Frailty, Comorbidity, Cardiovascular Disease Burden and Quality of Life in Older Patients with Non ST Elevation Acute Coronary Syndrome Managed by Invasive Strategy

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Abstract

Background: Acute coronary syndrome among older patients is associated with increased morbidity and mortality. In developed countries, there is an increase in the number of older patients managed by invasive strategy. Frailty is emerging as an independent marker of adverse cardiovascular outcomes and its prevalence among older patients undergoing invasive treatment in the setting of Non ST Elevation Acute Coronary Syndrome (NSTEACS) is not known. The impact of frailty, co-morbidity and cardiovascular status on cardiovascular outcomes and quality of life in older patients with NSTEACS managed by invasive strategy is not known.

Aims:

1. To determine the prevalence of frailty and compare frailty status by Fried and Rockwood Frailty scales

2. To assess adverse cardiovascular outcomes at one month according to frailty status in older NSTEACS patients managed by invasive strategy

3. To assess cardiovascular disease burden in relation to frailty status

4. To assess comorbidity burden according to frailty status and asses its relation to adverse CV outcomes at one month

5. To evaluate cardiac symptom burden and the quality of life in older NSTEACS patients managed by invasive strategy

6. Assess cognitive function in older NSTEACS patients and its association with frailty

Methods: This prospective observational study was conducted in Freeman Hospital, Newcastle upon Tyne. The study participants underwent invasive management of NSTEACS as per the guidelines. Fried Frailty Classification (FFC) was used to group patients as frail (F), pre-frail (PF) and robust (R); and Rockwood Frailty Classification (RFC) grouped patients as frail (F) and non-frail (NF). Charlson co-morbidity index was calculated to quantify co-morbidity burden. To assess the cognitive status of patients during admission, the Montreal Cognitive Assessment was utilised. Arterial stiffness, peripheral arterial tonometry, carotid intima media thickness (CIMT) and left ventricular function were evaluated for cardiovascular status assessment. Quality of life was assessed using Short Form 36 and EuroQoL questionnaires. All these assessments

were done prior to invasive management. Procedural complications, in-hospital complications and cardiovascular outcomes at 30 days were recorded.

Results: Frailty was three times more common by FFC (30.8%) tool compared to RFC (10.1%). There was no significant difference by frailty status in adverse CV outcomes, in-hospital (9.6% vs. 4.2% vs. 2.2%, p=0.157 for F vs. PF vs. R by FFC and 4.2% vs. 5.6%, p=1.0 for F vs. NF by RFC) and at 30-days (11.0% vs. 5.9% vs. 4.3%, p=0.302 and 8.3% vs. 7.0%, p=0.685 respectively). Measures of arterial stiffness, endothelial dysfunction and CIMT did not vary between the patient groups. LV systolic function was similar in frail patients, but increased E/e' was noted in frail patients suggestive of diastolic dysfunction. Frail patients had worsening dyspnoea severity by both frailty classifications but angina was worse in frail patients by RFC alone. Higher comorbidity burden was noted in frail patients by both FFC (43.8% vs. 24.6% vs. 13.0%, p=0.001 respectively) and RFC (54.2% vs 25.4%, p=0.007) but did not have an association with rate of adverse CV outcomes. Subclinical cognitive impairment was more common in frail patients by Fried (67.2 % vs. 39.6% vs. 42.2%, p=0.002) and Rockwood (86.4% vs. 31.8%, P<0.001) classification. Physical components of QoL measures by EQ5D and SF-36 were lower in frail patients by both frailty classification but mental component by SF-36 was lower in frail patients by RFC only.

Conclusion: Frailty was common among older patients with NSTAECS managed by invasive treatment strategy and the prevalence of frailty varied according to the assessment tool used. Frailty was not associated with short-term adverse CV outcomes, but long-term outcomes need to be studied. Higher comorbidity burden, subclinical cognitive impairment and poor QoL measures were more prevalent in frail patients. Vascular status measures like arterial stiffness, endothelial dysfunction and CIMT were not associated with frailty. Dedicated frailty assessment tool for older patients with coronary artery disease need to be developed. Frail patients may stand to benefit more from contemporary management strategy in the short term and frailty should not preclude them from being offered invasive treatment for coronary artery disease.

Dedication

To my parents, wife, daughters, teachers and patients

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Declaration

I declare that this thesis submitted in partial fulfilment of the requirements of the Doctor of Medicine to Newcastle University is my original work and not submitted elsewhere for a degree or diploma. The study and protocol was designed by chief investigator Dr Vijay Kunadian, as a prospective observational study and my thesis project was a part of this study. I was responsible for the recruitment of patients, data collection, data management, analysis of the data and research governance. I have appropriately acknowledged contributions by others.

Contents

List of Tables

List of Figures

Abbreviations

ACE-i	Angiotensin Converting Enzyme Inhibitor
ACS	Acute Coronary Syndrome
ADL	Activities of Daily Living
ADMA	Asymmetric Dimethyl Arginine
ARB	Angiotensin II Receptor Blocker
AUC	Area under the Curve
BES	Biolimus-Eluting Stent
BMI	Body Mass Index
BMS	Bare Metal Stent
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CBF	Coronary Blood Flow
CCA	Common Carotid Artery
CCI	Charlson Comorbidity Index
CCS	Canadian Cardiovascular Society
CFR	Coronary Flow Reserve
cGMP	cyclic Guanosine Monophosphate
CHD	Coronary Heart Disease
CI	Confidence Interval
CIMT	Carotid Intima Media Thickness
CRP	C-reactive Protein
CVD	Cardiovascular Disease
CVR	Coronary Vascular Resistance
CSHA	Canadian Study of Health and Aging
CURE	Clopidogrel in Unstable Angina to Prevent Recurrent Events
CVA	Cerebrovascular Accident
CVD	Cardiovascular Disease
eNOS	endothelial Nitric Oxide Synthase

