	X
Geriatric depression scale	X	X	X
Hand-grip strength	X	X	X
Hearing	X	X	X
Spirometry and oximetry	X	X	X
Standardised mini-mental state examination (sMMSE)	X		X
Timed “up and go” test	X		
Timed up and go test (with pam)		X	X
Tooth count	X		X
Waist and hip circumference	X		

Appendix 5

NEWCASTLE 85+ STUDY
CARDIOVASCULAR PHENOTYPING- PHASE 2/3
ABNORMAL RESULTS PROTOCOL

ECHOCARDIOGRAMS

Following abnormal findings will be reported back to GPs.

- Significant impairment of LV function (ejection fraction less than 35%)
- Significant Valvular heart disease
    - Severe Aortic stenosis/regurgitation
    - Severe Mitral stenosis/regurgitation
    - Severe Tricuspid stenosis/regurgitation
- Significant other findings such as Hypertrophied obstructive cardiomyopathy (HOCM), Atrial myxoma.

In the presence of any of the above abnormalities, study will be discussed with Dr Antoinette Kenny or Prof Bernard Keavney before informing the participant's GP.

A letter will also be sent to concerning GP mentioning the abnormality detected along with a copy of scan report and copy of abnormal results protocol.

Appendix 6

Newcastle 85+ Phase 2 ECG PROTOCOL

Send ECG to Glasgow for URGENT report if:

- Interview 3: GGG6 'Yes' to unexplained falls or GGG28: 'Yes' to fits, faints, funny turns, blackouts
- ECG Print out report states complete or 3rd degree heart block or A-V dissociation.
- ECG Print out report states ventricular arrhythmia, ventricular tachycardia
- ECG Print out report states something else alarming: check with Karen first.

Depending on report from Glasgow, you *may* then need to inform the GP urgently by telephone and faxed letter; Glasgow will advise.
Please complete the spreadsheet with details of all ECGs sent for urgent report

For all other ECGs, transmit to Glasgow routinely.
All the automatic print out reports are checked by Professor MacFarlane, amended as necessary and copies sent back to us.

Wait for these CONFIRMED reports before contacting GPs with other 'notifiable' abnormalities. Send a copy of the confirmed report ECG. If there is a 'notifiable abnormality' state whether or not they have symptoms (GGG1 any falls, GGG6 unexplained falls and GGG28 fits, faints, funny turns, blackouts).

Only clinically significant arrhythmias and heart block will be notified:

1. Atrial fibrillation or flutter; with or without symptoms

Inform within 1 month

2. Sinus bradycardia <50; only if associated with symptoms: falls (GGG1) or fits, faints, funny turns, blackouts or *severe* dizziness (GGG28)
Inform within 1 week

3. Sinus bradycardia between 50 and 60 only if in conjunction with 1st degree heart block and then only if associated with symptoms (as above)
Inform within 1 week.

4. 1st degree heart block ONLY if associated with symptoms (as above).

5. 2nd or 3rd degree A-V block; with or without symptoms
3rd degree (complete) heart block: Inform urgently by phone and fax letter
2nd degree heart block: Inform within 1 week

6. Right bundle branch block only if in conjunction with left or right axis deviation; only if associated with symptoms (as above).
Inform within 1 week.

7. Left bundle branch block only if in conjunction with 1st degree heart block; only if associated with symptoms (as above)
Inform within 1 week

8. WPW: only if associated with symptoms (as above)
Inform within 1 week

9. Long QTc: only if associated with symptoms (as above)
Inform within 1 week

Newcastle 85+ Phase 3 ECG PROTOCOL

Send ECG to Glasgow for URGENT report if:

- Interview 2: EE5 'Yes' to unexplained falls or EE13: 'Yes' to fits, faints, funny turns, blackouts
- ECG Print out report states complete or 3rd degree heart block or A-V dissociation.
- ECG Print out report states ventricular arrhythmia, ventricular tachycardia
- ECG Print out report states something else alarming: check with Karen first.

Depending on report from Glasgow, you *may* then need to inform the GP urgently by telephone and faxed letter; Fahad/Glasgow will advise.
Please complete the spreadsheet with details of all ECGs sent for urgent report

For all other ECGs, transmit to Glasgow routinely.
All the automatic print out reports are checked by Professor MacFarlane, amended as necessary and copies sent back to us.

Wait for these CONFIRMED reports before contacting GPs with other 'notifiable' abnormalities. Send a copy of the confirmed report ECG. If there is a 'notifiable abnormality' state whether or not they have symptoms (EE1 any falls, EE5 unexplained falls and EE13 fits, faints, funny turns, blackouts).

Only clinically significant arrhythmias and heart block will be notified:

1. Atrial fibrillation or flutter; with or without symptoms

Inform within 1 month

2. Sinus bradycardia <40; with or without symptoms
Inform within 1 week

3. Sinus bradycardia between 40 and 50 only if associated with symptoms: falls (GGG1) or fits, faints, funny turns, blackouts (GGG28)
Inform within 1 week

4. Sinus bradycardia between 50 and 60 only if in conjunction with 1st degree heart block and then only if associated with symptoms (as above)
Inform within 1 week.

5. 1st degree heart block ONLY if associated with symptoms (as above).

6. 2nd or 3rd degree A-V block; with or without symptoms
3rd degree (complete) heart block: Inform urgently by phone and fax letter
2nd degree heart block: Inform within 1 week

7. Right bundle branch block only if in conjunction with left or right axis deviation; only if associated with symptoms (as above).
Inform within 1 week.

8. Left bundle branch block only if in conjunction with 1st degree heart block; only if associated with symptoms (as above)
Inform within 1 week

9. WPW: only if associated with symptoms (as above)
Inform within 1 week

10. Long QTc: only if associated with symptoms (as above)
Inform within 1 week

Appendix 7

MM. SHORTNESS OF BREATH (Questionnaire)

POSSIBLE WITH AN INFORMANT

I would now like to find out whether shortness of breath limits your day to day activities. I am not just asking

whether or not you GET short of breath but whether the shortness of breath LIMITS you. I am interested in how

you have been over the last 4 weeks that is since.....(State date 4 weeks previously)

1 So in the last 4 weeks, has shortness of breath limited your ability to move around your home (on one level)?

DO NOT INCLUDE STAIRS

- Yes
- No SKIP'MM.2(8)
- Limited for reason(s) unrelated to shortness of breath SKIP'MM.2(8)
- *Don't know*
- *Not applicable*
- *Refused to answer*
- *Not asked*

2 How much has shortness of breath limited your ability to move around your home (on one level)?

- A bit
- A lot
- Completely unable to move around the home due to shortness of breath
- *Don't know*
- *Not applicable*
- *Refused to answer*
- *Not asked*

3 In the last 4 weeks, has shortness of breath limited your ability to walk outdoors, on the level, at your own pace?

- Yes
- No SKIP'MM.4(8)

- Limited for reason(s) unrelated to shortness of breath SKIP'MM.4(8)
- *Don't know*
- *Not applicable*
- *Refused to answer*
- *Not asked*

4 How much has shortness of breath limited your ability to walk outdoors, on the level, at your own pace?

- A bit
- A lot
- Completely unable to walk outdoors, on the level, at own pace due to shortness of breath
- *Don't know*
- *Not applicable*
- *Refused to answer*
- *Not asked*

5 In the last 4 weeks, has shortness of breath limited your ability to hurry on the level?

- Yes
- No SKIP'MM.6(8)
- Limited for reason(s) unrelated to shortness of breath SKIP'MM.6(8)
- *Don't know*
- *Not applicable*
- *Refused to answer*
- *Not asked*

6 How much has shortness of breath limited your ability to hurry on the level?

- A bit
- A lot
- Completely unable to hurry on the level due to shortness of breath
- *Don't know*
- *Not applicable*
- *Refused to answer*
- *Not asked*

-

7 Over the past 4 weeks, have you had any swelling in your feet, ankles or legs?

ONLY RECORD BILATERAL SWELLING

- Yes
- No SKIP'MM.8(8)
- *Don't know*
- *Not applicable*
- *Refused to answer*
- *Not asked*

8 Was this swelling ever so bad that you were unable to put on your shoes?

- Yes
- No
- *Don't know*
- *Not applicable*
- *Refused to answer*
- *Not asked*

9 Shortness of breath section answered by

- Participant alone SKIP'MM.10(8)
- Informant/consultee alone SKIP'MM.10(8)
- Participant and informant/consultee
- *Not applicable*
- *Item not completed*

10 If participant and informant/consultee, was this

- Mainly participant
- Mainly informant/consultee
- Equal contribution
- *Not applicable*
- *Item not completed*

11 Was this section omitted?

- Yes SKIP'MM.1(8) MM.2(8) MM.3(8) MM.4(8) MM.5(8) MM.6(8) MM.7(8) MM.8(8) MM.9(8)MM.10(8)
- No SKIP'MM.12(98) MM.13(8)
- *Not applicable*
- *Item not completed*

12 Why was it omitted?

- Interviewer decision - Participant frailty/fatigue SKIP'MM.13(8)
- Interviewer decision - Participant distress SKIP'MM.13(8)
- Interviewer decision - Participant unwell SKIP'MM.13(8)
- Interviewer decision - Participant too busy SKIP'MM.13(8)
- Interviewer decision - Concern re interviewer safety SKIP'MM.13(8)
- Interviewer error SKIP'MM.13(8)
- Participant refused
- Relative/carer refused
- Other reason (specify) SKIP'MM.13(8)
- *Not applicable*
- *Item not completed*

13 Why did they refuse?

- No reason given
- Distress/anxiety
- Unwell
- Fatigue
- Other reason (specify)
- *Not applicable*
- *Item not completed*

NN. CHEST PAIN (Questionnaire)

NOT POSSIBLE WITH AN INFORMANT

Now I would like to ask you some questions about chest pain, again I am interested in what has happened over

the last 4 weeks that is since (STATE DATE 4 WEEKS PREVIOUSLY)

1 In the last 4 weeks, have you had any pain or discomfort in your chest?

- Yes SKIP'NN.2(8)
- No
- *Don't know*
- *Not applicable*
- *Refused to answer*
- *Not asked*

2 In the last 4 weeks, have you had any pressure, heaviness or tightness in your chest?

- Yes
- No SKIP'NN.3(8) NN.4(8) NN.5(8) NN.6(8) NN.7(8) NN.8(8) NN.9(8)
- *Don't know*
- *Not applicable*
- *Refused to answer*
- *Not asked*

3 Did the 'symptom' **come on when you exerted yourself?**

- Yes
- No SKIP'NN.4(8) NN.5(8) NN.6(8) NN.7(8) NN.8(8) NN.9(8)
- Completely unable to exert self for reason unrelated to 'symptom'
- *Don't know*
- *Not applicable*
- *Refused to answer*
- *Not asked*

4 Did the 'symptom' limit your ability to move around your home (on one level)?

DO NOT INCLUDE STAIRS

- Yes
- No SKIP'NN.5(8)
- Limited for reason(s) unrelated to 'symptom' SKIP'NN.5(8)
- *Don't know*
- *Not applicable*
- *Refused to answer*
- *Not asked*

5 How much did the 'symptom' limit your ability to move around your home (on one level)?

- A bit
- A lot
- Completely unable to move around home due to 'symptom'
- *Don't know*
- *Not applicable*
- *Refused to answer*
- *Not asked*

6 Did the 'symptom' limit your ability to walk outdoors, on the level, at your own pace?

- Yes
- No SKIP'NN.7(8)
- Limited for reason(s) unrelated to 'symptom' SKIP'NN.7(8)
- *Don't know*
- *Not applicable*
- *Refused to answer*
- *Not asked*

7 How much did the 'symptom' limit your ability to walk outdoors, on the level, at your own pace?

- A bit
- A lot
- Completely unable to walk outdoors, on level, at own pace due to 'symptom'
- *Don't know*
- *Not applicable*
- *Refused to answer*
- *Not asked*

8 Did the 'symptom' limit your ability to hurry on the level?

- Yes
- No SKIP'NN.9(8)
- Limited for reason(s) unrelated to 'symptom' SKIP'NN.9(8)
- *Don't know*
- *Not applicable*
- *Refused to answer*
- *Not asked*

9 How much did the 'symptom' limit your ability to hurry on the level?

- A bit
- A lot
- Completely unable to hurry on the level due to 'symptom'
- *Don't know*
- *Not applicable*
- *Refused to answer*
- *Not asked*

10 Was this section omitted?

- Yes SKIP'NN.1(8) NN.2(8) NN.3(8) NN.4(8) NN.5(8) NN.6(8) NN.7(8) NN.8(8) NN.9(8)
- No SKIP'NN.11(98) NN.12(8)
- *Not applicable*
- *Item not completed*

11 Why was it omitted?

- Interviewer decision - Participant frailty/fatigue SKIP'NN.12(8)
- Interviewer decision - Participant distress SKIP'NN.12(8)
- Interviewer decision - Participant unwell SKIP'NN.12(8)
- Interviewer decision - Participant too busy
- Interviewer decision - Informant/consultee ONLY answering - section not possible with
- informant SKIP'NN.12(8)
- Interviewer decision - Concern re interviewer safety SKIP'NN.12(8)
- Interviewer error SKIP'NN.12(8)
- Participant refused
- Relative/carer refused
- Other reason (specify) SKIP'NN.12(8)
- *Not applicable*
- *Item not completed*

12 Why did they refuse?

- No reason given
- Distress/anxiety
- Unwell
- Fatigue
- Other reason (specify)
- *Not applicable*
- *Item not completed*

Appendix 8

Standard Operational Procedure For The Cardiac Examination (Echocardiography) Using Vivid-I Within The Newcastle 85+ Study

Document Number: 0003/IAH/85+
Title: SOP for cardiac examination (Echocardiography)
Version: Final Draft
Author: Fahad Yousaf

Responsibilities:

Research investigators trained in the method are responsible for:

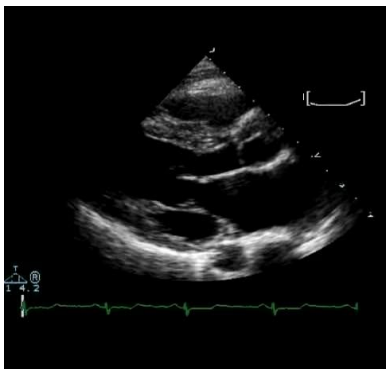
- Accurate measurement and recording of cardiac examination (echocardiography) by using Vivid-I from participants
- Clear explanation of the procedure to participants and
- Ensuring that equipment is in optimal working order.

Equipment:

- Vivid I (BT06 system)
- 3S-RS phased array cardiac USG probes with lead
- ECG leads (3: red, green & black)
- Wedge foam Pillow (help position the participant)

General Precautions:

- Make sure all the connections are secure.
- Make sure all equipment is fully charged before going to participant's house.
- Make sure to put paper towel on the bed on to avoid smearing of participant's clothe or bedding with gel.



- Try to be very gentle while performing the scan and provide paper towels to participant to wipe off the gel from the chest
- Do follow the manufacturer's instruction for maintenance and specific cleaning and disinfection for probe.
- For cleaning of probe always disconnect it from the unit.

Instructions for using the Vivid-I (Cardiac BT06 package)

The investigator must read the accompanying instruction manual carefully, and then familiarise themselves with the equipment. Step-by-step instructions for day-to day use will be kept with each device.

Creating a new Participant's record

- Press PATIENT

The patient handling screen will come up

- Press CREAT NEW PATIENT

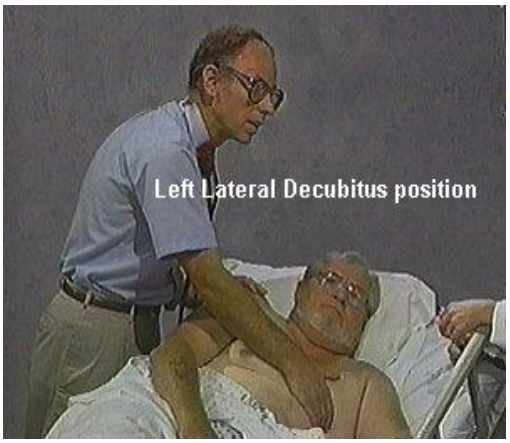
An operator log window will appear. Press log on. The search/create Patient window will come up.

- Enter participant's details (last name, first name, date of birth and ID). We ll use PID number instead of last and first name due to confidentiality issues.

- Than press 'Create Patient' to store participant details.

Participant's positioning

- Ask participant to lye down on the bed, ideally in steep left lateral decubitus position. Consistent with their comfort. A sofa would be an acceptable alternative if participant prefers. If participant is too immobile to achieve an appropriate position for study, this should be noted but the data should, as far as is possible, still be recorded.



- Participant has to undress down to waist/ umbilicus level.

- Put 3 ECG stickers on participant body, (Red-Right shoulder; Yellow-Left shoulder; Black- Right flank) and connect these with respective ECG leads.

Selecting the cardiac probe

- Ensure a cardiac probe 3S-RS is connected and selected for cardiac scan (Echocardiogram)

Capturing participant's data

- All standard views (parasternal long axis, parasternal short axis, apical 4 chamber, apical 5 chamber, apical 2 chamber, apical 3 chamber and epigastric views w ill be obtained in above mentioned position.

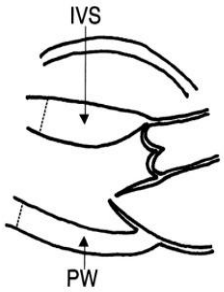
- All standard view images will be stored as cine loop for min 5 cardiac cycles, by pressing the **Store** button twice.

- All still images will be stored by (Press **Freeze** button initially to get a still frame) pressing **Store** button once.

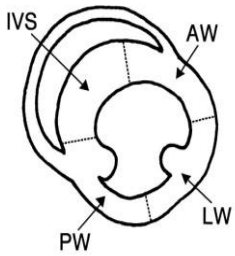
- Still images will be taken by freezing the frames for all M-mode, CW Doppler, and PW Doppler measurements. (these functions can be activated by moving the **Cursor** and Pressing the respective buttons (**MM, CW and PW**)

Parasternal view: Long Axis

- Store a cine loop
- M-mode the LV and Ao/LA- and store still frames
- Put colour on MV and AV and record as cine loop.



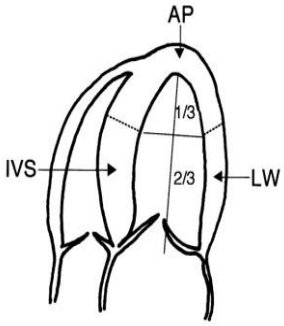
Parasternal Long Axis



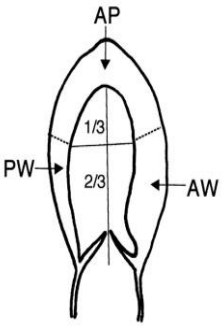
Parasternal Short Axis

Parasternal view: Short Axis

- At AV level- Store a cine loop with and with out colour on each valve (AV, TV, PV)
- Obtain CW Doppler frames through TV and PV but moving the cursers, and store still frames.
- At MV level- Store a cine loop with and with out colour.
- At papillary muscle level- Store a cine loop.



Apical 4-chamber



Apical 2-chamber

Apical 4 chamber view:

- Store a cine loop
- Press TVI button and store a TVI loop as well (analysed later in FRH on vivid 7)
- Press TDI button and move he cursor on lateral and medial MV annulus respectively, to get E' recording. Store as a still frame.
- Put colour on MV and store as a cine loop.
- Get PW Doppler on MW to record E & A waves, store as still frame.
- Get PW Doppler on Pulmonary veins, if visible.
- Put colour on TV, store cine loop.
- Get CW Doppler on TV to record TR Vmax, store as a still frame.
- Put M-mode cursor on TV lateral annulus to record TAPSE. Store as a still frame.

Apical 5 chamber view

- Store a cine loop.
- Put colour on AV, store a cine loop.

- Put cursor thought AV and record PW and CW for AV. Store as a still frame.

Apical 2 chamber view

- Store a cine loop.
- Put colour on MV, store cine loop.

Apical 3 chamber view

- Store a cine loop.
- Put colour on MV and AV, store cine loop.

Epigastric view

- Store a cine loop.
- Put colour on IAS, store a cine loop.
- M-mode the IVC, store cine loop and still frame as well.
- If IVC appears dilated, get an image with sneezing manoeuvre as well.
- Give paper towel to participant to wipe off the gel from his/her chest.
- Remove the ECG stickers from participant's chest.
- Press **Review** button and **End exam** button to end and store the examination.
- Clean the probe & ECG leads, remove from the machine and pack them away.
- Examination will be analysed offline in 85+study's office according to our study protocol.

Archiving and exporting the data in to database

- Insert a removable media in the drive (CD-R)
- Press **PATIENT** on the front panel, and then select **Patient List**.
- Select the source archive in Dataflow field: **Local Archive-Int.HD**
- Press **Export**, then select **CD/DVD Archive** as a destination
- Press **OK,** a window'll appear saying: Current media is not formatted. Do you wish to format it? Select **Yes**.
- Select the examination from **Patient List** that you want to export.
- Press **Copy** and then press **Ok** to resume export**.** And finally press **Done** in the **Export patient widow** to complete the process**.**
- Press Alt + E to eject the CD.
- Make another copy of the same exam by using the same procedure.

To export data in excel and pdf format, insert the Encrypted USB memory disk (Kingston-8GB) in USB slot on the back of Vivid I. Repeat the above procedure but select **excel file** and **pdf file** respectively**,** when you'll press **Export**. And also select **Removable memory disk** as a **destination**.
Data will than be stored on 85+ study's shared hard drive on university's network.

Approval and sign off
Author:
Name: Dr Fahad Yousaf
Position: Clinical Research Associate
Signature: Date: 31/10/2008
Approved by:
Name: Prof Bernard Keavney
Position: Consultant Cardiologist
Signature: Date:

Standard Operational Procedure For The Recording Of Carotid Intima-Media Thickness (CIMT) Measurements Within The Newcastle 85+ Study

Document Number: 0003/IAH/85+
Title: SOP for recording CIMT measurements
Version: Final Draft
Author: Fahad Yousaf

Responsibilities:

Research investigators trained in the method are responsible for:

- Accurate measurement and recording of carotid intima-media thickness (CIMT) by using Vivid I from participants
- Clear explanation of the procedure to participants and
- Ensuring that equipment is in optimal working order.

Equipment:

- Vivid I
- 12L-RS linear USG probes with lead

General Precautions:

- Make sure all the connections are secure.
- Make sure all equipment is fully charged before going to participant's house.
- Make sure to put paper towel on the collar to avoid searing of participant's clothe with gel.
- Try to be very gentle while performing the scan and provide paper towels to participant to wipe off the gel from neck.
- Do follow the manufacturer's instruction for maintenance and specific cleaning and disinfection for probe.
- For cleaning of probe always disconnect it from the unit.

Instructions for using the Vivid-I (CIMT package)

The investigator must read the accompanying instruction manual carefully, and then familiarise themselves with the equipment. Step-by-step instructions for day-to day use will be kept with each device.

Creating a new Participant's record

- Press PATIENT

The patient handling screen will come up

- Press CREAT NEW PATIENT

An operator log window will appear. Press log on. The search/create Patient window will come up.

- Enter participant's details (last name, first name, date of birth and ID). We ll use PID number instead of last and first name due to confidentiality issues.

- Than press 'Create Patient' to store participant details.

Participant's positioning

- Ask participant to lye down on the bed as flat as is consistent with their comfort. A sofa would be an acceptable alternative if participant prefers. If participant is too immobile to achieve an appropriate position for study, this should be noted but the data should, as far as is possible, still be recorded.

- Ideally participants are placed in supine position with head rotated by 45° to the left/right, with their arm rested at their sides.

Selecting the vascular probe

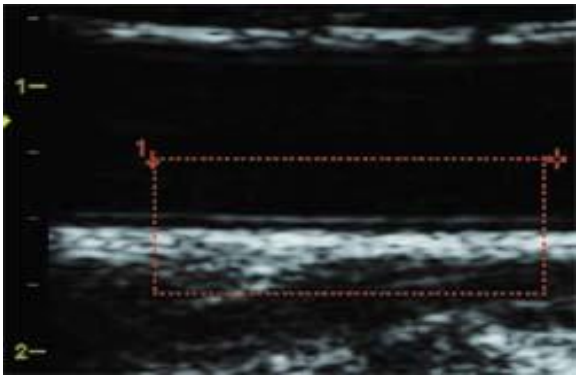
- Ensure a vascular probe 12L-RS is connected and selected for carotid scan to measure CIMT.

Capturing participant's data

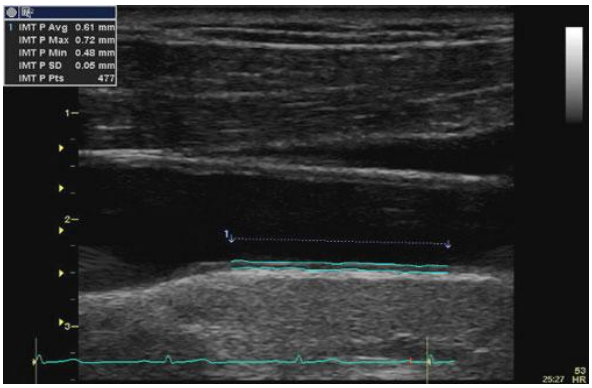
- A longitudinal image of carotid artery will be obtained as mentioned in CIMT imaging protocol.

- Optimize the image by using depth and focus settings.

- Press freeze



- Scroll to end-diastolic frame where the intima layer is clearly visible
- Press measure
- Select the appropriate IMT measurement. If measuring the IMT of posterior wall of the right common carotid select Rt and CCA IMT Post.
- Place the cursor in the artery closer to the posterior wall and press SET to anchor the start of search region.



- Move the cursor parallel to the artery to define the end point of the search region. Make sure the intima and media layer are with in the search region. Press SET to anchor the point. Automated software will automatically detect the IMT and will do the calculations. The measurements are displayed in the Measurement result table on top left hand side of the screen.
- Images will be stored by using STORE button.
- Finish the exam by clicking END EXAM button.
- Clean the probe, remove from the machine and pack it away.
- Give paper towel to participant to wipe off the gel from the neck.

Exporting that data in to database

By selecting the given participant measurement will be exported in to an excel format to an encrypted USB memory disk (Kingston-8Gb). Data will than be stored on 85+ study's shared hard drive on university's network.

Approval and sign off

Author:
Name: Dr Fahad Yousaf
Position: Clinical Research Associate
Signature: Date: 30/09/2008
Approved by:
Name: Prof Bernard Keavney
Position:
Signature: Date:

Standard Operational Procedure For The Recording Of Pulse Wave Velocity (PWV) And Ankle Brachial Index (ABI) Measurements Within The Newcastle 85+ Study

Document Number: 0002/IAH/85+
Title: SOP for recording PWV and ABI measurements
Version: Final Draft
Author: Fahad Yousaf

Responsibilities:

Research investigators trained in the method are responsible for:

- Accurate measurement and recording of pulse wave velocity (PWV) and ankle brachial index (ABI) measurements by using Vicorder from participants,
- Clear explanation of the procedure to participants and
- Ensuring that equipment is in optimal working order.

Equipment:

Vicorder Instrument
USB Lead x 1
Pressure Cuffs (limbs) x 5
Pressure Cuffs (neck) x 1
Pressure Hoses x 2
PPG Sensors x 2 (Photoplethysmography)
5 MHz and 8 MHz Doppler probes with lead
Laptop (Toshiba – Satellite Pro)

General Precautions:

- Make sure all the connections are secure
- Make sure all equipment is fully charged before going to participant's house
- When using neck cuff or any other cuffs the participant should be advised that a mild constriction will be felt when they inflate.
- Cuffs should automatically deflate but if for some reason they fail to deflate, unplug the pneumatic cuff connectors.
- Cleaning the Vicorder, its components and leads should only be undertaken by wiping with a soft cloth moistened with mild soap or antiseptic solution.
- Vicorder will require periodic calibration of its pressure channels to maintain its accuracy.

Instructions for using the 'Vicorder'

The investigator must read the accompanying instruction manual carefully, and then familiarize him with the equipment. Step-by-step instructions for day-to -day use will be kept with each device.

Entering participant's details

- Click 'File' → 'New Patient'. (New patient's window will appear).
- Enter participant's details (last name, first name, date of birth and ID). We shall use PID number instead of last and first name due to confidentiality issues.
- Then click 'Finish' to store participant details.

Participant's positioning

- Participant will be in a supine position with the head and shoulders raised by approximately 30 degrees; this will prevent venous contamination of arterial signals.
- We will use a pillow or a neck wedge for this purpose.

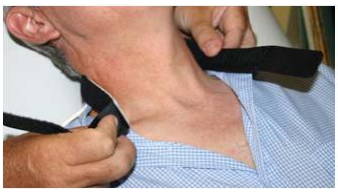
System setup

- Connect the Vicorder instrument with the laptop using USB cable.
- Connect the 2 coloured pneumatic hoses to 'PRESS 1' & 'PRESS 2' on the front panel of the Vicorder.
- Connect the 2 coloured PPG connectors to 'PPG 1' & 'PPG 2' on the front panel of the Vicorder.
- Start the Vicorder software by double clicking the icon on computer's screen.

Capturing participant's data

- Select the PWA ABI protocol

- Apply cuffs, as shown in the pictures below:



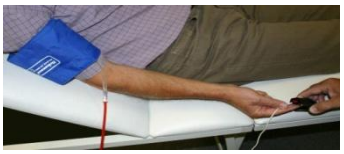
○ *neck cuff*
(The neck cuff is placed around participant's neck with pressure pad over right carotid area – just below the cricoid cartilage)

○ *arm cuffs on each side*
(Place just above cubital fossa)

○ *thigh cuff on right side*
(Placed over upper part of the thigh, as high as possible)

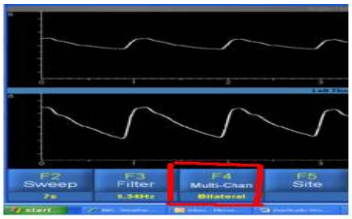
- *ankle cuffs on each side*

(Place just above the ankles joints)



Step 1- Arm Pressures

- Now attach the Red Hose to the Right Arm and Blue Hose to Left Arm.

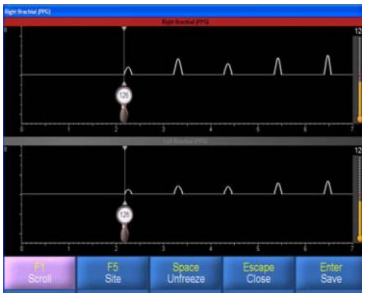


- Apply PPG sensors to the largest finger on the left and right hands. (Red PPG to right hand and Blue PPG to left hand)

- The Right Arm Pressure button starts the ABI measurements.

- Note: if software only displays a single channel/trace than
- press the F4 Multi-Chan button and it will show 2 traces, one for each limb.

- Press 'Space Bar' to inflate the cuffs.

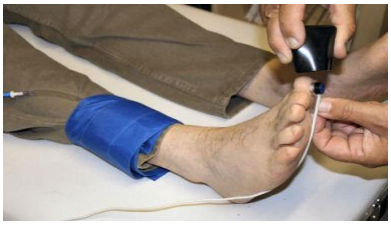


- Once you get a decent trace, press 'Save' key to store the results.

Step 2 – Leg Pressures

Now attach the Red Hose to Right Ankle and Blue Hose to Left Ankle.

Apply PPG sensors to the big toe of each foot. (Red PPG to right hand and Blue PPG to left hand)



The Right Ankle Pressure button starts the ABI measurements.

Press Space Bar to inflate the cuffs.

Once you get a decent trace, press 'Save' key to store the results.

Step 3 – Aortic Pulse Wave Velocity

Now attach Red Hose to neck cuff and Blue Hose to right thigh cuff.

Click on the large white area in ‘Right Arm Box’ as shown to enter the PWV Mode.

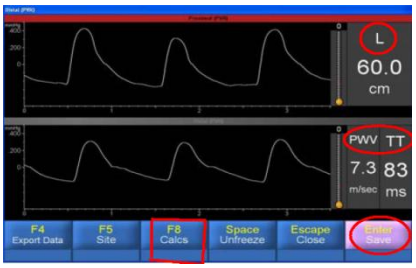
Measure the distance between Supra-sternal notch and the top of Thigh cuff in centimetres. (L)

*(The distance between carotid and femoral sampling sites will be measured above the body surface with a metal tape measure to avoid over-estimation)

Click on F8 button to enter the data (L) in ‘length’ box.

Now press the Space Bar to inflate the cuffs (do remember to mention to the patient that you are about to inflate the cuffs).

Once stable wave forms are obtained, press space bar again. It will give us PWV and TT (transient time) measurements.



Press Return/Save to finish the measurement and save the reading.

Remove the cuffs and pack all the equipment properly.

Exporting that data in to database

In the end result be stored in Vicorder database, which should be backed up in University network database. Database should be backed up after every visit.

Approval and sign off

Author:
Name: Dr Fahad Yousaf
Position: Clinical Research Associate
Signature: Date: 09/09/2008

Approved by:
Name: Prof Bernard Keavney
Position:

Standard Operational Procedure For The Recording Of Pulse Wave Analysis (PWA) Measurements Within The Newcastle 85+ Study

Document Number: 0001/IAH/85+

Title: SOP for recording PWA measurements

Version: 1st Draft

Author: Fahad Yousaf

Responsibilities:

Research investigators trained in the method are responsible for:
Accurate measurement and recording of pulse wave analysis measurements (PWA) by using SphygmoCor ® Px from participants,
Clear explanation of the procedure to participants and
Ensuring that equipment is in optimal working order.

Equipment:

SphygmoCor Electronics Module – Px
AtCor Tonometer (In module Tray)
Serial Cable
Power Cable
Carry Bag
Laptop (Dell)
Omron 705IT Blood pressure apparatus

General Precautions:

Make sure all the connections are secure
Make sure all equipment is fully charged before going to participants house
When tonometer is not in use, protect it by putting the plastic dome cover over it.
Tonometer should be routinely cleaned every month with mixture of warm water and mild detergent.

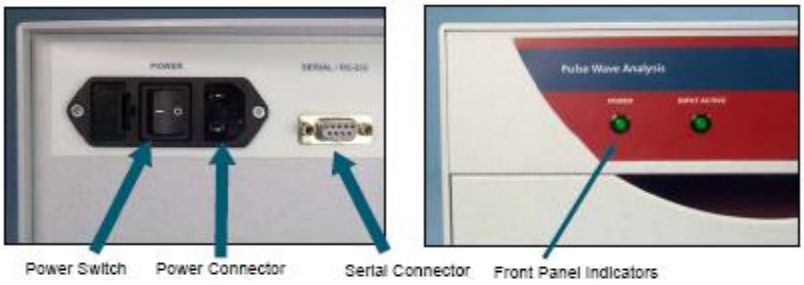
Instructions for using the SphygmoCor ® Px.

The investigator must read the accompanying instruction manual carefully, and then familiarise themselves with the equipment. Step-by-step instructions for day-to day use will be kept with each device.

System setup

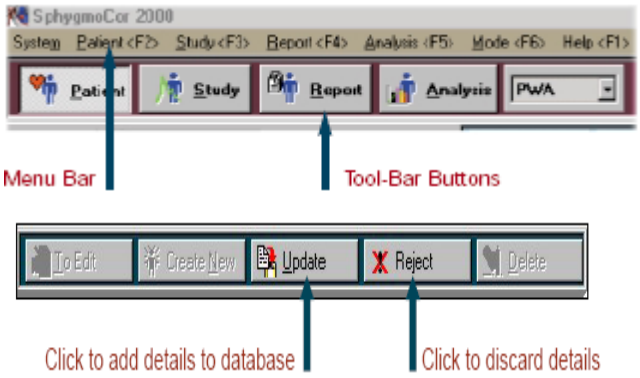
Connect the SphygmoCor Module with the laptop using serial cable.
Plug the electronic module power cable into the main power.