EFS	Edmonton Frailty Scale
FATE	Fire fighters And Their Endothelium study
FFC	Fried Frailty Classification
FMD	Flow-mediated Dilatation
GFR	Glomerular Filtration Rate
GRACE	Global Registry of Acute Coronary Events
HOPE	Heart Outcomes Prevention Evaluation study
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
ICAM	Intercellular Adhesion Molecule
IHD	Ischemic Heart Disease
IL-6	Interleukin 6
LFMC	Low Flow Mediated Constriction
LDF	Laser Doppler Flowmetry
MAP	Mean Arterial Pressure
MCP	Macrophage Chemo attractant Peptide
MACE	Major Adverse Cardiovascular Events
MESA	Multi-Ethnic study of Atherosclerosis
MI	Myocardial Infarction
MINAP	Myocardial Ischaemia National Audit Project
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
NSTEACS	Non ST Elevation Acute Coronary Syndrome
NSTEMI	Non ST Elevation Myocardial Infarction
NYHA	New York Heart Association
NO	Nitric Oxide
OR	Odds Ratio
PAT	Peripheral Arterial Tonometry

PAI	Plasminogen Activator Inhibitor
PCI	Percutaneous Coronary Intervention
PES	Paclitaxel-Eluting Stent
PET	Positron Emission Tomography
PWA	Pulse Wave Analysis
PWV	Pulse Wave Velocity
RCT	Randomised Control Trial
RFC	Rockwood Frailty Classification
RHI	Reactive Hyperaemia Index
ROS	Reactive Oxygen Species
RR	Relative Risk
SCI	Simple Comorbidity Index
SD	Standard Deviation
SES	Sirolimus-Eluting Stent
SOD	Superoxide Dismutase
STEMI	ST Elevation Myocardial Infarction
TNF∞	Tumor Necrosis Factor alpha
TREND	Trial on Reversing ENdothelial Dysfunction
TTE	Transthoracic Echocardiogram
UA	Unstable Angina
VAS	Visual Analog Scale
VACM	Vascular Adhesion Molecule
VEGF	Vascular Endothelial Growth Factor
VTI	Velocity Time Integral
ZES	Zotarolimus-Eluting Ste

List of Publications

Abstracts

Major adverse cardiovascular events at 30-days were not significantly different between frail and non-frail older (≥75 years) patients with non ST elevation acute coronary syndrome managed by invasive strategy: an analysis from the ICON1 study

Veerasamy M, Sinclair H, Bagnall A, Das R, Ahmed J, Egred M, Edwards R, Zaman A, Purcell I, Qiu W, Kunadian V

Heart 2015; 101:A3-A4 (British Cardiovascular Society Conference 2015)

Frailty is associated with undiagnosed early cognitive impairment in older patients (≥75 years) with non ST elevation acute coronary syndrome managed by invasive strategy

Veerasamy M, Sinclair H, Qiu W, Kunadian V

Heart 2015; 101:A4 (British Cardiovascular Society Conference 2015)

Frailty is associated with increased GRACE risk score in older patients with non-ST elevation acute coronary syndrome

Hannah Sinclair H, **Veerasamy M**, Teoh X, Lima Jr JAC, Qiu W, Kunadian V

European Heart Journal, 2015 36(supplement 1):71-72 (European Society for Cardiology Conference 2014)

Frailty status varies by fried and rockwood frailty assessment tools in older patients with non ST elevation acute coronary syndrome managed by invasive Strategy

Veerasamy M, Sinclair H, Qiu W, Kunadian V

Journal of American College of Cardiology, March 17 2015, Volume 65, 10S

(American College of Cardiology Conference 2015)

Left ventricular function and severity of dyspnoea according to frailty status in older patients (≥75 Years) with non ST elevation myocardial infarction managed by invasive strategy

Veerasamy M, Sinclair H, Qiu W, Kunadian V

Journal of American College of Cardiology, March 17 2015, Volume 65, 10S

(American College of Cardiology Conference 2015)

Procedural and in-hospital complications, time from presentation to invasive treatment and length of hospital stay in frail versus non-frail older (≥75 years) patients with non ST elevation acute coronary syndrome

Veerasamy M, Sinclair H, Qiu W, Kunadian V

Journal of American College of Cardiology, March 17 2015, Volume 65, 10S

(American College of Cardiology Conference 2015)

Prevalence of vitamin D deficiency is more common among frail older patients (≥75 Years) with non ST elevation myocardial infarction managed by invasive strategy

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Association of Aging, Arterial Stiffness and Cardiovascular Disease

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Cardiology in Review 2015 Jan-Feb; 23(1):26-32

Endothelial Dysfunction and Coronary Artery Disease: A State of the Art Review

Veerasamy M, Bagnall A, Neely D, John Allen J, Sinclair H, Kunadian V

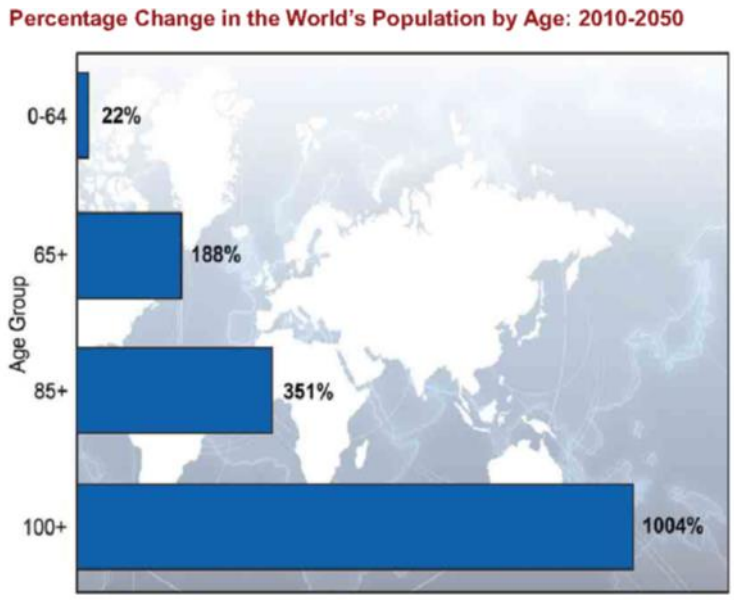
Cardiology in Review 2015 May-Jun; 23(3):119-29

CHAPTER 1: INTRODUCTION

1.1 Importance of understanding Health of Ageing Population

Life expectancy now is the longest due to control and eradication of communicable diseases in the last century. This has resulted in ageing population with oldest old (>85 years) making up 12% of proportion of over 65years old in the developed countries. 85 years and over population is projected to increase by 351 percent by 2050 (**Figure 1.1**). ('Global Health and Ageing,' 2011). It has to be mentioned that the functional status of older people is diverse and not directly related to the chronological age. Advancing age is associated with increased prevalence of non-communicable diseases like cardiovascular disease, dementia and cancer. This has huge impact on health care infrastructure and social care. More importantly there is evidence gap in caring for these older patients in hospitals. It is not known whether longer life expectancy translates into better health and wellbeing, independence and good quality of life. The main component of the policy framework of active ageing by world health organisation (WHO) is to prevent and reduce excess disabilities and chronic diseases, so poor health need not be the dominant and limiting factor of old age. ('WHO World Report on Ageing and Health,' 2015)

Figure 1.1: Projected change in older age population by 2050



Source: United Nations, *World Population Prospects: The 2010 Revision.*
Available at: http://esa.un.org/unpd/wpp.

Ischemic heart disease is a leading cause of mortality and morbidity especially in old age. Limited evidence is currently available in the management of these older patients. It is important to understand the interplay between older age, frailty, comorbidity and ischemic heart disease to better treat these patients with IHD. In trying to do so, understanding older patients in the context of non ST elevation acute coronary syndrome in relation to invasive treatment, comorbidities and frailty is the main aim of this thesis. Moreover subclinical cognitive impairment and quality of life measures will be assessed in detail. In addition, to know more about the cardiovascular disease burden in this group of patients; arterial stiffness, endothelial dysfunction and carotid intima media thickness are to be assessed. This will give broader understanding of the older patients to better streamline treatment for acute coronary syndromes in future.

1.2 Literature Review

In the introductory chapters the current literature has been reviewed mainly in the context of acute coronary syndrome in older patients in relation to frailty, comorbidity and quality of life. In addition the association of cardiovascular disease burden including arterial stiffness, endothelial dysfunction and carotid intima media thickness in relation to cardiovascular outcomes has been discussed from the currently available literature.

The literature review was based on PubMed search terms including “acute coronary syndrome”, “elderly”, “frailty”, “comorbidity”, “percutaneous coronary intervention” and “coronary artery bypass surgery”. Further search was done for “arterial stiffness”, “endothelial dysfunction”, “carotid intima media thickness”, “quality of life” and “cognitive impairment”. Reviews, randomised control trials, subgroup analysis and retrospective studies were included that were relevant to the discussion. Cross references from the citation lists were examined and included for relevant material. It has to be noted this literature review is not systematic but includes selected relevant evidence for each of the topic discussed and efforts made to avoid selection bias. The review has been structured to discuss the selected literature in relation to older patients and coronary artery disease. Evidence for cardiovascular burden in relation to older patients is limited and has been discussed in general to focus on the study aims.

1.3 Acute Coronary Syndrome

Acute coronary syndrome (ACS) comprises of symptoms of sudden onset cardiac sounding chest pain associated with or without ECG changes. ACS broadly includes three group of patients. Symptoms of ongoing chest pain with persistent ST elevation on ECG are grouped as STEMI presentation and the other group of presentation is Non ST Elevation Acute Coronary Syndrome (NSTEACS). NSTEACS is further classified as Non ST elevation MI (NSTEMI) with troponin raise or Unstable Angina (UA) in which there is no troponin rise. STEMI needs emergency reperfusion by either angioplasty or fibrinolysis (ideally within 6 hours of symptom onset) and NSTEACS group of patients need to be considered for urgent invasive treatment (ideally within 72 hours) based on risk stratification.(Roffi *et al.*, 2015)

Diagnosis of NSTEACS is based on history and clinical assessment, 12 lead electrocardiogram and biomarker assay with troponin. The initial treatment comprises of pharmacotherapy (systemic anticoagulation, oral antiplatelets, beta-blockers, angiotensin converting enzyme inhibitors and statins). Further invasive management with percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG) according to findings on coronary angiogram and risk benefit analysis.

1.3.1 Pathophysiology of Acute Coronary Syndrome

Atherosclerosis results in plaque formation in large and medium sized arteries. The risk factors include advancing age, smoking, hypertension, diabetes and hyperlipidaemia. These risk factors initiate endothelial dysfunction which leads on to inflammation of the intima, resulting in intimal thickness and plaque formation. ACS results due to plaque rupture and erosion, precipitated by thrombogenicity of exposed sub endothelium.(Fuster *et al.*, 1988)

Platelet-rich ‘white’ thrombus forms in areas of high shear stress and fibrin rich ‘red’ thrombus is formed due to activated coagulation cascade. Red thrombus superimposed on white thrombus results in total occlusion of the vessel.(Mizuno *et al.*, 1992)

In NSTEACS, pharmacotherapy with antiplatelets prevent further thrombus formation and PCI is performed to prevent occlusion and recurrent ischemia. In STEMI, reperfusion by PCI or fibrinolysis leads to restoration of flow in an occluded coronary artery.(Roffi *et al.*, 2015)

1.4 Non ST elevation acute coronary syndrome in older population

In the following section IHD in older patients especially NSTEACS, from current available evidence will be discussed.