Turn the Module ‘on’ by switching the on/off button.
Connect the tonometer’s socket to its matching connector located in the module’s tray.



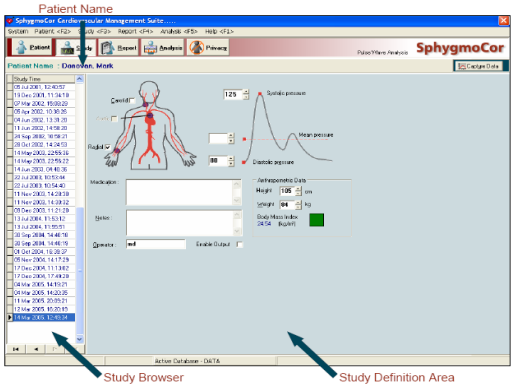
Entering participant details

Open the ‘Patient’ screen by clicking on the Patient Button, select the ‘Create New’ button and enter the participant details. Enter PID number, Date of Birth and Sex. Click on the ‘Update’ button to add the details of the participant to the database. (Name, sex and DOB are mandatory in the software, but we ll use PID number in Name field because of confidentiality issues.)



Capturing participant’s data

Open the study screen by clicking on ‘study icon.
Following screen will appear

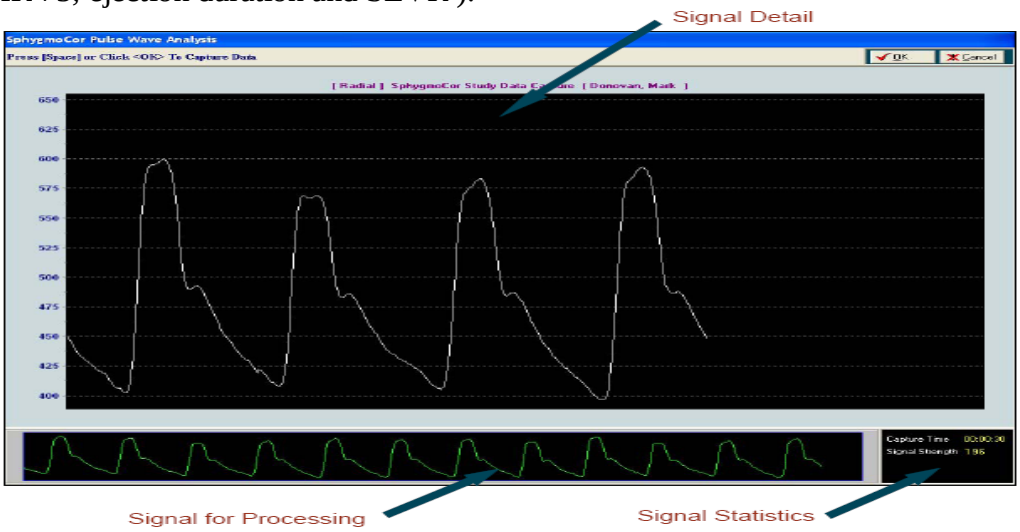


Make sure radial box is ticked
Enter systolic and diastolic BP readings (BP should be taken by Omron 705IT as per 85+ study protocol)

Performing the Data capture

Now we are ready to take the capture data. To go on data capture screen press enter from laptop keyboard or click on icon ‘Capture Data’

Participant will be in supine position, with shoulders and neck elevated by around 30 degrees.
Feel for the location of the strongest pulse at radial artery of the participant’s wrist and place the tonometer on the skin at this point.
Gently press the tonometer into the skin until a waveform signal appears on the screen. (Tonometer should be perpendicular to the wrist)
Once achieved a consistent waveform, hold it steady for 12 seconds and press ‘space bar’ that will capture the data.
After that report screen will automatically displayed with all the required measurements. (Aortic systolic pressure, aortic pulse pressure, augmentation pressure, augmentation index @ HR 75, ejection duration and SEVR).

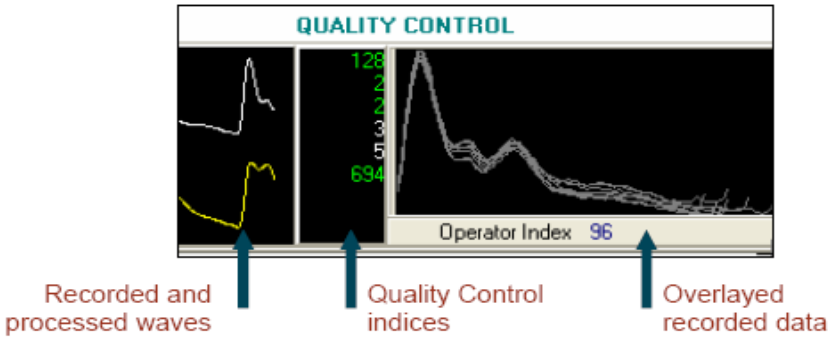


Examine the report for Quality control

Operator Index is an indicator of overall quality of captured data. Anything more than 80 is acceptable. It is calculated by assigning a weighting to Quality Control Indices (as mentioned below)

Minimum average pulse height: 100 units
Maximum pulse height variation: 5%
Maximum diastolic variation: 5%
Minimum quality index: minimum 80

Augmentation index: <50%
If any of above criteria is not met study should be repeated.



Exporting that data in to database

In the end result be stored in SphygmoCor database, which should be backed up in University network database.

Standard Operational Procedure For The Recording Of Electrocardiograph Within The Newcastle 85+ Study

Responsibilities:

Research investigators trained in the method are responsible for accurate measurement and recording of echocardiographs from volunteers. Clear explanation of the procedure to volunteers. Ensuring that equipment is in optimal working order.

Equipment:

- Atria 6100 ECG machine
- Power cable and adaptor
- Leads with clips attached
- Electrodes
- Moist Wipes to clean skin (if necessary)
- Recording paper

Instructions for using the ATRIA 6100

Before use

- The investigator must read the accompanying instruction manual carefully, and then familiarise themselves with the equipment and correct electrode / lead placement by using the device on one or more volunteers. Step-by-step instructions for day-to day use will be kept with each device.

Set the Date and Time

- Press *On/Stby*
- Press *Setup* then select *System* option in the menu
- Select *Date (DD.MM.YYYY)* option
- Enter date in required format (using number keys and delete key to correct errors)
- When date correct press *Enter* to review time
- Enter or change time using number keys and delete key to correct errors (time is entered in 24 hour format)
- Press *Home* to return to main display

Setting Required fields

- Press *Setup*
- Scroll down to *Patient* and press *Select*
- Ensure the following fields are tagged as ON (Patient ID is automatically selected as ON).

    Last Name
    Date of Birth
    Gender
    Technician
    Comment

All other fields should be turned off.

Changing the status of a field

- Scroll to required field and press *Select*
- Scroll to required status (ON or OFF) and press *Select*
- Continue to work through each field as required or press *Back* at any stage to skip to another field

Adding Participant Demographics

- Press *Patient* then select *Enter New Patient*
- Enter ID number, **must include letters NE and <u>all</u> numbers,** then press *Select*
- In *Last Name* field re-enter ID as before and press *Select*
- Enter date of birth in required format and press *Select*
- Choose gender and press *Select*
- Enter nurse ID number as 2 digit number and press *Select*
- Enter any comment if necessary eg. if ECG obtained with participant in sitting position (maximum of 25 characters allowed), then press *Select*

Acquiring an ECG

- Ensure that the individual is as relaxed as possible. Prepare volunteer and place electrodes and corresponding leads according to the diagram on Quick Steps page.
- Press *ECG* then scroll to *Acquire ECG, current patient data* and press *Select*
- ECG will now be acquired and printed
- ECG will automatically be saved in memory
- If print out not suitable then readjust leads, stickers etc until satisfied then highlight *Acquire new ECG on same patient* and press *Select*. **Do not press ECG button as this records ECG with no demographics.**

Retrieving Participant Details

- Press *Patient Directory*
- Select *View Patient Directory*
- Scroll to required ID number and press *Select*

Replacing Paper

- Remove the paper tray cover (on left side of machine) by squeezing lever until it clicks and pulling out tray
- Place the new stack of paper into the compartment so that:

  The black queue mark on the lower left hand corner of paper is visible

  The writing is on bottom of document

The red line that appears at the bottom of the paper is on last few sheets of paper (not first few) as this is a reminder that paper is about to run out

- Lift the top sheet up and replace the tray cover by laying it flat and sliding it back into machine. Push in until tray clicks into place. **Do not insert tray at an angle**
- To advance the paper to the start of the next sheet, ready for use, press the *Form Feed* button.

Transmitting ECG to Glasgow

- Press *Send/Rec* button
- Select *Select Records to Send*
- Highlight each record and either select *hold or send*
- When all required records have been selected to send (and all non-required records have been checked as *hold*) press *Back* button
- Ensure modem is switched on and connected to phone line
- Connect modem to ECG machine via 9 pin adaptor
- Highlight *Send All New or Selected ECGs* and press *Select*
- Machine should then connect to modem and transmit data
- Once transmission is complete a confirmation message will be displayed
- Print a copy of report to confirm ECG has been sent

General information

- The device should be calibrated according to the instruction manual chapter 2 p2-3.
- Do not clean the monitor with detergents; if dirty, wipe with a damp cloth

Standard Operational Procedure For The Measurement Of Blood Pressure Within The Newcastle 85+ Study

Responsibilities:
Research investigators trained in the method are responsible for:

- Ensuring equipment is in optimal working order
- Clearly explain procedure to participant
- Accurately measure and document blood pressure
- The safety of the participant throughout the procedure

Equipment:

- Digital blood pressure monitor (Omron HEM 705-IT)
- Blood pressure cuffs (1 regular 1 large)
- Tape measure
- AA batteries x4

Instructions for using the OMRON HEM 705-IT

Before use:

- Read the instruction manual carefully, insert batteries and then familiarise yourself by using the device on a few volunteers.
- Set the time and date.
- Keep step-by-step instructions for day to day use with each device.

General information:

- The device should be calibrated biannually (refer to instruction manual p20).
- Batteries should be replaced when the symbol indicating low battery power is shown. (Batteries should provide 500 measurements).
- The monitor automatically stores up to 28 readings, when this total is reached the oldest readings will be deleted and new reading stored.
- Do not clean the monitor with detergents; if dirty, wipe with a damp cloth.

Preparation of participant:

- Ideally participants should have an empty bladder, have not smoked and not consumed alcohol in the 30 minutes before blood pressure measurement.
- Ensure that the individual is as relaxed as possible. Ask the participant to sit with both feet parallel and flat on the floor.
- Participants should rest for five minutes in the sitting position before measurement.
- Participants should be asked not to talk during blood pressure measurement.

Choosing the correct cuff:

- Arm circumference (AC) should be measured midway between the shoulder tip and the olecranon process.
- If AC <32cm use regular cuff; if AC $\geq$32 use large cuff. If AC <22cm use small cuff.

ARM CIRCUMFERENCE	CUFF TO BE USED
17 – 22 cm	SMALL
22-32 cm	REGULAR
32-42 cm	LARGE

Positioning the cuff:

- See OMRON manual (pg 7,8) for correct placement of cuff.
- The cuffs are designed for blood pressure measurement on the **left arm**. If the cuff cannot be applied on the left arm, the right can be used – but be certain that the green strip on the lower boundary of the cuff is always on the brachial artery. THE SAME ARM SHOULD BE USED THROUGHOUT THE STUDY.
- The cuff can be placed over a thin shirt or blouse sleeve.
- Ensure the arm is supported on a cushion or table top, so the cuff position is in line with the level of participant's heart (see manual illustration p8).
- Instruct participant to relax and to take 3-4 deep breaths prior to commencing the procedure. This aids in stabilising their blood pressure.

Preparing the equipment and taking the blood pressure:

- Insert the air inflation tubing from the cuff into the air jack of the monitor. Switch on the device by pressing the 0/I button, and wait until the display shows a '0' and the heart symbol appears on the display.
- Press the START (inflation) button and immediately release it. Instruct the participant to remain still. A noise will be heard as cuff automatically inflates. The monitor automatically determines ideal inflation level. The monitor also automatically detects pulse even during inflation the display screen will flash a heart symbol during the process.
- Inflation stops automatically. As the cuff slowly deflates, decreasing numbers appear on the display. Once the recording has taken place. The cuff then completely deflates and the blood pressure and pulse will be displayed in the screen.
- In rare circumstances a higher inflation level may be necessary. In this case, the monitor re-inflates the cuff up to 30 mmHg higher than initial inflation.
- If it becomes necessary to stop the recording during inflation press the 0/I button again. The monitor will stop inflation and commence rapid deflation and then the monitor will turn off.
- If any error codes – 'E' – are displayed, refer to page 17 of the instruction manual.

Take 2 measurements in succession, with a 2 minute gap between each measurement.

Appendix 9

Newcastle 85+ Study: Cardiovascular Phenotyping
DETAILED SCRIPT – VERBATIM FOR CARDIAC STUDIES

Overview Of Researcher Responsibilities

Visit preparation

1. Ensure all equipment is in good working order and batteries are fully charged.
2. Ensure all required equipment is packed up correctly before each visit.

Start of each visit

1. Always be on time for each visit.
2. Register visit details and duration with Guardian 24.
3. Ensure mobile telephone is on silent/vibrate alert – do not turn off your mobile.

During each visit

1. Reconfirm verbally that consent is enduring
2. Always show respect towards the participants and their significant others.
3. Explain all procedures step by step using clear, 'non jargon' language.
4. Be prepared to speak loudly.
5. Be prepared to repeat the instructions and go over things as many times as the participant or significant other requires.
6. Continuously encourage the participant during the visit *"you are doing very well"*
7. Communicate your actions to the participant throughout the visit and particularly during the test e.g. *"I just need to move this monitor slightly", "I just need to enter this information onto the computer".*
8. Respect participants' dignity at every stage of the study visit.
9. Be aware of using too much pressure to gain carotid and/or cardiac scan.
10. Be prepared to stop tests at any time if the participant is uncomfortable.
11. Be prepared to stop tests if requested to do so by the participant or significant other.
12. Be prepared to stop tests at any time if you feel it is appropriate to do so.
13. Be prepared to go back again and finish the visit another day if participant gets exhausted or tired and wants you to stop

Detailed Researcher Instructions

- On arrival introduce yourself to the participant (show ID).

"Good morning/afternoon my name is Dr Yousaf and I am the heart doctor with the 85+ Study."

- Ask preferred name of participant.

"I have your name as Mr/Mrs…… is this what you prefer to be called?"

- Check participants'/ significant others understanding of the visit

"Did the nurse making the appointment explain to you why I was coming today?" (Wait for their response and then provide confirmation or clarification)

(Note: for those participants/ significant others who have not had the most up to date cardiac information this should be provided and explained)

"I am here to do some tests which will tell us something about the health of your heart and circulation. This will include scans of your heart and neck.

- Check consent is enduring

I will explain each test and step as I go along. If you have any questions please don't hesitate to ask me. You can stop me at any stage if you don't feel comfortable.

Is this ok with you?

Ok then let's start.

Ask participant if it is ok to do the test in their bedroom as this the best place for you and probably the most comfortable for them. Only think of alternative if they really don't want to use the bedroom. Offer them assistance to get there if necessary. When you get there explain to them that they need to take off their shoes and socks at this point and lie down flat. Make the participant is comfortable and supported.

- Blood Pressure

"OK first I would like to check your Blood Pressure. I will need to put this cuff on the top of your arm and the monitor blows up the cuff to tighten. I will tell you before the cuff starts to tighten." (Be prepared to deflate cuff and discontinue measurement if the participant indicates to do so)

"Ready to begin – you will now feel the cuff tightening on your arm." record measurement

(Note: If the participant asks about their blood pressure reading always be aware about causing anxiety. The safest response wherever appropriate is to say *"Its fine"* If the participant is extremely hypertensive explain that the measurement is *"up a little bit but blood pressure changes all of the time and the reason for it being high today is probably because they are having these tests done"* If very concerned check with nurse team when return to the 85+ study office).

Whilst discussing above pack away omron and set up for PWA (SphygmorCor)

- PWA - SphygmorCor

"Ok now I would like to measure your pulse and the softness of your arteries because we know these can stiffen up as we get older. To do this I will put this small monitor on your wrist where your pulse is. Ready to start?"

Perform radial tonometery.
If you need to do the test again, or it is taking some time explain that *"sometimes its difficult to pick up the pulse"* – need to think about how many times to re try something as may sicken people early on, consider trying again at end of assessments.

(Note: Let the participant know if they need to be quiet – sometimes best as if talking often move around.)

Once PWA data is obtained pack the SphygmorCor equipment away and set up the Vicorder equipment explaining about the test while you are doing so.

- Vicorder

"Now I would like to measure the speed of your pulse going through your body. To do this I am going to put these cuffs (show cuffs) *on your arms, ankles and thigh (top of leg). Like the BP cuff these will tighten, but again I will let you know before this happens.*
I am also going to put another cuff on your neck, but don't worry this one doesn't inflate much, its only about as tight as a shirt collar for just a few seconds, but let me know if it is uncomfortable for you and I will stop". (Support participants head to put the neck cuff behind participant neck- do not fasten this cuff until time to take the measurement)

Perform ABI part of (ABI0PWV) protocol first. (Inform at each stage which cuff will inflate)

Then Perform PWV part of (ABI-PWV) protocol. (Fasten neck cuff now and inform when cuff will inflate).

I just need to measure between the neck cuff and the thigh cuff. That will help me to work out the speed of your pulse.

Obtain measurement of the 'L' distance between neck and thigh cuffs.

Input all Vicorder data then pack away equipment and set up to perform the CIMT measurements explaining test as you are doing so.

- CIMT

"Sometimes as we age our blood vessels thicken up a little so I would like to take a picture of the main blood vessels/arteries in you neck with this scan (show scanner) to measure how healthy they are".