1.4.1 Burden of NSTE ACS in older population

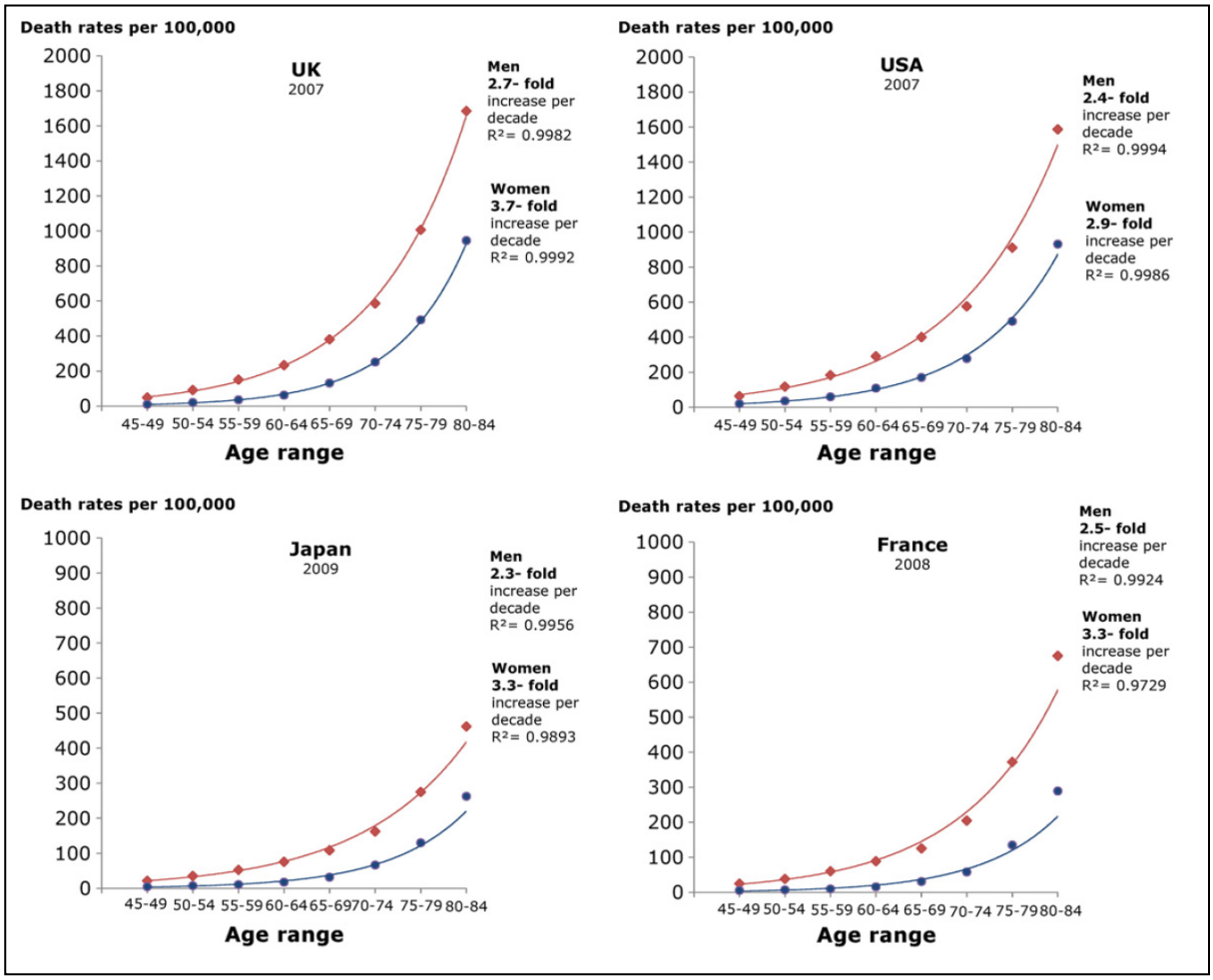
In the general population, ischaemic heart disease (IHD) is the leading cause of death worldwide.(Murray and Lopez, 1997) Globally, mortality due to IHD increases steeply among those aged >70 years of age.(Finegold *et al.*, 2013) In 2010, in the United Kingdom (UK), more than twice as many individuals >75 years of age (n=55,028) died from IHD compared to younger individuals <75 years (n=25,540).(Townsend *et al.*, 2012) According to the UK Myocardial Ischaemia National Audit Project (MINAP) Database annual public report 2012-13, there were 80,974 admissions with a final diagnosis of myocardial infarction (MI). Of these, 60% had non ST elevation myocardial infarction (NSTEMI). Of the patients with NSTEMI 59% were more than 70 years of age (26% were of age 70-79 years, 26% were 80-89 years and 7% were ≥90 years).(Gavalova L, 2013)

Mortality from IHD increases exponentially with age. In UK there is a 2.7-fold increase in IHD mortality for every decade of life for men and a 3.7-fold increase for women.(Finegold *et al.*, 2013) This is similar to other developed countries like US, France and Japan (**Figure 1.2**). Though age-standardised IHD related death rates have fallen significantly by almost 50% in the developed countries, IHD still remains the leading cause of death due to higher mortality rate in the increasing proportion of older and ageing population.

In the Global Registry of Acute Coronary Events (GRACE), increasing age was associated with increased incidence of NSTEMI. NSTEMI was diagnosed in <30% of patients aged <65 years compared with 41% in those aged ≥85 years. ST elevation myocardial infarction (STEMI) was more frequent in younger patients (36.5% in 45 to 74 years vs. 30.7% in >75years). All in-hospital events after ACS were more frequent among elderly patients. Cardiogenic shock was nearly 6 times more common in the oldest compared with the youngest group (9.8% vs. 1.6%, respectively). Rates of major bleeding were twice more in patients aged ≥85 years compared to <65 years (p<

0.0001). Each 10-year increase in age resulted in 75% increase in in-hospital mortality.(Avezum *et al.*, 2005)

Figure 1.2: Age specific IHD mortality trend in UK, USA, France and Japan



Reproduced from Finegold et al., Mortality from ischemic heart disease by country, region and age: Statistics from World Health Organisation and United Nations. International Journal of Cardiology 168 (2013) 934-945

1.4.2 Management of NSTEACS in Older Patients

Management of NSTEACS includes pharmacotherapy and revascularisation in suitable patients. In the following section role of invasive management strategy in older patients will be reviewed.

1.4.2.1 Invasive or Conservative Management Strategy for NSTEACS

In the Treat angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis In Myocardial Infarction 18 (TACTICS-TIMI 18) study (n=2220), patients aged >65 years (n=962) who were treated with an early invasive approach of catheterisation within 48 hours (n=491) and revascularisation if appropriate had a lower risk of death, subsequent MI or rehospitalisation for ACS at 6 months than patients who underwent a conservative strategy (n=471) of revascularisation only with objective evidence of ischemia (14.9% vs. 17.8% respectively), however this was not statistically significant.(Cannon *et al.*, 2001)

From the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) Quality Improvement Initiative, the unadjusted incidence of in-hospital mortality for all patients (n=17926) was 2.0% of 8037 patients who underwent early invasive management within 48 hours, compared with 6.2% of 9889 patients who did not undergo early invasive management (adjusted Hazard Ratio [HR]: 0.63, 95% Confidence Interval [CI] 0.52-0.77). In this study, younger and healthier patients (median age 63 years) generally receive the benefit of early invasive management, whereas older patients (median age 73 years), with more co-morbidities and a greater likelihood to benefit more from invasive treatment for NSTEMI, are more likely to be managed conservatively.(Bhatt *et al.*, 2004a)

In the Acute Coronary Syndromes Registry (ACOS) study, 1936 patients ≥75 years with NSTEMI were included and analysed by two groups. 1005 patients underwent coronary angiography and revascularisation if indicated and 931 patients received conservative treatment. The mean age was 78.7 years vs. 82.2 years ($p<0.0001$) and women comprised 48.3% vs. 58.6% ($p<0.0001$) of each group respectively. In-hospital mortality and the combined endpoint of death or non-fatal re-infarction were lower in the patients undergoing invasive management compared with the group managed by conservative strategy (6.0% vs. 12.5%, $p<0.0001$ and 9.6% vs. 17.3%, $p<0.0001$

respectively). There was a significant reduction in one-year mortality in the invasive treatment group compared to conservative treatment group (Odds Ratio [OR] 0.56, 95% CI 0.38 to 0.81).(Bauer *et al.*, 2007)

In a recent study comparing the different management strategies utilised among patients >75 years of age (n=3279) between two different cities (Goteborg [Sweden] – n=968 and Minneapolis St Paul [USA] – n=2311), it was observed that in Goteborg a smaller proportion of patients received PCI (7.3% vs. 32.8%; p< 0.0001 among men, 6.6% vs. 29.4%; p< 0.0001 among women). Subsequently, survival after 7.5 years follow up was observed to be lower in Goteborg (17.5% vs. 26.6%, [OR for survival at follow up: 0.66, 95% CI: 0.50-0.88] among men and 17.0% vs. 28.8% [OR: 0.49, 95% CI: 0.36–0.67] among women). Whilst the increased survival rate was thought to be attributable, at least in part, to the increased utilisation of PCI in Minneapolis cohort, it should be noted that several other factors could have contributed, such as differences in medical management and other geographical variables.(Smith *et al.*, 2013)

1.4.2.2 Timing of Revascularisation for NSTEACS

Benefits from early invasive strategy for ACS in low risk patients are minimal. (Antman *et al.*, 2000; Goto *et al.*, 2010; Lansky *et al.*, 2010) Current guidelines recommend early invasive strategy for high risk patients who would benefit more from early invasive treatment. (Anderson *et al.*, 2007; Anderson *et al.*, 2011a; Hamm *et al.*, 2011) Benefits from invasive treatment compared to non-invasive treatment are observed more in >65 year old patients compared to younger patients at 1 year and 5 years.(Wallentin *et al.*, 2000; Lagerqvist *et al.*, 2006) But in real-world practice older patients are less likely to be offered invasive treatment compared to younger patients.(Bhatt *et al.*, 2004b; Halon *et al.*, 2004; Alexander *et al.*, 2006)

In the meta-analysis by Angeli et al,(Angeli *et al.*, 2014) of 9 randomised control trials (RCTs) involving 9400 patients with NSTEACS, reduction in composite end-point (all-cause death and recurrent MI) by early invasive strategy (≤24 hours) compared to conservative strategy was larger in RCTs enrolling patients with a mean age >65 years (249/1440 patients of invasive strategy vs 319/1461 patients of conservative strategy) than in RCTs with a mean age <62 years (168/573 patients vs 150/598 patients, OR 0.65; 95% CI: 0.42–0.98; P=0.043). Similarly for rehospitalisation RCTs with a mean

age >65 years showed a 49% risk reduction (OR 0.51; 95% CI: 0.38-0.68) for this outcome when compared with trials with a mean age <62 years (P<0.0001). There was 15% risk reduction of the composite end-point of all-cause death and recurrent MI by early invasive strategy and the benefit was achieved in >65 year old patients. The outcomes were unaffected by gender and benefits were similar in both male and female patients >65 years old.

Of the 9 RCTs included in the above meta-analysis only one was specifically designed for patients ≥75 years while the others were sub-group analysis. In this Italian Elderly ACS study by Savonitto et al;(Savonitto *et al.*, 2012) from January 2008 and May 2010, 313 patients ≥75 years of age (mean 82 years) with NSTEACS were randomised within 48 hours from diagnosis to an early aggressive (EA) strategy (n=154, coronary angiography and, when indicated, revascularization within 72 hours) or an initially conservative (IC) strategy (n=159; angiography and revascularization only for recurrent ischemia). During admission, 136/154 (88.3%) and 85/154 (55.1%, 76 PCI and 9 CABG) of the patients randomized to the EA strategy underwent coronary angiogram and revascularisation respectively. This proportion in the IC strategy was 46/159 (28.9%) and 37/159 (23.2%, 36 PCI and 1 CABG). The primary endpoint (composite of all-cause mortality, non-fatal myocardial infarction (MI), stroke, repeat hospitalisation for cardiac causes and severe bleeding within 12 months) occurred in 43 (27.9%) patients in the EA group and 55 (34.6%) patients in the IC group (HR 0.80; 95% CI 0.53-1.19; log rank p=0.26). Patients with raised troponin levels at diagnosis had a significant 57% reduction in the primary endpoint rate (p for interaction <0.05). The power of the study was limited to arrive at a definite conclusion about the benefit of an EA approach among elderly patients with NSTEACS. The significant interaction of troponin level at baseline to the treatment benefit in EA group needs confirmation in a larger trial.