(Note: may be good here to explain that need to put gel on side of neck to get a good contact and therefore may prefer to take top clothing off – also need to do this anyway for heart scan – so will be prepared. If this is the case then cover participant through

CIMT measurement and ensure does not get cold. Only offer explanation of how scanner works if asked response along lines of : "*Its similar to when pregnant ladies have scans on their stomach to check the baby is ok".*)

Position participant always providing clear instruction e.g. *"Can I ask you to slightly turn your head to the left/right?"* Place protective cover at side of participant's neck to protect bed clothes from gel. Explain that need to put gel on side of neck to get a good contact and warn that gel may feel slightly cold. Be very gentle on participant's neck, don't press too hard!

Note: Keep checking that the participant is comfortable and be prepared to discontinue measurement if participant indicates to do so.

Record the CIMT data and then make separate folder for cardiac scan.

- Cardiac scan.

"Ok, you have done very well so far. We have now reached the measurement where I would like to take pictures of your heart using the same scanner" (again show scanner) For this test you have to undress to your waist (if not done so already) *and lie on your left hand side with your hand at the side of your head* (Demonstrate arm position). The test *will take 20-30 mins and again I will put some gel on different parts of your chest to take pictures of your heart from different angles.*

Prepare room i.e. protective cover on bed clothes, lights down, curtains closed – explaining to participant reason for doing this and asking their permission to do so.

Prepare participant assist with positioning explain if need to remain quiet, If support wedge or pillows are needed then explain each action to participant *"I am just going to place this support behind you back to make you more comfortable" OK are you ready to start?*

It is essential that you keep talking to the participant during the scan explaining each action along the way. This will help keep participants relaxed and focussed.

Explanations should always include "*You might feel some pressure on your ribs as I need to look through your ribs to get a good picture, but please tell me if it feels uncomfortable".* Explain just before it happens – "*during this test the machine will make some whooshing noises, this is normal, it is the blood flowing through your heart".*

- Withdraw from visit

Ensure all gel is removed from participant.
Don't forget to remove ECG stickers.
Ensure participant is appropriately dressed again, offering assistance where appropriate.
Pack up the equipment and make sure that you don't leave anything behind!

Thank the participant for their valuable contribution to the study.

Explain that need to take the pictures and all of the measurement back to the hospital to analyse them. Advise that if there is an abnormal result according to our study protocol, their GP will be notified and the GP would get in touch with them so they don't need to do anything. (This is also a good standard response if you are asked any questions about how the scan looks etc etc during the actual procedure)

Appendix 10

Letter of introduction

To Whom It May Concern:

Dr Fahad Yousaf is employed on the Newcastle 85+ Study, a research study into health and ageing in older people which is being conducted by the Institute for Ageing and Health at Newcastle University. He will be carrying out visits to older people in their own homes to perform cardiac assessments (heart scan and blood vessel scan). All appointments will have been made in advance by the 85+ Study research nurses. He will be carrying a photo identity badge from Newcastle University. If you have any queries about this study, please telephone the Newcastle 85+ study office on 0191 2481116; if no one is available to take your call please leave a message and someone will get back to you.

Thank you.

Karen Davies

Research Nurse Manager

Institute for Ageing and Health

The Newcastle 85+ Study
Institute for Ageing and Health,
Biogerontology Building
Newcastle University, Campus for Ageing and Vitality
Newcastle Upon Tyne, NE4 5PL
Telephone: **0191 248 1116** Fax: 0191 248 1119

Newcastle University

Appendix 11

The Institute for Ageing and Health
Newcastle University

The Newcastle

Study

Stage Two
Participant Consent Form

We are inviting you to take part in stage two of the Newcastle 85+ study.

Please ensure you have read the accompanying information booklet which explains why we are doing this research and what we are asking you to do in this stage. If you find reading or understanding the information difficult, please ask a family member or a carer to help you.

Please ask the research team any questions.

Remember:

- That participation in this study is entirely voluntary and you may withdraw from the whole or any part of the study at any time without affecting your usual medical care.

- It is unlikely that taking part will have any direct benefit for you.

I (name of participant)..……

of (address)……

……..……

agree to take part in stage two of The Newcastle 85+Study.

I understand the information that has been given to me about the study and this particular stage. I have been given time to think about the information and the opportunity to ask questions. I know that my consent is voluntary, and I can withdraw from the whole or any part of the study at any time. I understand that declining to participate will not affect my usual care.

I understand that during the course of this study it may become necessary for the research team to contact someone to represent my best interests (known as a consultee). In my opinion I would nominate,:
Name:……..……

Relationship to participant:……..

(Interviewer instruction: This individual would normally be a 'personal consultee' i.e. next of kin, closes relative or friend. If the nominated individual is NOT a 'personal consultee' but 'nominated consultee' i.e. a paid carer please provide information where possible to explain choice.)

……

…….

Address:……

…….

Contact number:……..

as the person best able to do this.

I understand that, in the event that something goes wrong and I am harmed during the research study, there are no special compensation arrangements. If I am harmed and this is due to someone's negligence then I may have grounds for a legal action for compensation against Newcastle University.

Please initial box	**Consent**	**Decline**
I agree to participate in stage two of the Newcastle 85+ study		
I agree that blood samples can be taken from me		
I agree that samples of my blood can be stored for future analysis of genetic and other factors involved in health in old age, ageing and life-span.		
I agree to allow my doctor to be contacted with the results of medical tests that are important for my health.		

The nature and demands of the study and this particular stage have been explained to me; I fully understand and accept them.

Signed:……Date……

Investigator Statement:
I confirm that I have explained the nature of the study and given every opportunity for ……..to receive and consider the information about the study and stage two.

Name……..……Signed…..……
Designation……Date…..……

Copied for participant ☐ *(Tick when completed)*

Consultee approval also obtained *(yes)* ☐ *(N/A)* ☐

The Newcastle 85+ Study
The Institute for Ageing and Health
Biogerontology Research Building
Newcastle University
Campus for Ageing and Vitality
Newcastle upon Tyne
NE4 5PL
Telephone: 0191 2481116

References

1. United Nations Department of Economic and Social Affairs Population Division, *World Population Ageing: 1950-2050*, 2002, United Nations: New York.
2. Office for National Statistics. *United Kingdom Population Estimates – mid-2009*. 2010; Available from: http://www.statistics.gov.uk/pdfdir/pop0610.pdf.
3. Office for National Statistics. *Population Trends 137 - Autumn 2009*. 2009; Available from: http://www.statistics.gov.uk/downloads/theme_population/PopTrends137web.pdf.
4. Office for National Statistics. *Ageing: Fastest increase in the 'oldest old'*. 2010 24/06/10]; Available from: http://www.statistics.gov.uk/cci/nugget.asp?id=949.
5. Ron Lesthaeghe, *EUROPE'S DEMOGRAPHIC ISSUES: FERTILITY, HOUSEHOLD FORMATION AND REPLACEMENT MIGRATION*, 2000, Population Division, Department of Economic and Social Affairs, United Nations: New York,.
6. Paula J Dobriansky, R.S., Richard J Hodes,. *Why Population Aging Matters: A Global Perspective*. 2007; Available from: http://www.nia.nih.gov/NR/rdonlyres/9E91407E-CFE8-4903-9875-D5AA75BD1D50/0/WPAM.pdf.
7. Julie Jefferies. *The UK population: past, present and future*. Focus on People and Migration: 2005 2005; Available from: http://www.statistics.gov.uk/downloads/theme_compendia/fom2005/01_FOPM_Population.pdf.
8. Louise O'Leary, E.N., Julie Jefferies, Ben Wilson, . *Fertility and partnership status in the last two decades*. Population Trends 140 2010; Available from: http://www.statistics.gov.uk/articles/population_trends/fertilityandpartnershipstatusinthelasttwodecades.pdf.
9. Grundy, E., *The Epidemiology of Ageing*, in *Brocklehurst's Textbook of Geriatric Medicine and Gerontology*, R. Tallis, Fillit, H.,, Editor 2003, Churchill Livingstone: London.

10. Oeppen, J. and J.W. Vaupel, *Demography. Broken limits to life expectancy.* Science, 2002. **296**(5570): p. 1029-31.
11. Frank W Notestein, *Some Demographic Aspects of Aging.* Proceedings of the American Philosophical Society, 1954. **98**(1): p. 38-45.
12. Nicholas Eberstadt, *World population implosion?* The Public Interest No. 129 (Fall), 1997: p. 3-22.
13. Deparment of Health, *Health Survey for England 2001*, 2003.
14. Deparment of Health. *Health Survey for England 2005: Health of Older People* 2007; Available from: http://www.ic.nhs.uk/statistics-and-data-collections/health-and-lifestyles-related-surveys/health-survey-for-england/health-survey-for-england-2005:-health-of-older-people-[ns].
15. Lloyd-Jones, D., et al., *Heart Disease and Stroke Statistics--2010 Update: A Report From the American Heart Association.* Circulation. **121**(7): p. e46-215.
16. Mosterd, A., et al., *Prevalence of heart failure and left ventricular dysfunction in the general population; The Rotterdam Study.* European Heart Journal, 1999. **20**(6): p. 447-455.
17. Mosterd, A. and A.W. Hoes, *Clinical epidemiology of heart failure.* Heart, 2007. **93**(9): p. 1137-1146.
18. Redfield, M.M., et al., *Burden of Systolic and Diastolic Ventricular Dysfunction in the Community: Appreciating the Scope of the Heart Failure Epidemic.* JAMA, 2003. **289**(2): p. 194-202.
19. S Stewart, et al., *Heart failure and the aging population: an increasing burden in the 21st century?* . Heart, 2003. **89**: p. 49-53.
20. Office for National Statistics. *Hospital and community health service expenditure: by age of recipient, 2001/02: Social Trends 34*. 2004; Available from: http://www.statistics.gov.uk/STATBASE/ssdataset.asp?vlnk=7400&More=Y.
21. Davis, R.C., F.D.R. Hobbs, and G.Y.H. Lip, *ABC of heart failure: History and epidemiology.* BMJ, 2000. **320**(7226): p. 39-42.
22. Katz, A.M., *Evolving concepts of heart failure: Cooling furnace, malfunctioning pump, enlarging muscle--Part I.* Journal of Cardiac Failure, 1997. **3**(4): p. 319-334.

23. Braunwald, E., *Pathophysiology of Heart Failure*, in *Braunwald's Heart Diseases: a textbook of cardiovascular medicine.*2005, Elsevier Saunders: Philidelphia. p. 509-538.
24. Dickstein, K., et al., *ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008.* European Heart Journal, 2008. **29**(19): p. 2388-2442.
25. Kessler, K., *Diastolic Heart Failure: Diagnosis and management.* Hospital Practice (Off Ed), 1989. **24**(7): p. 137-141.
26. Aurigemma, G.P., et al., *Predictive value of systolic and diastolic function for incident congestive heart failure in the elderly: The Cardiovascular Health Study.* J Am Coll Cardiol, 2001. **37**(4): p. 1042-1048.
27. Bella, J.N., et al., *Mitral Ratio of Peak Early to Late Diastolic Filling Velocity as a Predictor of Mortality in Middle-Aged and Elderly Adults: The Strong Heart Study.* Circulation, 2002. **105**(16): p. 1928-1933.
28. Wang, T.J., et al., *Natural History of Asymptomatic Left Ventricular Systolic Dysfunction in the Community.* Circulation, 2003. **108**(8): p. 977-982.
29. Redfield, M.M., et al., *Burden of Systolic and Diastolic Ventricular Dysfunction in the Community.* JAMA: The Journal of the American Medical Association, 2003. **289**(2): p. 194-202.
30. Gottdiener, J.S., et al., *Predictors of congestive heart failure in the elderly: the cardiovascular health study.* J Am Coll Cardiol, 2000. **35**(6): p. 1628-1637.
31. Karamanoglu, M., et al., *An analysis of the relationship between central aortic and peripheral upper limb pressure waves in man.* European Heart Journal. **14**(2): p. 160-167.
32. McMurray, J.J. and S. Stewart, *Epidemiology, aetiology, and prognosis of heart failure.* Heart, 2000. **83**(5): p. 596-602.
33. Writing Group, M., et al., *Heart Disease and Stroke Statistics--2009 Update: A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee.* Circulation, 2009. **119**(3): p. e21-181.
34. McDonagh, T.A., et al., *Symptomatic and asymptomatic left-ventricular systolic dysfunction in an urban population.* The Lancet, 1997. **350**(9081): p. 829-833.
35. Davies, M.K., et al., *Prevalence of left-ventricular systolic dysfunction and heart failure in the Echocardiographic Heart of England Screening study: a population based study.* The Lancet, 2001. **358**(9280): p. 439-444.

36. Kupari, M. and M. Lindroos, *Congestive heart failure in old age: prevalence, mechanisms and 4-year prognosis in the Helsinki Ageing Study.* Journal of Internal Medicine, 1997. **241**(5): p. 387-394.
37. Hogg, K., K. Swedberg, and J. McMurray, *Heart failure with preserved left ventricular systolic function: epidemiology, clinical characteristics, and prognosis.* J Am Coll Cardiol, 2004. **43**(3): p. 317-327.
38. Gottdiener, J.S., et al., *Outcome of Congestive Heart Failure in Elderly Persons: Influence of Left Ventricular Systolic Function: The Cardiovascular Health Study.* Annals of Internal Medicine, 2002. **137**(8): p. 631-639.
39. Cortina, A., et al., *Prevalence of heart failure in Asturias (a region in the North of Spain).* The American Journal of Cardiology, 2001. **87**(12): p. 1417-1419.
40. Hedberg, P., et al., *Left ventricular systolic dysfunction in 75-year-old men and women. A population-based study.* European Heart Journal, 2001. **22**(8): p. 676-683.
41. Ceia, F.t., et al., *Prevalence of chronic heart failure in Southwestern Europe: the EPICA study.* European Journal of Heart Failure, 2002. **4**(4): p. 531-539.
42. Devereux, R.B., et al., *Congestive heart failure despite normal left ventricular systolic function in a population-based sample: the Strong Heart Study.* The American Journal of Cardiology, 2000. **86**(10): p. 1090-1096.
43. Morgan, S., et al., *Prevalence and clinical characteristics of left ventricular dysfunction among elderly patients in general practice setting: cross sectional survey.* BMJ, 1999. **318**(7180): p. 368-372.
44. Bots, M.L., et al., *Common Carotid Intima-Media Thickness and Risk of Stroke and Myocardial Infarction : The Rotterdam Study.* Circulation, 1997. **96**(5): p. 1432-1437.
45. Cowie, M.R., et al., *Incidence and aetiology of heart failure; a population-based study.* European Heart Journal, 1999. **20**(6): p. 421-428.
46. Fox, K.F., et al., *Coronary artery disease as the cause of incident heart failure in the population.* European Heart Journal, 2001. **22**(3): p. 228-236.
47. Chatterjee, K. and B. Massie, *Systolic and Diastolic Heart Failure: Differences and Similarities.* Journal of Cardiac Failure, 2007. **13**(7): p. 569-576.
48. Mehta, P.A. and M.R. Cowie, *Gender and heart failure: a population perspective.* Heart, 2006. **92**(suppl 3): p. iii14-iii18.

49. Bleumink, G.S., et al., *Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure.* European Heart Journal, 2004. **25**(18): p. 1614-1619.
50. Somaratne, J.B., et al., *The prognostic significance of heart failure with preserved left ventricular ejection fraction: a literature-based meta-analysis.* European Journal of Heart Failure, 2009. **11**(9): p. 855-862.
51. Petersen S, R.M.a.W.J. *Coronary heart disease statistics: heart failure supplement*. 2002 28 June 2004; Available from: http://www.heartstats.org/datapage.asp?id=817.
52. Senni, M., et al., *Congestive Heart Failure in the Community : A Study of All Incident Cases in Olmsted County, Minnesota, in 1991.* Circulation, 1998. **98**(21): p. 2282-2289.
53. Gardin, J.M., et al., *Left ventricular diastolic filling in the elderly: the cardiovascular health study.* The American Journal of Cardiology, 1998. **82**(3): p. 345-351.
54. Kitzman, D.W., et al., *Importance of heart failure with preserved systolic function in patients ≥65 years of age.* The American Journal of Cardiology, 2001. **87**(4): p. 413-419.
55. Kupari, M., et al., *Congestive heart failure in old age: prevalence, mechanisms and 4-year prognosis in the Helsinki Ageing Study.* Journal of Internal Medicine, 1997. **241**(5): p. 387-394.
56. Nieminen, M.S., et al., *Executive summary of the guidelines on the diagnosis and treatment of acute heart failure.* European Heart Journal, 2005. **26**(4): p. 384-416.
57. Fischer, M., et al., *Prevalence of left ventricular diastolic dysfunction in the community.* European Heart Journal, 2003. **24**(4): p. 320-328.
58. European Study Group on Diastolic Heart, F., *How to diagnose diastolic heart failure.* European Heart Journal, 1998. **19**(7): p. 990-1003.
59. Carlson, K.J., et al., *AN ANALYSIS OF PHYSICIANS REASONS FOR PRESCRIBING LONG-TERM DIGITALIS THERAPY IN OUTPATIENTS.* Journal of Chronic Diseases, 1985. **38**(9): p. 733-739.
60. Nielsen, O.W., et al., *Cross sectional study estimating prevalence of heart failure and left ventricular systolic dysfunction in community patients at risk.* Heart, 2001. **86**(2): p. 172-178.