Overall, these studies suggest that there may be better outcomes with an early invasive management strategy in the elderly population in carefully selected patients presenting with NSTEMI compared with conservative medical therapy.

1.4.2.3 Risks of PCI in older patients

As older age predicts poor CV outcomes after ACS, age is an independent predictor of death after PCI. In a RCT to study anticoagulation during PCI comparing bivalirudin and heparin with glycoprotein IIb/IIIa inhibitor of 6010 patients undergoing PCI, 695 patients were >75 years. Mortality was 5.2% at 1 year in >75 years compared to 1.6% in ≤ 75 years (HR 1.05, 1.03-1.07 P<0.001). (Lincoff *et al.*, 2004)

In a retrospective study from Scotland of 3513 patients >75 years old which was 11.1% of the total number of non-emergency PCI (n=35888) done from 2000 to 2007, the overall risk of MACE at 30 days was 4.5% in >75 years old compared to 2.7% in <75 years old (OR 1.74, 95% CI 1.46 to 2.08, P<0.001).(Johnman *et al.*, 2010) Though this was a retrospective study it included all >75 years old and avoided selection bias.

Advanced age is an independent predictor of bleeding in acute coronary syndrome. (Moscucci *et al.*, 2003) Patients with major bleeding (588 out of 10974 patients, 5.4% included haemorrhagic stroke, gastrointestinal bleeding and retroperitoneal bleeding) after PCI were older compared to minor or no bleeding (68yerars vs 65 years, P<0.001). Multivariate analysis identified age >80years as a strong predictor of major bleeding (OR 1.9, 95% CI 1.4-2.7, P<0.0001). (Kinnaird *et al.*, 2003) This study included emergency procedures and almost all procedures were done from the femoral access site.

Major bleeding after PCI was associated with increased incidence of mortality (6.4% vs 1.9%, OR 3.6, 95% CI 2.3 – 5.5, I^2 89%) and MACE (22% vs 5.9%, OR 3.9, 95% CI 3.2-4.8, I^2 53%) at 1 year in a metanalysis of 42 studies.(Kwok *et al.*, 2014)

The increased rate of MACE after PCI in older patients are likely related to increased incidence of comorbidities, multivessel coronary artery disease, renal insufficiency and more frequent use of femoral access.(Feldman *et al.*, 2006)

1.4.2.4 PCI versus CABG

Older patients are more likely to have three vessel disease compared to younger patients.(Flather *et al.*, 2012) In a retrospective study of 10141 ACS patients with multi-vessel disease who were 85 years and older (mean age 87.2 years), patients were followed up for 3 years after either Coronary Artery Bypass Grafting (n=5803) or multivessel PCI (n=4338). Though lower survival was noted in the early months after CABG compared to PCI (80% vs 84%, OR 1.48, 95% CI 1.34-1.64, P<0.01), CABG provided significantly better survival (64% vs 60%, OR 0.60, 95% CI 0.53-0.69, P<0.05) and freedom from the composite outcome of death, repeat revascularization, stroke and acute myocardial infarction at 36 months (44% vs 37%, OR 0.83, 95% CI 0.76-0.91, P<0.01).(Sheridan *et al.*, 2010) Long term outcomes were poor in patients with heart failure, lung disease and peripheral vascular disease in the CABG group. Long term benefits of CABG need to be weighed against the perioperative morbidity and mortality in older patients.

In a meta-analysis of 10 randomised control trials by Flather et al, (Flather *et al.*, 2012) over a median follow-up of 5.9 years, the effect of CABG versus PCI with balloon angioplasty or bare metal stents (BMS), on mortality varied according to age. CABG (n=1279) led to an increased risk of mortality (11% vs 8%) among patients in the lowest tertile for age (n=2602, mean age 49.8), with adjusted CABG to PCI Hazard Ratio (HR) of 1.23 (95% CI 0.95-1.59). However, in the middle tertile (n=2602, mean age 61 years), the HR was 0.89 (95% CI 0.73-1.10), favouring CABG (n=1307, 14% vs 15%). In the oldest tertile (n=2602, mean age 70.5), the HR decreases further with CABG (n=1301) to 0.79 (20% vs 24%, 95% CI 0.67-0.94). It was observed that, above 59 years of age, the HR fell to <1, favouring CABG as a treatment strategy. A similar effect was observed with the composite outcome of death or further MI, with PCI favoured in the younger tertile compared to CABG in the more elderly groups. Though age was a predictor of outcomes for mortality and MI in the two groups, it was not significant in predicting repeat revascularisation (P=0.24) or the development of angina (P=0.94). Though benefit from CABG was noted in this meta-analysis, most of the patients underwent PCI with balloon angioplasty or BMS. There has been significant improvements with drug eluting stents (DES) and potent anti-platelets in the current era of PCI.

Similarly, in a collaborative analysis of data from 10 separate randomised trials comparing CABG (n=3889) to PCI (n=3923), patients' age modified the effect of treatment on mortality, with CABG to PCI HRs of 1.25 (10% vs 8%, 95% CI 0.94-1.66) in patients younger than 55 years, 0.90 (14% vs 15%, 95% CI 0.75-1.09) in patients aged 55-64 years, and 0.82 (20% vs 24%, 95% CI 0.70-0.97) in patients 65 years and older (p=0.002 for interaction). It was concluded that CABG might be a better option in patients ≥65 years as mortality was lower in this group. However, very few of the patients in these trials were >75 years old, and the older patients were physically healthier than many of their contemporaries, due to selection bias.(Hlatky *et al.*, 2009)

In an observational study, compared to younger patients, physiological and psychological recovery patterns after CABG among older patients was similar in the first 6 weeks postoperatively.(Artinian *et al.*, 1993) Slater and colleagues observed an increased risk of cognitive decline after CABG (n=202 out of which 58 had cognitive decline at 3 months) with advancing age (OR 1.76 per 10-year increase in age, p=0.055), and that cognitive decline was strongly associated with prolonged cerebral oxygen desaturation which can occur during the CABG procedure.(Slater *et al.*, 2009) Healthy older patients probably benefit long term from CABG but randomised data in >75 years age group is lacking.

1.4.3 Paucity of Evidence for Management of Older Patients

Evidence from clinical trials to inform the management of ACS in older patients is limited. More than half of all trials for coronary disease in the past decade failed to enrol patients >75 years of age, with this subgroup accounting for just 9% of all patients enrolled in trials.(Lee *et al.*, 2001) Analysis from the CRUSADE Quality Improvement Initiative demonstrated that among a community population with Non-ST Elevation Acute Coronary Syndrome (NSTE ACS), patients who were enrolled in a clinical trial (2.5% of the overall CRUSADE population) were younger (median 65 years vs. 68 years), more often male (67.9% vs. 59.3%), had less renal insufficiency (8.5% vs. 13.5%), and had less heart failure (13.2% vs. 19.0%) than those not enrolled in trials.(Kandzari *et al.*, 2005) Evidence-based recommendations from trials do not account for the age related differences in physiology and disease that may alter these relationships. The age gap between trials and community populations begins at age 75 years and widens with age.(Alexander *et al.*, 2007b) Even the older patients

included in trials are different from the older patients in the community. Trial populations have lower rates of traditional cardiovascular risk factors, less co-morbidity and better renal function in each age subgroup than do community populations.(Kandzari *et al.*, 2005) As older patients are at increased risk from cardiac events, the absolute benefit of treatment should increase if treatment risks can be balanced against benefits.(Alter *et al.*, 2004) Risks and benefits derived from trials cannot always be extrapolated to older patients in daily clinical practice due to the differences between the patient groups.(Tinetti *et al.*, 2004) Current evidence in the management of older ACS patients is limited due to less number of older patients in the randomised trials.

1.4.4 Interpretation of available evidence in NSTEACS in Older Patients

The definition of older and elderly when it comes to acute coronary syndrome is not clear. Though most of studies considered >65 years old as older/elderly in the current era of advancing age and life expectancy, >75 years need to be considered older. So the available evidence from these >65 years may not be the standard evidence for management of >75 year old patients. Advancing age is a risk factor for acute coronary syndrome and plays a role in the risk stratification of patients presenting with ACS. Evidence for management of older patients is limited from retrospective studies to sub group analysis. The proportion of older patients in RCT is small. From the limited evidence available patients with NSTEACS managed by early invasive strategy compared to conservative strategy, benefit older patients even when considering the risks associated with the procedure. This is because older patients perceived to be at higher risk are likely to benefit from intervention. With advancement in pharmacotherapy, radial access procedures and advanced PCI equipment, the role of intervention in >75 year old need to be studied in the current era. Older age also results in comorbidities and frailty, so assessing these >75 year old patients with NSTEACS in relation to frailty and comorbidity will play a key role in developing guidelines. Studies are needed to define risks and benefits of conservative versus invasive care in older patients with ACS, not just based on age but with comorbidity ad frailty especially the impact on quality of life.(Rich *et al.*, 2016) Limited clinical randomised controlled trial data to guide acute care in older patients and uncertainty about risk-benefit assessment with advanced age is likely to explain the underuse of appropriate

medications and invasive treatment strategies.(Lee *et al.*, 2001) Older patients who are at high risk of adverse outcomes following ACS are underrepresented in clinical trials despite the fact that older patients constitute a significant proportion of the patient population and are more likely to benefit from treatment strategies due to higher risk.(Hordijk-Trion *et al.*, 2006; Alexander *et al.*, 2007b) For gains in quality life-years following ACS to continue, survival from acute coronary syndrome will need to also extend to the very older population.(Gurwitz *et al.*, 1994; Sahyoun *et al.*, 2001) It is important to understand the risks and benefits of treatment in this group in order to improve outcomes. Frailty assessment might usefully be incorporated into the management of older patients with ACS. Future large scale randomised studies evaluating novel therapies in addition to contemporary care are required for the ageing patients presenting with ACS. In older patients with ACS, predictors of adverse cardiovascular outcomes and quality of life need to be evaluated in detail in 'real world' patients. Frailty, comorbidity and quality of life in the context of ACS will be reviewed in the following sections.

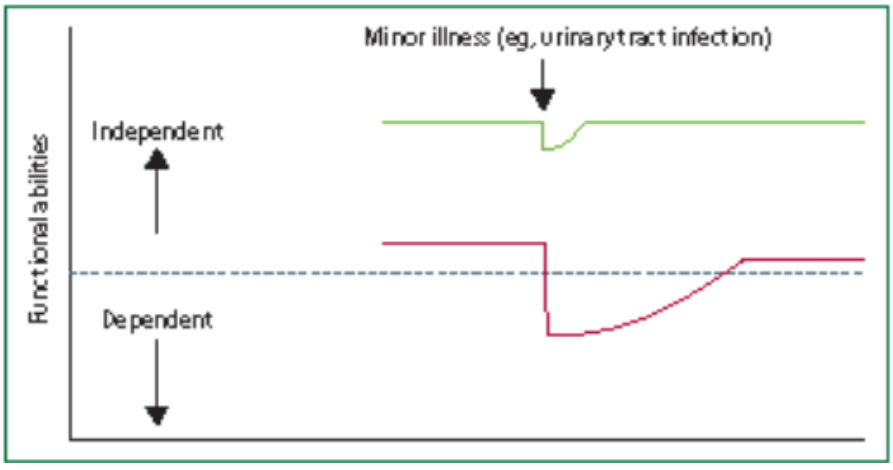
1.5 Prevalence and impact of frailty on cardiovascular outcomes

This section covers frailty, including the origins of the concept of frailty and its definition. Also the common frailty measures used and helpful in clinical practice and research are discussed. The impact of frailty on cardiovascular disease in community population and in patients with acute coronary syndrome is discussed.