61. Packer, M., *Pathophysiology of chronic heart failure.* Lancet, 1992. **340**: p. 88-92.
62. Sonnenblick, E.H., D. Spiro, and H.M. Spotnitz, *The ultrastructural basis of Starling's law of the heart. The role of the sarcomere in determining ventricular size and stroke volume.* American Heart Journal, 1964. **68**(3): p. 336-346.
63. Capasso JM, P.T., Anversa P., *Ventricular remodelling induced severe myocardial dysfunction in the aging rat heart.* Am J Physiol, 1990. **259**: p. H1086-96.
64. Chen, H.H. and R.W. Schrier, *Pathophysiology of Volume Overload in Acute Heart Failure Syndromes.* The American Journal of Medicine, 2006. **119**(12, Supplement 1): p. S11-S16.
65. McDonagh, T.A., et al., *Left ventricular dysfunction, natriuretic peptides, and mortality in an urban population.* Heart, 2001. **86**(1): p. 21-26.
66. Levin, E.R., D.G. Gardner, and W.K. Samson, *Natriuretic Peptides.* N Engl J Med, 1998. **339**(5): p. 321-328.
67. Moe, G.W., et al., *Response of atrial natriuretic factor to acute and chronic increases of atrial pressures in experimental heart failure in dogs. Role of changes in heart rate, atrial dimension, and cardiac tissue concentration.* Circulation, 1991. **83**(5): p. 1780-1787.
68. Farre, A.L. and S. Casado, *Heart Failure, Redox Alterations, and Endothelial Dysfunction.* Hypertension, 2001. **38**(6): p. 1400-1405.
69. Januzzi, J.L., et al., *NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients.* European Heart Journal, 2006. **27**(3): p. 330-337.
70. Yusuf, S., et al., *Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial.* The Lancet, 2003. **362**(9386): p. 777-781.
71. Kawaguchi, M., et al., *Combined Ventricular Systolic and Arterial Stiffening in Patients With Heart Failure and Preserved Ejection Fraction: Implications for Systolic and Diastolic Reserve Limitations.* Circulation, 2003. **107**(5): p. 714-720.
72. Kulminski, A.M., et al., *Cumulative Deficits and Physiological Indices as Predictors of Mortality and Long Life.* J Gerontol A Biol Sci Med Sci, 2008. **63**(10): p. 1053-1059.

73. Kass, D.A., J.G.F. Bronzwaer, and W.J. Paulus, *What Mechanisms Underlie Diastolic Dysfunction in Heart Failure?* Circ Res, 2004. **94**(12): p. 1533-1542.
74. Ouzounian, M., D.S. Lee, and P.P. Liu, *Diastolic heart failure: mechanisms and controversies.* Nat Clin Pract Cardiovasc Med, 2008. **5**(7): p. 375-386.
75. Aronow, W., *Effects of ageing on the heart*, in *Brocklehurst's Textbook of Geriatric Medicine and Gerontology*2003, Churchill Livingstone: Edinburgh. p. 341-348.
76. Yamamoto, K., et al., *Myocardial stiffness is determined by ventricular fibrosis, but not by compensatory or excessive hypertrophy in hypertensive heart.* Cardiovascular Research, 2002. **55**(1): p. 76-82.
77. Zile, M.R. and D.L. Brutsaert, *New Concepts in Diastolic Dysfunction and Diastolic Heart Failure: Part II.* Circulation, 2002. **105**(12): p. 1503-1508.
78. Hundley, W.G., et al., *Cardiac cycle-dependent changes in aortic area and distensibility are reduced in older patients with isolated diastolic heart failure and correlate with exercise intolerance.* J Am Coll Cardiol, 2001. **38**(3): p. 796-802.
79. Kelly, R.P., et al., *Effective arterial elastance as index of arterial vascular load in humans.* Circulation, 1992. **86**(2): p. 513-521.
80. Redfield, M.M., et al., *Age- and Gender-Related Ventricular-Vascular Stiffening.* Circulation, 2005. **112**(15): p. 2254-2262.
81. Lam, C.S.P., et al., *Cardiac Structure and Ventricular–Vascular Function in Persons With Heart Failure and Preserved Ejection Fraction From Olmsted County, Minnesota.* Circulation, 2007. **115**(15): p. 1982-1990.
82. Lewis, T., *Diseases of the Heart*1933, London: MacMillan.
83. Hunt, S.A., et al., *ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult--Summary Article: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): Developed in Collaboration With the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: Endorsed by the Heart Rhythm Society.* Circulation, 2005. **112**(12): p. 1825-1852.
84. Cleland, J., *Diagnosis of heart failure.* Heart, 1998. **79**.

85. Spiteri, M.A., D.G. Cook, and S.W. Clarke, *RELIABILITY OF ELICITING PHYSICAL SIGNS IN EXAMINATION OF THE CHEST*. The Lancet, 1988. **331**(8590): p. 873-875.

86. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels.* 9th ed. The Criteria Committee of the New York Heart Association1994, New York: Little Brown & Co.

87. Heart Failure Society Of, A., *HFSA guidelines for management of patients with heart failure caused by left ventricular systolic dysfunction--pharmacological approaches.* Journal of Cardiac Failure, 1999. **5**(4): p. 357-382.

88. Davie, A.P., et al., *Assessing diagnosis in heart failure: which features are any use?* QJM, 1997. **90**(5): p. 335-339.

89. Badgett RG, M.C., Otto PM, Ramirez G., *How well can the chest radiograph diagnose left ventricular dysfunction?* Journal of General Internal Medicine, 1996. **11**: p. 625-634.

90. Maisel, A.S., et al., *Rapid Measurement of B-Type Natriuretic Peptide in the Emergency Diagnosis of Heart Failure.* New England Journal of Medicine, 2002. **347**(3): p. 161-167.

91. Teichholz LE, K.T., Herman MV, Gorlin R., *Problems in echocardiographic volume determinations: echocardiographic—angiographic correlations in the presence or absence of asynergy.* The American Journal of Cardiology, 1976. **37**: p. 7-11.

92. Jensen-Urstad, K., *Comparison of Different Echocardiographic Methods With Radionuclide Imaging for Measuring Left Ventricular Ejection Fraction During Acute Myocardial Infarction Treated by Thrombolytic Therapy.* The American Journal of Cardiology, 1998. **81**: p. 538-544.

93. Jensen-Urstad Md, K., et al., *Comparison of Different Echocardiographic Methods With Radionuclide Imaging for Measuring Left Ventricular Ejection Fraction During Acute Myocardial Infarction Treated by Thrombolytic Therapy.* The American Journal of Cardiology, 1998. **81**(5): p. 538-544.

94. Schiller NB, S.P., Crawford M, De Maria A, Devereux R, Feigenbaum H, Gutgesell H, Reicheck N, Sahn D, Schnittger I, Silverman NH, Tajik AJ, *Recommendations for quantitation of the left ventricle by two-dimensional echocardiography.* Journal of American Society of Echocardiography, 1989(2): p. 358-367.

95. Lang, R.M., et al., *Recommendations for Chamber Quantification: A Report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, Developed in Conjunction with the European Association of Echocardiography, a Branch of the European Society of Cardiology.* Journal of the American Society of Echocardiography, 2005. **18**(12): p. 1440-1463.

96. Berning J, R.J., Launbjerg J, Fogh J, Mickley H, Andersen PE, *Rapid estimation of left ventricular ejection fraction in acute myocardial infarction by echocardiographic wall motion analysis.* Cardiology, 1992. **80**: p. 257.

97. van Royen, N., et al., *Comparison and reproducibility of visual echocardiographic and quantitative radionyclide left ventricular ejection fractions.* The American Journal of Cardiology, 1996. **77**(10): p. 843-850.

98. Smart, N., et al., *Determinants of functional capacity in patients with chronic heart failure: Role of filling pressure and systolic and diastolic function.* American Heart Journal, 2005. **149**(1): p. 152-158.

99. Cleland, J.G.F., A. Torabi, and N.K. Khan, *Epidemiology and management of heart failure and left ventricular systolic dysfunction in the aftermath of a myocardial infarction.* Heart, 2005. **91**(suppl 2): p. ii7-ii13.

100. Sohn, D.-W., et al., *Assessment of Mitral Annulus Velocity by Doppler Tissue Imaging in the Evaluation of Left Ventricular Diastolic Function.* Journal of the American College of Cardiology, 1997. **30**(2): p. 474-480.

101. Nagueh, S.F., et al., *Hemodynamic determinants of the mitral annulus diastolic velocities by tissue Doppler.* Journal of the American College of Cardiology, 2001. **37**(1): p. 278-285.

102. Idler, E.L., S.V. Kasl, and J.H. Lemke, *Self-evaluated health and mortality among the elderly in New Haven, Connecticut, and Iowa and Washington counties, Iowa, 1982-1986.[see comment].* American Journal of Epidemiology, 1990. **131**(1): p. 91-103.

103. Paulus, W.J., et al., *How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology.* European Heart Journal, 2007. **28**(20): p. 2539-2550.

104. Nagueh, S.F., et al., *Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography.* Journal of the American Society of Echocardiography, 2009. **22**(2): p. 107-133.

105. Kirkpatrick, J.N., et al., *Echocardiography in Heart Failure: Applications, Utility, and New Horizons.* J Am Coll Cardiol, 2007. **50**(5): p. 381-396.

106. Adamson, J.A., et al., *Are older people dying of depression? Findings from the Medical Research Council trial of the assessment and management of older people in the community.* Journal of the American Geriatrics Society, 2005. **53**(7): p. 1128-32.

107. *Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). CONSENSUS Trial Study Group.* The New England Journal of Medicine, 1987. **316**: p. 1429-1435.

108. *Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators.* The New England Journal of Medicine, 1991. **325**: p. 293-302.

109. McMurray, J., et al., *Practical recommendations for the use of ACE inhibitors, beta-blockers, aldosterone antagonists and angiotensin receptor blockers in heart failure: Putting guidelines into practice.* European Journal of Heart Failure, 2005. **7**(5): p. 710-721.

110. Cohn, J.N., et al., *Noninvasive Pulse Wave Analysis for the Early Detection of Vascular Disease.* Hypertension, 1995. **26**(3): p. 503-508.

111. Brophy, J.M., L. Joseph, and J.L. Rouleau, *Î²-Blockers in Congestive Heart Failure: A Bayesian Meta-Analysis.* Annals of Internal Medicine, 2001. **134**(7): p. 550-560.

112. *Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF).* Lancet, 1999. **353**: p. 2001-2007.

113. Thatcher, A.R., *The long-term pattern of adult mortality and the highest attained age.* J Roy Statist Soc Series A, 1999. **162**: p. 5-30.

114. Packer M, F.M., Roecker EB, Coats AJ, Katus HA, Krum H, Mohacsi P,, *Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study.* Circulation, 2002. **106**: p. 2194-2199.

115. Flather MD, S.M., Coats AJ, Van Veldhuisen DJ, Parkhomenko A,, *Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS).* European Heart Journal, 2005. **26**: p. 215-225.
116. O'Rourke, M.F. and M.E. Safar, *Relationship Between Aortic Stiffening and Microvascular Disease in Brain and Kidney: Cause and Logic of Therapy.* Hypertension, 2005. **46**(1): p. 200-204.
117. Hood, W.B., et al., *Digitalis for treatment of congestive heart failure in patients in sinus rhythm: a systematic review and meta-analysis.* Journal of Cardiac Failure, 2004. **10**(2): p. 155-164.
118. Cleland, J.G.F., et al., *The Warfarin/Aspirin study in heart failure (WASH): a randomized trial comparing antithrombotic strategies for patients with heart failure.* American Heart Journal, 2004. **148**(1): p. 157-164.
119. Kjekshus, J., et al., *Rosuvastatin in Older Patients with Systolic Heart Failure.*
120. Rivero-Ayerza, M.x., et al., *Effects of cardiac resynchronization therapy on overall mortality and mode of death: a meta-analysis of randomized controlled trials.* European Heart Journal, 2006. **27**(22): p. 2682-2688.
121. Connolly, S.J., et al., *Canadian Implantable Defibrillator Study (CIDS) : A Randomized Trial of the Implantable Cardioverter Defibrillator Against Amiodarone.* Circulation, 2000. **101**(11): p. 1297-1302.
122. Ahmed, A., et al., *Effects of Digoxin on Morbidity and Mortality in Diastolic Heart Failure: The Ancillary Digitalis Investigation Group Trial.* Circulation, 2006. **114**(5): p. 397-403.
123. Karen Hogg, J.M., *The treatment of heart failure with preserved ejection fraction ("diastolic heart failure")* Heart Failure Reviews, 2006. **11**(2): p. 141-146.
124. Shah, S.J. and M. Gheorghiade, *Heart Failure With Preserved Ejection Fraction: Treat Now by Treating Comorbidities.* JAMA, 2008. **300**(4): p. 431-433.
125. Cleland, J.G.F., et al., *The perindopril in elderly people with chronic heart failure (PEP-CHF) study.* European Heart Journal, 2006. **27**(19): p. 2338-2345.
126. Naohito Yamasaki, H.K., et al, *Heart Failure in Elderly.* Internal Medicine, 2003. **42**(5).

127. RS Stafford, e.a., *National patterns of angiotensin-converting enzyme inhibitor use in congestive heart failure.* Archives of internal medicine, 1997. **157**: p. 2460-2464.

128. *Indications for ACE Inhibitors in the Early Treatment of Acute Myocardial Infarction : Systematic Overview of Individual Data From 100 000 Patients in Randomized Trials.* Circulation, 1998. **97**(22): p. 2202-2212.

129. StrÃ¶mberg, A., *The crucial role of patient education in heart failure.* European Journal of Heart Failure, 2005. **7**(3): p. 363-369.

130. McMurray, J.J.V. and S. Stewart, *Nurse led, multidisciplinary intervention in chronic heart failure.* Heart, 1998. **80**(5): p. 430-431.

131. Stewart, S., J.E. Marley, and J.D. Horowitz, *Effects of a multidisciplinary, home-based intervention on planned readmissions and survival among patients with chronic congestive heart failure: a randomised controlled study.* The Lancet, 1999. **354**(9184): p. 1077-1083.

132. Jaarsma, T., et al., *Effects of education and support on self-care and resource utilization in patients with heart failure.* European Heart Journal, 1999. **20**(9): p. 673-682.

133. Benetos, A., et al., *Influence of age, risk factors, and cardiovascular and renal disease on arterial stiffness: clinical applications.* American Journal of Hypertension, 2002. **15**(12): p. 1101-1108.

134. Najjar, S.S., A. Scuteri, and E.G. Lakatta, *Arterial Aging: Is It an Immutable Cardiovascular Risk Factor?* Hypertension, 2005. **46**(3): p. 454-462.

135. Relf, I.R., et al., *Risk factors for changes in aorto-iliac arterial compliance in healthy men.* Arterioscler Thromb Vasc Biol, 1986. **6**(1): p. 105-108.

136. O'Rourke, M., *Mechanical Principles in Arterial Disease.* Hypertension, 1995. **26**(1): p. 2-9.

137. Belz, G.G., *Elastic properties and Windkessel function of the human aorta* Cardiovascular Drugs and Therapy, 1995. **9**(1): p. 73-83.

138. Frank, O., *The basic shape of the arterial pulse. First treatise: Mathematical analysis.* Journal of Molecular and Cellular Cardiology, 1990. **22**(3): p. 255-277.

139. Young, T., *On the function of the heart and arteries: The Croonian lecture*, in *Phil Trans Roy Soc* 1809. p. 1-31.

140. O'Rourke, M., *Vascular impedance*, in *McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles*, 5th, Editor 2005, Edward Arnold: London. p. 54–97.

141. Lamina, C., et al., *Association of ankle-brachial index and plaques in the carotid and femoral arteries with cardiovascular events and total mortality in a population-based study with 13 years of follow-up.* European Heart Journal, 2006. **27**(21): p. 2580-2587.

142. O'Rourke, *Arterial aging: pathophysiological principles.* Vascular Medicine 2007(12).

143. Dart, A.M. and B.A. Kingwell, *Pulse pressure--a review of mechanisms and clinical relevance.* Journal of the American College of Cardiology, 2001. **37**(4): p. 975-984.

144. O'Rourke, M.F. and W.W. Nichols, *Aortic Diameter, Aortic Stiffness, and Wave Reflection Increase With Age and Isolated Systolic Hypertension.* Hypertension, 2005. **45**(4): p. 652-658.

145. Drexler, H., et al., *Endothelial function in congestive heart failure.* American Heart Journal, 1993. **126**(3, Part 2): p. 761-764.

146. Kinlay, S., et al., *Endothelium-Derived Nitric Oxide Regulates Arterial Elasticity in Human Arteries In Vivo.* Hypertension, 2001. **38**(5): p. 1049-1053.

147. Oliver, J.J. and D.J. Webb, *Noninvasive Assessment of Arterial Stiffness and Risk of Atherosclerotic Events.* Arterioscler Thromb Vasc Biol, 2003. **23**(4): p. 554-566.

148. McEniery, C.M., et al., *Normal Vascular Aging: Differential Effects on Wave Reflection and Aortic Pulse Wave Velocity: The Anglo-Cardiff Collaborative Trial (ACCT).* J Am Coll Cardiol, 2005. **46**(9): p. 1753-1760.

149. Mitchell, G.F., et al., *Changes in Arterial Stiffness and Wave Reflection With Advancing Age in Healthy Men and Women: The Framingham Heart Study.* Hypertension, 2004. **43**(6): p. 1239-1245.

150. Mackey, R.H., et al., *Correlates of aortic stiffness in elderly individuals: a subgroup of the cardiovascular health study[ast].* Am J Hypertens, 2002. **15**(1): p. 16-23.

151. Smulyan, H., et al., *Influence of Body Height on Pulsatile Arterial Hemodynamic Data.* Journal of the American College of Cardiology, 1998. **31**(5): p. 1103-1109.

152. Wilkinson, I.B., et al., *Heart rate dependency of pulse pressure amplification and arterial stiffness.* American Journal of Hypertension, 2002. **15**(1): p. 24-30.
153. Lantelme, P., et al., *Heart Rate: An Important Confounder of Pulse Wave Velocity Assessment.* Hypertension, 2002. **39**(6): p. 1083-1087.
154. McEniery, C., *AGE, HYPERTENSION AND ARTERIAL FUNCTION.* Clinical and Experimental Pharmacology and Physiology, 2007. **34**(7): p. 665-671.
155. Asmar, R., et al., *Aortic Distensibility in Normotensive, Untreated and Treated Hypertensive Patients.* Blood Pressure, 1995. **4**(1): p. 48-54.
156. Hasegawa, M., et al., *Increased Pulse Wave Velocity and Shortened Pulse Wave Transmission Time in Hypertension and Aging.* Cardiology, 1997. **88**(2): p. 147-151.
157. Safar M, Laurent T, and L. M., *Hypertension and the arterial system: clinical and therapeutic aspects.* J Hypertens. , 1990. **8**(suppl 7): p. S113-S119.
158. Riley, W.A., et al., *Variation of common carotid artery elasticity with intimal-medial thickness: The ARIC study.* Ultrasound in Medicine & Biology, 1997. **23**(2): p. 157-164.
159. Stehouwer, C., R. Henry, and I. Ferreira, *Arterial stiffness in diabetes and the metabolic syndrome: a pathway to cardiovascular disease.* Diabetologia, 2008. **51**(4): p. 527-539.
160. Aronson, D., *Cross-linking of glycated collagen in the pathogenesis of arterial and myocardial stiffening of aging and diabetes.* Journal of Hypertension, 2003. **21**(1): p. 3-12.
161. McEniery, C.M., et al., *Endothelin-1 regulates arterial pulse wave velocity in vivo.* Journal of the American College of Cardiology, 2003. **42**(11): p. 1975-1981.
162. Wilkinson, I.B., et al., *Nitric Oxide Regulates Local Arterial Distensibility In Vivo.* Circulation, 2002. **105**(2): p. 213-217.
163. Kinlay, S., et al., *Endothelium-Derived Nitric Oxide Regulates Arterial Elasticity in Human Arteries In Vivo.* Hypertension, 2001. **38**(5): p. 1049-1053.
164. Mattace-Raso., et al., *Arterial Stiffness and Risk of Coronary Heart Disease and Stroke: The Rotterdam Study.* Circulation, 2006. **113**(5): p. 657-663.
165. DeLoach, S., *Vascular Stiffness: Its Measurement and Significance for Epidemiologic and Outcome Studies.* Clin J Am Soc Nephrol, 2008. **3**(1): p. 184-192.

166. Mitchell, G.F., *Increased Aortic Stiffness: An Unfavorable Cardiorenal Connection.* Hypertension, 2004. **43**(2): p. 151-153.

167. Safar, M., *Arterial Stiffness and Kidney Function.* Hypertension, 2004. **43**(2): p. 163-168.

168. Blacher, J., et al., *Arterial Calcifications, Arterial Stiffness, and Cardiovascular Risk in End-Stage Renal Disease.* Hypertension, 2001. **38**(4): p. 938-942.

169. Franklin, S.S., et al., *Hemodynamic Patterns of Age-Related Changes in Blood Pressure : The Framingham Heart Study.* Circulation, 1997. **96**(1): p. 308-315.

170. Bramwell, J.C. and A.V. Hill, *VELOCITY OF TRANSMISSION OF THE PULSE-WAVE : AND ELASTICITY OF ARTERIES.* The Lancet, 1922. **199**(5149): p. 891-892.

171. Franklin, S.S., et al., *Is Pulse Pressure Useful in Predicting Risk for Coronary Heart Disease? : The Framingham Heart Study.* Circulation, 1999. **100**(4): p. 354-360.

172. Benetos, A., et al., *Pulse Pressure : A Predictor of Long-term Cardiovascular Mortality in a French Male Population.* Hypertension, 1997. **30**(6): p. 1410-1415.

173. Domanski, M.J., et al., *Isolated Systolic Hypertension : Prognostic Information Provided by Pulse Pressure.* Hypertension, 1999. **34**(3): p. 375-380.

174. Pauca, A.L., et al., *Does radial artery pressure accurately reflect aortic pressure?* Chest, 1992. **102**(4): p. 1193-1198.

175. Deague, J.A., et al., *Physiological relationships between central vascular haemodynamics and left ventricular structure.* Clin. Sci., 2001. **101**(1): p. 79-85.

176. Lewington S, C.R., Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration, *Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies.* The Lancet, 2002. **360**(9349): p. 1903-1913.

177. Rajzer, M.W., et al., *Comparison of aortic pulse wave velocity measured by three techniques: Complior, SphygmoCor and Arteriograph.* Journal of Hypertension, 2008. **26**(10): p. 2001-2007 10.1097/HJH.0b013e32830a4a25.

178. Salvi, P., et al., *Comparative study of methodologies for pulse wave velocity estimation.* J Hum Hypertens, 2008. **22**(10): p. 669-677.

179. Hickson, S.S., et al., *Validity and repeatability of the Vicorder apparatus: a comparison with the SphygmoCor device.* Hypertens Res, 2009. **32**(12): p. 1079-1085.

180. Laurent, S., et al., *Expert consensus document on arterial stiffness: methodological issues and clinical applications.* European Heart Journal, 2006. **27**(21): p. 2588-2605.

181. Meaume, S., et al., *Aortic Pulse Wave Velocity Predicts Cardiovascular Mortality in Subjects >70 Years of Age.* Arterioscler Thromb Vasc Biol, 2001. **21**(12): p. 2046-2050.

182. Mohiaddin, R.H., D.N. Firmin, and D.B. Longmore, *Age-related changes of human aortic flow wave velocity measured noninvasively by magnetic resonance imaging.* J Appl Physiol, 1993. **74**(1): p. 492-497.

183. Chen, C.-H., et al., *Estimation of Central Aortic Pressure Waveform by Mathematical Transformation of Radial Tonometry Pressure : Validation of Generalized Transfer Function.* Circulation, 1997. **95**(7): p. 1827-1836.

184. Fetics, B., et al., *Parametric model derivation of transfer function for noninvasive estimation of aortic pressure by radial tonometry.* Biomedical Engineering, IEEE Transactions on, 1999. **46**(6): p. 698-706.

185. Sharman, J.E., et al., *Validation of a Generalized Transfer Function to Noninvasively Derive Central Blood Pressure During Exercise.* Hypertension, 2006. **47**(6): p. 1203-1208.

186. Cameron, J.D., B.P. McGrath, and A.M. Dart, *Use of radial artery applanation tonometry and a generalized transfer function to determine aortic pressure augmentation in subjects with treated hypertension.* Journal of the American College of Cardiology, 1998. **32**(5): p. 1214-1220.

187. Wilkinson, I.B., et al., *Increased central pulse pressure and augmentation index in subjects with hypercholesterolemia.* Journal of the American College of Cardiology, 2002. **39**(6): p. 1005-1011.

188. Wilkinson, I.B., et al., *Increased augmentation index and systolic stress in type 1 diabetes mellitus.* QJM, 2000. **93**(7): p. 441-448.

189. Weber, T., et al., *Prolonged mechanical systole and increased arterial wave reflections in diastolic dysfunction.* Heart, 2006. **92**(11): p. 1616-1622.

190. Weber, T., et al., *Arterial Stiffness, Wave Reflections, and the Risk of Coronary Artery Disease.* Circulation, 2004. **109**(2): p. 184-189.

191. Weber, T., et al., *Arterial Stiffness, Wave Reflections, and the Risk of Coronary Artery Disease.* Circulation, 2004. **109**(2): p. 184-189.
192. London, G.M., et al., *Arterial Wave Reflections and Survival in End-Stage Renal Failure.* Hypertension, 2001. **38**(3): p. 434-438.
193. Blacher, J., et al., *Carotid Arterial Stiffness as a Predictor of Cardiovascular and All-Cause Mortality in End-Stage Renal Disease.* Hypertension, 1998. **32**(3): p. 570-574.
194. Touboul, P.J., et al., *Mannheim Intima-Media Thickness Consensus.* Cerebrovascular Diseases, 2004. **18**(4): p. 346-349.
195. Bots, M.L. and D.E. Grobbee, *Intima Media Thickness as a Surrogate Marker for Generalised Atherosclerosis.* Cardiovascular Drugs and Therapy, 2002. **16**(4): p. 341-351.
196. Virmani, R., et al., *Effect of aging on aortic morphology in populations with high and low prevalence of hypertension and atherosclerosis. Comparison between occidental and Chinese communities.* Am J Pathol, 1991. **139**(5): p. 1119-1129.
197. Nagai, Y., et al., *Increased Carotid Artery Intimal-Medial Thickness in Asymptomatic Older Subjects With Exercise-Induced Myocardial Ischemia.* Circulation, 1998. **98**(15): p. 1504-1509.
198. Vaitkevicius, P.V., et al., *Effects of age and aerobic capacity on arterial stiffness in healthy adults.* Circulation, 1993. **88**(4): p. 1456-1462.
199. O'Leary, D.H., et al., *Carotid-Artery Intima and Media Thickness as a Risk Factor for Myocardial Infarction and Stroke in Older Adults.*
200. Belcaro, G., et al., *Carotid and femoral ultrasound morphology screening and cardiovascular events in low risk subjects: a 10-year follow-up study (the CAFES-CAVE study).* Atherosclerosis, 2001. **156**(2): p. 379-387.
201. Joakimsen, O., K.H. Bonaa, and E. Stensland-Bugge, *Reproducibility of Ultrasound Assessment of Carotid Plaque Occurrence, Thickness, and Morphology : The Tromso Study.* Stroke, 1997. **28**(11): p. 2201-2207.
202. Stork, S., et al., *Carotid Artery Plaque Burden, Stiffness, and Mortality Risk in Elderly Men: A Prospective, Population-Based Cohort Study.* Circulation, 2004. **110**(3): p. 344-348.
203. Rosvall, M., et al., *Incidence of stroke is related to carotid IMT even in the absence of plaque.* Atherosclerosis, 2005. **179**(2): p. 325-331.

204. Bernard, S., et al., *Incremental Predictive Value of Carotid Ultrasonography in the Assessment of Coronary Risk in a Cohort of Asymptomatic Type 2 Diabetic Subjects.* Diabetes Care, 2005. **28**(5): p. 1158-1162.

205. Bonithon-Kopp, C., et al., *Relation of Intima-Media Thickness to Atherosclerotic Plaques in Carotid Arteries : The Vascular Aging (EVA) Study.* Arterioscler Thromb Vasc Biol, 1996. **16**(2): p. 310-316.

206. Lorenz, M.W., et al., *Carotid Intima-Media Thickening Indicates a Higher Vascular Risk Across a Wide Age Range: Prospective Data From the Carotid Atherosclerosis Progression Study (CAPS).* Stroke, 2006. **37**(1): p. 87-92.

207. Touboul, P.-J., et al., *Carotid Intima-Media Thickness, Plaques, and Framingham Risk Score as Independent Determinants of Stroke Risk.* Stroke, 2005. **36**(8): p. 1741-1745.

208. Anderson, T.J., *Assessment and treatment of endothelial dysfunction in humans.* Journal of the American College of Cardiology, 1999. **34**(3): p. 631-638.

209. Katz, S.D., et al., *Impaired endothelium-mediated vasodilation in the peripheral vasculature of patients with congestive heart failure.* Journal of the American College of Cardiology, 1992. **19**(5): p. 918-925.

210. Bank, A.J., et al., *Endothelium-dependent vasodilation of peripheral conduit arteries in patients with heart failure.* Journal of Cardiac Failure, 1994. **1**(1): p. 35-43.

211. Kubo, S.H., et al., *Endothelium-dependent vasodilation is attenuated in patients with heart failure.* Circulation, 1991. **84**(4): p. 1589-1596.

212. Meyer, B., et al., *Flow-Mediated Vasodilation Predicts Outcome in Patients With Chronic Heart Failure: Comparison With B-Type Natriuretic Peptide.* Journal of the American College of Cardiology, 2005. **46**(6): p. 1011-1018.

213. Soga, J., et al., *Relationship between Augmentation Index and Flow-Mediated Vasodilation in the Brachial Artery.* Hypertens Res, 2008. **31**(7): p. 1293-1298.

214. McEniery, C.M., et al., *Endothelial Function Is Associated With Pulse Pressure, Pulse Wave Velocity, and Augmentation Index in Healthy Humans.* Hypertension, 2006. **48**(4): p. 602-608.

215. Hoffman, J.I.E. and G.D. Buckberg, *The myocardial supply:Demand ratio--A critical review.* The American Journal of Cardiology, 1978. **41**(2): p. 327-332.

216. Franklin, S.S., et al., *Predominance of Isolated Systolic Hypertension Among Middle-Aged and Elderly US Hypertensives : Analysis Based on National*

Health and Nutrition Examination Survey (NHANES) III. Hypertension, 2001. **37**(3): p. 869-874.

217. Levy, D., et al., *Prognostic Implications of Echocardiographically Determined Left Ventricular Mass in the Framingham Heart Study.* New England Journal of Medicine, 1990. **322**(22): p. 1561-1566.
218. Brown, D.W., W.H. Giles, and J.B. Croft, *Left ventricular hypertrophy as a predictor of coronary heart disease mortality and the effect of hypertension.* American Heart Journal, 2000. **140**(6): p. 848-856.
219. Mattace-Raso, F.U.S., et al., *Arterial Stiffness and Risk of Coronary Heart Disease and Stroke: The Rotterdam Study.* Circulation, 2006. **113**(5): p. 657-663.
220. O'Rourke, M.F., *Steady and Pulsatile Energy Losses in the Systemic Circulation under Normal Conditions and in Simulated Arterial Disease.* Cardiovascular Research, 1967. **1**(4): p. 313-326.
221. Pantoni, L. and J.H. Garcia, *Pathogenesis of Leukoaraiosis : A Review.* Stroke, 1997. **28**(3): p. 652-659.
222. Cullen, K.M., Z. Kocsi, and J. Stone, *Pericapillary haem-rich deposits: evidence for microhaemorrhages in aging human cerebral cortex.* J Cereb Blood Flow Metab, 2005. **25**(12): p. 1656-1667.
223. Yasue, H., et al., *Localization and mechanism of secretion of B-type natriuretic peptide in comparison with those of A-type natriuretic peptide in normal subjects and patients with heart failure.* Circulation, 1994. **90**(1): p. 195-203.
224. de Lemos, J.A., D.K. McGuire, and M.H. Drazner, *B-type natriuretic peptide in cardiovascular disease.* The Lancet, 2003. **362**(9380): p. 316-322.
225. Semenov, A.G., et al., *Processing of Pro-B-Type Natriuretic Peptide: Furin and Corin as Candidate Convertases.* Clin Chem. **56**(7): p. 1166-1176.
226. Yoshihiro, O., I. Hiroshi, and N. Kazuwa, *MOLECULAR BIOLOGY AND BIOCHEMISTRY OF NATRIURETIC PEPTIDE FAMILY.* Clinical and Experimental Pharmacology and Physiology, 1995. **22**(1): p. 49-54.
227. Daniels, L.B. and A.S. Maisel, *Natriuretic Peptides.* J Am Coll Cardiol, 2007. **50**(25): p. 2357-2368.
228. Potter, L.R., S. Abbey-Hosch, and D.M. Dickey, *Natriuretic Peptides, Their Receptors, and Cyclic Guanosine Monophosphate-Dependent Signaling Functions.* Endocrine Reviews, 2006. **27**(1): p. 47-72.

229. Redfield, M.M., et al., *Plasma brain natriuretic peptide concentration: impact of age and gender.* J Am Coll Cardiol, 2002. **40**(5): p. 976-982.
230. Costello-Boerrigter, L.C., et al., *Amino-Terminal Pro-B-Type Natriuretic Peptide and B-Type Natriuretic Peptide in the General Community: Determinants and Detection of Left Ventricular Dysfunction.* J Am Coll Cardiol, 2006. **47**(2): p. 345-353.
231. McDonagh, T.A., et al., *NT-proBNP and the diagnosis of heart failure: a pooled analysis of three European epidemiological studies.* European Journal of Heart Failure, 2004. **6**(3): p. 269-273.
232. Galasko, G.I.W., et al., *What is the normal range for N-terminal pro-brain natriuretic peptide? How well does this normal range screen for cardiovascular disease?* European Heart Journal, 2005. **26**(21): p. 2269-2276.
233. Raymond, I., et al., *The influence of age, sex and other variables on the plasma level of N-terminal pro brain natriuretic peptide in a large sample of the general population.* Heart, 2003. **89**(7): p. 745-751.
234. Abhayaratna, W.P., et al., *Population-based detection of systolic and diastolic dysfunction with amino-terminal pro–B-type natriuretic peptide.* American Heart Journal, 2006. **152**(5): p. 941-948.
235. Chang, A.Y., et al., *Associations Among Androgens, Estrogens, and Natriuretic Peptides in Young Women: Observations From the Dallas Heart Study.* J Am Coll Cardiol, 2007. **49**(1): p. 109-116.
236. Lainchbury, J.G., et al., *Brain natriuretic peptide and n-terminal brain natriuretic peptide in the diagnosis of heart failure in patients with acute shortness of breath.* Journal of the American College of Cardiology, 2003. **42**(4): p. 728-735.
237. Maisel, A.S., et al., *Rapid Measurement of B-Type Natriuretic Peptide in the Emergency Diagnosis of Heart Failure.* N Engl J Med, 2002. **347**(3): p. 161-167.
238. Mueller, T., et al., *Diagnostic accuracy of B type natriuretic peptide and amino terminal proBNP in the emergency diagnosis of heart failure.* Heart, 2005. **91**(5): p. 606-612.
239. Januzzi, J.J.L., et al., *The N-terminal Pro-BNP Investigation of Dyspnea in the Emergency department (PRIDE) study.* The American Journal of Cardiology, 2005. **95**(8): p. 948-954.

240. Alehagen, U., J.P. Goetze, and U. Dahlström, *Reference intervals and decision limits for B-type natriuretic peptide (BNP) and its precursor (Nt-proBNP) in the elderly*. Clinica Chimica Acta, 2007. **382**(1-2): p. 8-14.

241. Tschope, C., et al., *The role of NT-proBNP in the diagnostics of isolated diastolic dysfunction: correlation with echocardiographic and invasive measurements.* European Heart Journal, 2005. **26**(21): p. 2277-2284.

242. Thomas J. Wang, M.D., Martin G. Larson, Sc.D., Daniel Levy, M.D., Emelia J. Benjamin, M.D., Eric P. Leip, M.S., Torbjorn Omland, M.D., Philip A. Wolf, M.D., and Ramachandran S. Vasan, M.D., *Plasma Natriuretic Peptide Levels and the Risk of Cardiovascular Events and Death.* The New England Journal of Medicine, 2004. **350**: p. 655-663.

243. Sanz, M.P., et al., *Comparison of BNP and NT-proBNP assays in the approach to the emergency diagnosis of acute dyspnea.* Journal of Clinical Laboratory Analysis, 2006. **20**(6): p. 227-232.

244. Lainchbury, J.G., et al., *Brain natriuretic peptide and n-terminal brain natriuretic peptide in the diagnosis of heart failure in patients with acute shortness of breath.* J Am Coll Cardiol, 2003. **42**(4): p. 728-735.

245. Ewald, B., et al., *Meta-analysis of B type natriuretic peptide and N-terminal pro B natriuretic peptide in the diagnosis of clinical heart failure and population screening for left ventricular systolic dysfunction.* Internal Medicine Journal, 2008. **38**(2): p. 101-113.

246. Vaes, B., et al., *The accuracy of plasma natriuretic peptide levels for diagnosis of cardiac dysfunction and chronic heart failure in community-dwelling elderly: a systematic review.* Age and Ageing, 2009. **38**(6): p. 655-662.

247. Hildebrandt, P., et al., Age-dependent values of N-terminal pro-B-type natriuretic peptide are superior to a single cut-point for ruling out suspected systolic dysfunction in primary care. European Heart Journal, 2010. **31**(15): p. 1881-1889.

248. Levy, D., et al., *Associations of Plasma Natriuretic Peptide, Adrenomedullin, and Homocysteine Levels With Alterations in Arterial Stiffness: The Framingham Heart Study.* Circulation, 2007. **115**(24): p. 3079-3085.

249. Shroff, G.R., et al., *Relationship between carotid artery stiffness index, BNP and high-sensitivity CRP.* J Hum Hypertens, 2009. **23**(12): p. 783-787.

250. Parliament, *Mental Capacity Act 2005*, 2005, The Stationery Office.

251. Collerton, J., et al., *Health and disease in 85 year olds: baseline findings from the Newcastle 85+ cohort study*. BMJ, 2009. **339**.

252. Collerton, J., et al., *Telomere length is associated with left ventricular function in the oldest old: the Newcastle 85+ study*. European Heart Journal, 2007. **28**(2): p. 172-176.

253. Navroz Masani (Chair), G.W.L.A., Jane Allen, John Chambers, Jane Graham, Richard Jones, Bushra Rana, Richard Steeds. *Echocardiography: Guidelines for Valve Quantification*. [Guidelines] 2009; Available from: http://www.bsecho.org/Guidelines%20for%20Valve%20Quantification.pdf.

254. Navroz Masani (Chair), G.W.L.A., Jane Allen, John Chambers, Jane Graham, Richard Jones, Bushra Rana, Richard Steeds. *Echocardiography: Guidelines for Chamber Quantification*. 2009; Available from: http://www.bsecho.org/Guidelines%20for%20Valve%20Quantification.pdf.

255. Teichholz, L.E., et al., *Problems in echocardiographic volume determinations: Echocardiographic-angiographic correlations in the presence or absence of asynergy*. The American Journal of Cardiology, 1976. **37**(1): p. 7-11.

256. Wallerson, D.C., et al., *Measurement of cardiac output by M-mode and two-dimensional echocardiography: application to patients with hypertension.* European Heart Journal, 1990. **11**(suppl I): p. 67-78.

257. Rich, S., et al., *Determination of left ventricular ejection fraction by visual estimation during real-time two-dimensional echocardiography.* American Heart Journal, 1982. **104**(3): p. 603-606.

258. Amico, A.F., et al., *Superiority of visual versus computerized echocardiographic estimation of radionuclide left ventricular ejection fraction.* American Heart Journal, 1989. **118**(6): p. 1259-1265.

259. Khouri, S.J., et al., *A practical approach to the echocardiographic evaluation of diastolic function.* Journal of the American Society of Echocardiography, 2004. **17**(3): p. 290-297.

260. Ommen, S.R., et al., *Clinical Utility of Doppler Echocardiography and Tissue Doppler Imaging in the Estimation of Left Ventricular Filling Pressures : A Comparative Simultaneous Doppler-Catheterization Study*. Circulation, 2000. **102**(15): p. 1788-1794.

261. Ghio, S., et al., *Prognostic usefulness of the tricuspid annular plane systolic excursion in patients with congestive heart failure secondary to idiopathic or*

ischemic dilated cardiomyopathy. The American Journal of Cardiology, 2000. **85**(7): p. 837-842.

262. Devereux, R.B. and N. Reichek, *Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method.* Circulation, 1977. **55**(4): p. 613-618.
263. Devereux, R.B., et al., *Echocardiographic assessment of left ventricular hypertrophy: Comparison to necropsy findings.* The American Journal of Cardiology, 1986. **57**(6): p. 450-458.
264. Cohen, J., *A coefficient of agreement for nominal scales.* Educational and Psychological measurent, 1960. **20**(1): p. 37-46.
265. Martin Bland, J. and D. Altman, *STATISTICAL METHODS FOR ASSESSING AGREEMENT BETWEEN TWO METHODS OF CLINICAL MEASUREMENT.* The Lancet, 1986. **327**(8476): p. 307-310.
266. Pearson, K. and E.S. Pearson, *On Polychoric Coefficients of Correlation.* Biometrika, 1922. **14**(1/2): p. 127-156.
267. Liang, Y.L., et al., *Non-invasive measurements of arterial structure and function: repeatability, interrelationships and trial sample size.* Clin. Sci., 1998. **95**(6): p. 669-679.
268. Wilkinson, I.B., et al., *Reproducibility of pulse wave velocity and augmentation index measured by pulse wave analysis.* Journal of Hypertension, 1998. **16**(12): p. 2079-2084.
269. Siebenhofer A, K.C., Sutton AJ, Williams B, *The reproducibility of central aortic blood pressure measurements in healthy subjects using applanation tonometry and sphygmocardiography.* JOURNAL OF HUMAN HYPERTENSION, 1999. **13**(9): p. 625-629.
270. Stacey S Hickson, M.B., Jeremy Broad, Alberto P Avolio, Ian B Wilkinson and Carmel M McEniery, *Validity and repeatability of the Vicorder apparatus: a comparison with the SphygmoCor device* HYPERTENSION RESEARCH, 2009. **32**(12): p. 1079-1085.
271. Macfarlane, P.W. and S. Latif, *Automated serial ECG comparison based on the Minnesota code.* Journal of Electrocardiology, 1996. **29 Suppl**: p. 29-34.
272. Prineas R.J., Crow R.S., and B. H., *The Minnesota Code Manual of Electrocardiographic findings. Standards and Procedures for Measurement and Classification*1982, Bristol: John Wrght.

273. DeLong ER, D.D., Clarke-Pearson DL., *Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach.* Biometrics, , 1988. **44**: p. 837–45.

274. National Institute for Health and Clinical Excellence, *The management of atrial fibrillation.* 2006.

275. Gardin, J.M., et al., *Echocardiographic design of a multicenter investigation of free-living elderly subjects: the Cardiovascular Health Study.* Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography, 1992. **5**(1): p. 63-72.

276. van Bemmel, T., et al., *Impact of valvular heart disease on activities of daily living of nonagenarians: the leiden 85-plus study a population based study.* BMC Geriatrics, 2010. **10**(1): p. 17.

277. Abhayaratna, W.P., et al., *Prevalence of heart failure and systolic ventricular dysfunction in older Australians: the Canberra Heart Study.* Med J Aust, 2006. **184**(4): p. 151-4.

278. Halley, C.M., et al., *Mortality Rate in Patients With Diastolic Dysfunction and Normal Systolic Function.* Arch Intern Med, 2011. **171**(12): p. 1082-1087.

279. Galasko, G.I.W., R. Senior, and A. Lahiri, *Ethnic differences in the prevalence and aetiology of left ventricular systolic dysfunction in the community: the Harrow heart failure watch.* Heart, 2005. **91**(5): p. 595-600.

280. Wheeldon, N.M., et al., *Echocardiography in chronic heart failure in the community.* QJM, 1993. **86**(1): p. 17-23.

281. Remes, J., et al., *Validity of clinical diagnosis of heart failure in primary health care.* European Heart Journal, 1991. **12**(3): p. 315-321.

282. Owen, A. and S. Cox, *Diagnosis of heart failure in elderly patients in primary care.* Eur J Heart Fail, 2001. **3**(1): p. 79-81.

283. NHS: The Information Centre for Health and Social Care. *The Quality and Outcomes Framework 2010/11*. 2011; Available from: http://www.ic.nhs.uk/qof.

284. Remes, J., E. Lansimies, and K. Pyorala, *USEFULNESS OF M-MODE ECHOCARDIOGRAPHY IN THE DIAGNOSIS OF HEART-FAILURE.* Cardiology, 1991. **78**(3): p. 267-277.

285. Majeed, A., et al., *Management of heart failure in primary care after implementation of the National Service Framework for Coronary Heart Disease: a cross-sectional study.* Public Health, 2005. **119**(2): p. 105-111.

286. van Bemmel, T., et al., *Impact of valvular heart disease on activities of daily living of nonagenarians: the Leiden 85-plus study a population based study.* BMC Geriatr, 2010. **10**: p. 17.

287. Yusuf, S., et al., *Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial.* Lancet, 2003. **362**(9386): p. 777-81.

288. Massie, B.M., et al., *Irbesartan in patients with heart failure and preserved ejection fraction.* New England Journal of Medicine, 2008. **359**(23): p. 2456-67.

289. Cleland, J.G.F., et al., *The perindopril in elderly people with chronic heart failure (PEP-CHF) study.* European Heart Journal, 2006. **27**(19): p. 2338-45.

290. Kitzman, D.W., et al., *A randomized double-blind trial of enalapril in older patients with heart failure and preserved ejection fraction: effects on exercise tolerance and arterial distensibility.* Circ Heart Fail, 2010. **3**(4): p. 477-85.

291. Fonarow, G.C., et al., *Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry.* Journal of the American College of Cardiology, 2007. **50**(8): p. 768-77.

292. Hernandez, A.F., et al., *Clinical effectiveness of beta-blockers in heart failure: findings from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) Registry.* Journal of the American College of Cardiology, 2009. **53**(2): p. 184-92.

293. Shah, R.V., A.S. Desai, and M.M. Givertz, *The effect of renin-angiotensin system inhibitors on mortality and heart failure hospitalization in patients with heart failure and preserved ejection fraction: a systematic review and meta-analysis.* Journal of Cardiac Failure, 2010. **16**(3): p. 260-7.

294. Tehrani, F., et al., *Value of medical therapy in patients >80 years of age with heart failure and preserved ejection fraction.[Erratum appears in Am J Cardiol. 2009 Sep 1;104(5):744].* American Journal of Cardiology, 2009. **103**(6): p. 829-33.

295. NHS National Institute for Health and Clinical Excellence. *Chronic heart failure: management of chronic heart failure in adults in primary and secondary care*. 2010 2010 [cited 2011; Available from: http://www.nice.org.uk/guidance/index.jsp?action=byID&o=13099.

296. *Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group.* New England Journal of Medicine, 1987. **316**(23): p. 1429-35.

297. *Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators.* New England Journal of Medicine, 1991. **325**(5): p. 293-302.

298. *Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The SOLVD Investigattors.[Erratum appears in N Engl J Med 1992 Dec 10;327(24):1768].* New England Journal of Medicine, 1992. **327**(10): p. 685-91.

299. Garg, R., et al., *Overview of Randomized Trials of Angiotensin-Converting Enzyme Inhibitors on Mortality and Morbidity in Patients With Heart Failure.* JAMA, 1995. **273**(18): p. 1450-1456.

300. Pitt, B., et al., *Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial--the Losartan Heart Failure Survival Study ELITE II.* Lancet, 2000. **355**(9215): p. 1582-7.

301. Cohen-Solal, A., et al., *Benefits and safety of candesartan treatment in heart failure are independent of age: insights from the Candesartan in Heart failure--Assessment of Reduction in Mortality and morbidity programme.* European Heart Journal, 2008. **29**(24): p. 3022-8.

302. *The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial.* Lancet, 1999. **353**(9146): p. 9-13.

303. Packer, M., et al., *The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group.* New England Journal of Medicine, 1996. **334**(21): p. 1349-55.

304. *Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF).* Lancet, 1999. **353**(9169): p. 2001-7.

305. Hjalmarson, A., et al., *Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group.* JAMA, 2000. **283**(10): p. 1295-302.

306. Flather, M.D., et al., *Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS).* European Heart Journal, 2005. **26**(3): p. 215-25.

307. Pitt, B., et al., *The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators.* New England Journal of Medicine, 1999. **341**(10): p. 709-17.

308. Lam, C.S.P., et al., *Cardiac Dysfunction and Noncardiac Dysfunction as Precursors of Heart Failure With Reduced and Preserved Ejection Fraction in the Community.* Circulation, 2011. **124**(1): p. 24-30.

309. Kane, G.C., et al., *Progression of Left Ventricular Diastolic Dysfunction and Risk of Heart Failure.* JAMA, 2011. **306**(8): p. 856-863.

310. Aurigemma, G.P., et al., *Predictive value of systolic and diastolic function for incident congestive heart failure in the elderly: the cardiovascular health study.* Journal of the American College of Cardiology, 2001. **37**(4): p. 1042-8.

311. Pfeffer, M.A., et al., *Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators.* New England Journal of Medicine, 1992. **327**(10): p. 669-77.

312. Hunt, S.A., et al., *2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation.* Circulation, 2009. **119**(14): p. e391-479.

313. von Haehling, S., et al., *Anaemia among patients with heart failure and preserved or reduced ejection fraction: results from the SENIORS study.* Eur J Heart Fail, 2011. **13**(6): p. 656-663.

314. Mogensen, U.M., et al., *Clinical characteristics and major comorbidities in heart failure patients more than 85 years of age compared with younger age groups.* Eur J Heart Fail, 2011. **13**(11): p. 1216-1223.

315. Ahluwalia SC, G.C., Chaudhry SI, Ning YM, Leo-Summers L, Van Ness PH, Fried TR,, *Impact of Comorbidity on Mortality Among Older Persons with Advanced Heart Failure.* J Gen Intern Med, 2011.

316. Collerton, J., et al., *Health and disease in 85 year olds: baseline findings from the Newcastle 85+ cohort study.* BMJ, 2009. **339**: p. b4904.
317. Nielsen, O.W., et al., *Value of N-terminal pro brain natriuretic peptide in the elderly: data from the prospective Copenhagen Hospital Heart Failure study (CHHF).* European Journal of Heart Failure, 2004. **6**(3): p. 275-279.
318. Vaes, B., et al., *Diagnostic accuracy of plasma NT-proBNP levels for excluding cardiac abnormalities in the very elderly.* BMC Geriatrics, 2010. **10**(1): p. 85.
319. Vasan, R.S., et al., *Plasma Natriuretic Peptides for Community Screening for Left Ventricular Hypertrophy and Systolic Dysfunction.* JAMA: The Journal of the American Medical Association, 2002. **288**(10): p. 1252-1259.
320. Blondé-Cynober, F., et al., *Diagnostic and prognostic value of brain natriuretic peptide (BNP) concentrations in very elderly heart disease patients: Specific geriatric cut-off and impacts of age, gender, renal dysfunction, and nutritional status.* Arch Gerontol Geriatr, 2011. **52**(1): p. 106-110.
321. Kuster, G.M., et al., *B-type natriuretic peptide for diagnosis and treatment of congestive heart disease.* SWISS MED WKLY, 2003(103): p. 623-628.
322. Jourdain, P., et al., *Bedside B-type natriuretic peptide and functional capacity in chronic heart failure.* European Journal of Heart Failure, 2003. **5**(2): p. 155-160.
323. Frankenstein, L., et al., *The prognostic value of individual NT-proBNP values in chronic heart failure does not change with advancing age.* Heart, 2009. **95**(10): p. 825-829.
324. Daniels, L.B. and A.S. Maisel, *Natriuretic peptides.* Journal of the American College of Cardiology, 2007. **50**(25): p. 2357-2368.
325. Zaphiriou, A., et al., *The diagnostic accuracy of plasma BNP and NTproBNP in patients referred from primary care with suspected heart failure: Results of the UK natriuretic peptide study.* European Journal of Heart Failure, 2005. **7**(4): p. 537-541.
326. Cowie, M.R., et al., *Clinical applications of B-type natriuretic peptide (BNP) testing.* European Heart Journal, 2003. **24**(19): p. 1710-1718.
327. Fuat, A., et al., *The diagnostic accuracy and utility of a B-type natriuretic peptide test in a community population of patients with suspected heart failure.* British Journal of General Practice. **56**(526): p. 327-333.

328. Gustafsson, F., et al., *Diagnostic and Prognostic Performance of N-Terminal ProBNP in Primary Care Patients With Suspected Heart Failure.* Journal of Cardiac Failure, 2005. **11**(5, Supplement): p. S15-S20.

329. Redfield, M.M., et al., *Plasma Brain Natriuretic Peptide to Detect Preclinical Ventricular Systolic or Diastolic Dysfunction.* Circulation, 2004. **109**(25): p. 3176-3181.

330. Hetmanski, D.J., et al., *Failure of plasma brain natriuretic peptide to identify left ventricular systolic dysfunction in the community.* Heart, 2000. **84**(4): p. 440-441.

331. Schnabel, R., et al., *Analysis of N-terminal-pro-brain natriuretic peptide and C-reactive protein for risk stratification in stable and unstable coronary artery disease: results from the AtheroGene study.* European Heart Journal, 2005. **26**(3): p. 241-249.

332. Richards, M. and R.W. Troughton, *NT-proBNP in heart failure: therapy decisions and monitoring.* European Journal of Heart Failure, 2004. **6**(3): p. 351-354.

333. Silver, M.A., et al., *BNP Consensus Panel 2004: A Clinical Approach for the Diagnostic, Prognostic, Screening, Treatment Monitoring, and Therapeutic Roles of Natriuretic Peptides in Cardiovascular Diseases.* Congestive Heart Failure, 2004. **10**: p. 1-30.

334. Takeda, Y., et al., *Effects of carvedilol on plasma B-type natriuretic peptide concentration and symptoms in patients with heart failure and preserved ejection fraction.* American Journal of Cardiology, 2004. **94**(4): p. 448-453.

335. Murdoch, D.R., et al., *Brain natriuretic peptide is stable in whole blood and can be measured using a simple rapid assay: Implications for clinical practice.* Heart, 1997. **78**(6): p. 594-597.

336. Jong, P., et al., *Effect of enalapril on 12-year survival and life expectancy in patients with left ventricular systolic dysfunction: a follow-up study.* The Lancet, 2003. **361**(9372): p. 1843-1848.

337. Moukarbel, G. and S. Solomon, *Treatment of asymptomatic left ventricular dysfunction.* Current Treatment Options in Cardiovascular Medicine, 2008. **10**(6): p. 476-485.

338. Swedberg, K., et al., *Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005).* European Heart Journal, 2005. **26**(11): p. 1115-1140.

339. Garg, R., et al., *Overview of Randomized Trials of Angiotensin-Converting Enzyme Inhibitors on Mortality and Morbidity in Patients With Heart Failure.* JAMA: The Journal of the American Medical Association, 1995. **273**(18): p. 1450-1456.

340. Heidenreich, P.A., T.T. Lee, and B.M. Massie, *Effect of Beta-Blockade on Mortality in Patients With Heart Failure: A Meta-Analysis of Randomized Clinical Trials.* Journal of the American College of Cardiology, 1997. **30**(1): p. 27-34.

341. Gupta, S., M.H. Drazner, and J.A. de Lemos, *Newer Biomarkers in Heart Failure.* Heart Failure Clinics, 2009. **5**(4): p. 579-588.

342. Lok, D.J.A., et al., *Prognostic value of galectin-3, a novel marker of fibrosis,in patients with chronic heart failure: Data from the DEAL-HF study.* Clinical Research in Cardiology, 2010. **99**(5): p. 323-328.

343. Tereschenko, S.N. and I.V. Zhirov, *Chronic cardiac failure in the xxi century.* Ter Arkh, 2011. **83**(9): p. 60-66.

344. Senior, R., et al., *Screening for left ventricular dysfunction in the community: role of hand held echocardiography and brain natriuretic peptides.* Heart, 2003. **89**(suppl 3): p. iii24-iii28.

345. Jeyaseelan, S., et al., *Agreement between community echocardiography and hospital echocardiography in patients suspected of having left ventricular systolic dysfunction.* Postgraduate Medical Journal, 2005. **81**(962): p. 777-779.

346. Galasko, G.I.W., et al., *What is the most cost-effective strategy to screen for left ventricular systolic dysfunction: natriuretic peptides, the electrocardiogram, hand-held echocardiography, traditional echocardiography, or their combination?* European Heart Journal, 2006. **27**(2): p. 193-200.

347. John J, A., *Screening for Left Ventricular Systolic Dysfunction: Is Imaging a Solution?* JACC: Cardiovascular Imaging, 2010. **3**(4): p. 421-428.

348. deFilippi, C.R., et al., *Left Ventricular Ejection Fraction Assessment in Older Adults: An Adjunct to Natriuretic Peptide Testing to Identify Risk of New-Onset Heart Failure and Cardiovascular Death?* J Am Coll Cardiol, 2011. **58**(14): p. 1497-1506.

349. Suominen, V., et al., *Peripheral arterial disease and its clinical significance in nonagenarians.* Aging Clinical and Experimental Research, 2008. **20**: p. 211-215.

350. Criqui, M.H., et al., *The prevalence of peripheral arterial disease in a defined population.* Circulation, 1985. **71**(3): p. 510-515.

351. Diehm, C., et al., *High prevalence of peripheral arterial disease and co-morbidity in 6880 primary care patients: cross-sectional study.* Atherosclerosis, 2004. **172**(1): p. 95-105.

352. Bergiers, S., B. Vaes, and J. Degryse, *To screen or not to screen for peripheral arterial disease in subjects aged 80 and over in primary health care: a cross-sectional analysis from the BELFRAIL study.* BMC Family Practice, 2011. **12**(1): p. 39.

353. Hirsch, A.T., et al., *Peripheral Arterial Disease Detection, Awareness, and Treatment in Primary Care.* JAMA: The Journal of the American Medical Association, 2001. **286**(11): p. 1317-1324.

354. Sigvant, B., et al., *A population-based study of peripheral arterial disease prevalence with special focus on critical limb ischemia and sex differences.* Journal of Vascular Surgery, 2007. **45**(6): p. 1185-1191.

355. Hirsch, A.T., et al., *ACC/AHA 2005 Practice Guidelines for the Management of Patients With Peripheral Arterial Disease (Lower Extremity, Renal, Mesenteric, and Abdominal Aortic).* Circulation, 2006. **113**(11): p. e463-e654.

356. Norgren, L., et al., *Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II).* Journal of vascular surgery : official publication, the Society for Vascular Surgery [and] International Society for Cardiovascular Surgery, North American Chapter, 2007. **45**(1): p. S5-S67.

357. Leng, G.C., et al., *Incidence, Natural History and Cardiovascular Events in Symptomatic and Asymptomatic Peripheral Arterial Disease in the General Population.* International Journal of Epidemiology, 1996. **25**(6): p. 1172-1181.

358. Hooi, J.D., et al., *Asymptomatic peripheral arterial occlusive disease predicted cardiovascular morbidity and mortality in a 7-year follow-up study.* Journal of Clinical Epidemiology, 2004. **57**(3): p. 294-300.

359. Diehm, C., et al., *Mortality and Vascular Morbidity in Older Adults With Asymptomatic Versus Symptomatic Peripheral Artery Disease.* Circulation, 2009. **120**(21): p. 2053-2061.

360. Doobay, A.V. and S.S. Anand, *Sensitivity and Specificity of the Ankle–Brachial Index to Predict Future Cardiovascular Outcomes.* Arteriosclerosis, Thrombosis, and Vascular Biology, 2005. **25**(7): p. 1463-1469.

361. Ankle Brachial Index, C., *Ankle Brachial Index Combined With Framingham Risk Score to Predict Cardiovascular Events and Mortality.* JAMA: The Journal of the American Medical Association, 2008. **300**(2): p. 197-208.

362. Bemmel, T.v., et al., *In a population-based prospective study, no association between high blood pressure and mortality after age 85 years.* Journal of Hypertension, 2006. **24**(2): p. 287-292.

363. Oates, D.J., et al., *Blood Pressure and Survival in the Oldest Old.* J Am Geriatr Soc, 2007. **55**(3): p. 383-388.

364. Rastas, S., et al., *Association Between Blood Pressure and Survival over 9 Years in a General Population Aged 85 and Older.* J Am Geriatr Soc, 2006. **54**(6): p. 912-918.

365. Wouter de, R., et al., *Use of Framingham risk score and new biomarkers to predict cardiovascular mortality in older people: population based observational cohort study.* BMJ, 2009. **338**.

366. Perlstein, T.S. and M.A. Creager, *The Ankle-Brachial Index as a Biomarker of Cardiovascular Risk.* Circulation, 2009. **120**(21): p. 2033-2035.

367. Hirsch, A.T., et al., *ACC/AHA 2005 Guidelines for the Management of Patients With Peripheral Arterial Disease (Lower Extremity, Renal, Mesenteric, and Abdominal Aortic): A Collaborative Report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease).* J Am Coll Cardiol, 2006. **47**(6): p. e1-192.

368. Scottish Intercollegiate Guidelines Network, *Diagnosis and management of peripheral arterial disease.* 2006.

369. Olin, J.W., et al., *ACCF/AHA/ACR/SCAI/SIR/SVM/SVN/SVS 2010 Performance Measures for Adults With Peripheral Artery Disease.* J Am Coll Cardiol, 2010. **56**(25): p. 2147-2181.

370. Antithrombotic Trialists Collaboration, *Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients.* BMJ, 2002. **324**(7329): p. 71-86.

371. CAPRIE Steering Committee, *A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE).* The Lancet, 1996. **348**(9038): p. 1329-1339.

372. Bhatt, D.L. and E.J. Topol, *Clopidogrel added to aspirin versus aspirin alone in secondary prevention and high-risk primary prevention: Rationale and design of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial.* American Heart Journal, 2004. **148**(2): p. 263-268.

373. Heart Protection Study Collaborative Group, *Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular and other major vascular outcomes in 20,536 people with peripheral arterial disease and other high-risk conditions.* Journal of vascular surgery : official publication, the Society for Vascular Surgery [and] International Society for Cardiovascular Surgery, North American Chapter, 2007. **45**(4): p. 645-654.e1.

374. Lange, S., et al., *High Prevalence of Peripheral Arterial Disease and Low Treatment Rates in Elderly Primary Care Patients with Diabetes.* Exp Clin Endocrinol Diabetes, 2004. **112**(10): p. 566,573.

375. Oka, R.K., et al., *Suboptimal intensity of risk factor modification in PAD.* Vascular Medicine, 2005. **10**(2): p. 91-96.

376. Conte, M.S., et al., *Risk factors, medical therapies and perioperative events in limb salvage surgery: Observations from the PREVENT III multicenter trial.* Journal of Vascular Surgery, 2005. **42**(3): p. 456-464.

377. Kundhal, K.K., et al., *Patterns of medical therapy in patients with peripheral artery disease in a tertiary care centre in Canada.* The Canadian journal of cardiology, 2007. **23**(5): p. 357-361.

378. Singer, D.E., et al., *Antithrombotic Therapy in Atrial Fibrillation*.* Chest, 2008. **133**(6 suppl): p. 546S-592S.

379. Rastas, S., et al., *Atrial Fibrillation, Stroke, and Cognition.* Stroke, 2007. **38**(5): p. 1454-1460.

380. Heeringa, J., et al., *Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study*. European Heart Journal, 2006. **27**(8): p. 949-953.

381. Go, A.S., et al., *Prevalence of Diagnosed Atrial Fibrillation in Adults.* JAMA: The Journal of the American Medical Association, 2001. **285**(18): p. 2370-2375.
382. G Y Lip, D.J.G., M Nazir, D G Beevers, D L Child, R I Fletcher, *A survey of atrial fibrillation in general practice: the West Birmingham Atrial Fibrillation Project.* British journal of general practice 1997. **47**(418): p. 285-289.
383. Israel, C.W., et al., *Long-term risk of recurrent atrial fibrillation as documented by an implantable monitoring device: Implications for optimal patient care.* J Am Coll Cardiol, 2004. **43**(1): p. 47-52.
384. Sudlow, M., R. Thomson, and R. Kenny, *Prevalence of atrial fibrillation and eligibility for anticoagulants in the community.* The Lancet, 1998. **352**(9135): p. 1167-1171.
385. McCormick, D., et al., *Prevalence and Quality of Warfarin Use for Patients With Atrial Fibrillation in the Long-term Care Setting.* Arch Intern Med, 2001. **161**(20): p. 2458-2463.
386. Go, A.S., et al., *Warfarin Use among Ambulatory Patients with Nonvalvular Atrial Fibrillation: The AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study.* Annals of Internal Medicine, 1999. **131**(12): p. 927-934.
387. Friberg, L., et al., *Stroke prophylaxis in atrial fibrillation: who gets it and who does not?* European Heart Journal, 2006. **27**(16): p. 1954-1964.
388. Aliot, E., et al., *An international survey of physician and patient understanding, perception, and attitudes to atrial fibrillation and its contribution to cardiovascular disease morbidity and mortality.* Europace, 2010. **12**(5): p. 626-633.
389. Lip, G.Y.H., et al., *Oral anticoagulation in atrial fibrillation: A pan-European patient survey.* European Journal of Internal Medicine, 2007. **18**(3): p. 202-208.
390. Kutner, M., G. Nixon, and F. Silverstone, *Physicians' Attitudes Toward Oral Anticoagulants and Antiplatelet Agents for Stroke Prevention in Elderly Patients With Atrial Fibrillation.* Arch Intern Med, 1991. **151**(10): p. 1950-1953.
391. Fuster, V., et al., *ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation.* Circulation, 2006. **114**(7): p. e257-e354.
392. Gage, B.F., et al., *Validation of Clinical Classification Schemes for Predicting Stroke.* JAMA: The Journal of the American Medical Association, 2001. **285**(22): p. 2864-2870.

393. Lip, G.Y.H., et al., *Refining Clinical Risk Stratification for Predicting Stroke and Thromboembolism in Atrial Fibrillation Using a Novel Risk Factor-Based Approach.* Chest, 2010. **137**(2): p. 263-272.

394. Lip, G.Y.H. and J.L. Halperin, *Improving Stroke Risk Stratification in Atrial Fibrillation.* The American Journal of Medicine, 2010. **123**(6): p. 484-488.

395. Aguilar, M., R. Hart, and L. Pearce, *Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks.* . Cochrane Database of Systematic Reviews, 2003(3).

396. Lin, H.-J., et al., *Stroke Severity in Atrial Fibrillation: The Framingham Study.* Stroke, 1996. **27**(10): p. 1760-1764.

397. Mant, J., et al., *Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial.* The Lancet, 2007. **370**(9586): p. 493-503.

398. Rash, A., et al., *A randomised controlled trial of warfarin versus aspirin for stroke prevention in octogenarians with atrial fibrillation (WASPO).* Age and Ageing, 2007. **36**(2): p. 151-156.

399. Fang, M.C., J. Chen, and M.W. Rich, *Atrial Fibrillation in the Elderly.* The American Journal of Medicine, 2007. **120**(6): p. 481-487.

400. Connolly, S.J., et al., *Dabigatran versus Warfarin in Patients with Atrial Fibrillation.* New England Journal of Medicine, 2009. **361**(12): p. 1139-1151.

401. Wann, L.S., et al., *2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation (Update on Dabigatran): A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines.* Heart rhythm : the official journal of the Heart Rhythm Society, 2011. **8**(3): p. e1-e8.

402. Developed with the special contribution of the European Heart Rhythm, A., et al., *Guidelines for the management of atrial fibrillation.* European Heart Journal, 2010. **31**(19): p. 2369-2429.

403. Cairns, J.A., et al., *Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2010: Prevention of Stroke and Systemic Thromboembolism in Atrial Fibrillation and Flutter.* The Canadian journal of cardiology, 2011. **27**(1): p. 74-90.

404. Investigators, S.E.S.C.f.t.S.V., *Ximelagatran vs Warfarin for Stroke Prevention in Patients With Nonvalvular Atrial Fibrillation.* JAMA: The Journal of the American Medical Association, 2005. **293**(6): p. 690-698.

405. Raymond, I., et al., *Prevalence of impaired left ventricular systolic function and heart failure in a middle aged and elderly urban population segment of Copenhagen.* Heart, 2003. **89**(12): p. 1422-9.

406. Abhayaratna, W.P., et al., *Prevalence of heart failure and systolic ventricular dysfunction in older Australians: the Canberra Heart Study.* Medical Journal of Australia, 2006. **184**(4): p. 151-4.

407. Davies, M., et al., *Prevalence of left-ventricular systolic dysfunction and heart failure in the Echocardiographic Heart of England Screening study: a population based study.* Lancet, 2001. **358**(9280): p. 439-44.

408. Gardin, J.M., et al., *Sex, age, and disease affect echocardiographic left ventricular mass and systolic function in the free-living elderly. The Cardiovascular Health Study.* Circulation, 1995. **91**(6): p. 1739-48.

409. Collerton, J., et al., *The Newcastle 85+ study: biological, clinical and psychosocial factors associated with healthy ageing: study protocol.* BMC Geriatr, 2007. **7**: p. 14.

410. Simpson, C.F., et al., *Agreement between self-report of disease diagnoses and medical record validation in disabled older women: factors that modify agreement.* J Am Geriatr Soc, 2004. **52**(1): p. 123-7.

411. Kriegsman, D.M., et al., *Self-reports and general practitioner information on the presence of chronic diseases in community dwelling elderly. A study on the accuracy of patients' self-reports and on determinants of inaccuracy.* J Clin Epidemiol, 1996. **49**(12): p. 1407-17.

412. Office for National Statistics, *2001 Census. Standard tables for health areas* 2004.

413. Kannel, W.B. and E.J. Benjamin, *Status of the Epidemiology of Atrial Fibrillation.* The Medical clinics of North America, 2008. **92**(1): p. 17-40.

414. Stewart, S., et al., *A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study.* The American Journal of Medicine, 2002. **113**(5): p. 359-364.

415. Abhayaratna, W.P., et al., *Population-based detection of systolic and diastolic dysfunction with amino-terminal pro-B-type natriuretic peptide.* American Heart Journal, 2006. **152**(5): p. 941-8.

416. Costello-Boerrigter, L.C., et al., *Amino-terminal pro-B-type natriuretic peptide and B-type natriuretic peptide in the general community: determinants and detection of left ventricular dysfunction.* Journal of the American College of Cardiology, 2006. **47**(2): p. 345-53.

417. Hedberg, P., et al., *Electrocardiogram and B-type natriuretic peptide as screening tools for left ventricular systolic dysfunction in a population-based sample of 75-year-old men and women.* American Heart Journal, 2004. **148**(3): p. 524-9.

418. Vaes, B., et al., *Diagnostic accuracy of plasma NT-proBNP levels for excluding cardiac abnormalities in the very elderly.* BMC Geriatrics, 2010. **10**: p. 85.

419. McDonagh, T.A., et al., *NT-proBNP and the diagnosis of heart failure: a pooled analysis of three European epidemiological studies.* Eur J Heart Fail, 2004. **6**(3): p. 269-73.

420. Redfield, M.M., et al., *Plasma brain natriuretic peptide concentration: impact of age and gender.* Journal of the American College of Cardiology, 2002. **40**(5): p. 976-82.