1.5.1 Frailty

Frailty can be regarded as a complex syndrome in older age due to decreased reserve and resistance to stressors resulting in delayed and decreased resolution to baseline homeostasis following a stressor event (**Figure 1.3**). Frailty results from declining physiological systems in older age leading to adverse health outcomes including falls, hospitalisation and mortality.(Rockwood et al., 1996; Fried et al., 2001) Declining physiological reserve and resulting impaired resistance to stressors leads to frailty syndrome.(Bergman *et al.*, 2007) 25% to 50% of patients with cardiovascular disease (CVD) can be identified as frail depending on the frailty scale used and the population group studied.(Afilalo, 2011).

Figure 1.3: Response to stressor in frailty



In response to a stressor non-frail patients (green line) return to baseline independence earlier compared to frail patients (red line) who become dependent and takes longer and do not return to baseline homeostasis.
Adapted from Clegg et al, Lancet 2013

1.5.2 Concept of Frailty

The two main models of frailty are phenotype model and cumulative deficit model. The phenotype model was developed from secondary analysis of the Cardiovascular Health Study (CHS) and identified five variables (unintentional weight loss, self-reported exhaustion, low energy expenditure, slow gait speed and weak grip strength) establishing the frailty phenotype.(Fried *et al.*, 2001a) Frailty criteria developed from this phenotype model is explained in the following sections.

The cumulative deficit model was developed as a frailty index as part of the Canadian Study of Health and Ageing (CSHA).(Rockwood *et al.*, 2005) This model included 92 variables recorded as deficits in the form of symptoms, signs, abnormal laboratory values, disease states and disabilities. The frailty index in this model was calculated from the total number of deficits out of the 92 deficits present in an individual. Without reducing the predictive ability the cumbersome list of 92 deficits have been reduced to a manageable number of 30 in subsequent work on this model. Distinction of older frail patients should be an essential assessment prior to an invasive procedure. This will help patients to weigh the risks and benefits to make informed choices and also will make sure that older patients are not denied interventions based on age alone.(Clegg *et al.*, 2013)

1.5.3 Frailty Measures

Frailty can be assessed by a number of clinical instruments and scores.(Abellan van Kan *et al.*, 2008; de Vries *et al.*, 2011) The variables measured include physical inactivity, strength, exhaustion, co-morbid conditions and cognitive impairment as main components. A task force on frailty assessment in older people suggested that gait speed could represent the most suitable instrument to be implemented in both research and clinical evaluation of older people to assess frailty.(Abellan van Kan *et al.*, 2008) The 5-minute gait speed test is a simple and effective way of objectively measuring frailty in patients with CVD and should be incorporated in risk assessment.

Fried et al.(Fried *et al.*, 2001b) used data from the Cardiovascular Health Study to develop a tool for assessment of frailty among adults aged ≥65 years. 5317 participants ≥65 years were assessed annually. Examinations and surveillance was conducted assessing for the presence of incident disease, hospitalisation, falls, disability and

mortality. Frailty was defined as “a clinical syndrome in which three or more of the following criteria were present: unintentional weight loss (10 pounds in past year), self-reported exhaustion, weakness (grip strength), slow walking speed and low physical activity”. According to the above criteria, 6.9% of the study population were frail. The prevalence increased with increasing age, and was greater in women than in men. Over a three year period, frailty was independently associated with increased incident falls, worsening mobility, disability in ADL, hospitalisation and mortality. The presence of one or two of the Fried frailty criteria indicating intermediate frail status showed intermediate risk of these outcomes as well as an elevated risk of becoming frail over a period of three to four years.

Rockwood et al.(Rockwood *et al.*, 2005) developed the 7 point Clinical Frailty Scale (category 1: Very fit - Robust, active, energetic, well-motivated and fit; these people commonly exercise regularly and are in the most fit group for their age to category 7: Severely frail - Completely dependent on others for the activities of daily living, or terminally ill) and utilised it to measure frailty in 2305 elderly patients participating in the Canadian Study of Health and Aging (CSHA). After adjustment for age, sex and education each 1-category increment of the clinical frailty scale significantly increased the risks of death (21.2%, 95% CI 12.5%-30.6%) and entry into an institution (23.9%, 95% CI 8.8%-41.2%) within six years.

1.5.4 Prevalence of Frailty in Community Population with CVD

The prevalence of frailty in community population with CVD is summarised in **Table 1.1**. The cause for decline in physiological reserve is multifactorial and involves multiple organ systems. Frailty has become increasingly relevant in the field of cardiovascular medicine as the patient population is ageing and also there is an increasing evidence in the association of CVD and frailty both at the mechanistic level and the epidemiologic level.(Afilalo *et al.*, 2009) Activities of daily living (ADL), physiological reserves, nutritional status (albumin, weight loss) and functional status are all important markers of older patients at increased risk of morbidity and mortality.(Ferrucci *et al.*, 2004) Altered cognition, hearing and vision may delay presentation and result in increased risks due to delays in commencing interventional treatment. Impaired communication affects decision making and these patients would find it difficult to adhere to treatment plan and consent for invasive procedures. As

frailty includes a number of components, better understanding of age-related health issues separate from disease-related risk is needed.(Fried *et al.*, 2004)

Frailty is not reflected by disabilities in ADL (for example, getting dressed unassisted) or instrumental ADL (such as going shopping unassisted) alone. Frailty occurs earlier than disability and can be elicited in a large number of well-functioning older adults. Disability can be viewed as the end-result of longstanding frailty and co-morbidity burden.(Afilalo, 2011) Though there is an overlap between frailty, disability and co-morbid conditions, these represent distinct domains.(Fried *et al.*, 2004)

Table 1.1: Prevalent Frailty in Older Patients with CVD

Study	**Design Population**	**Number Total, Frail**	**Key Variables**	**Frailty,CVD, Mortality**
Zutphen Elderly Men's Study(Chin *et al.*, 1999)	Secondary analysis Community dwellers	450 F=29	Frailty (Chin), prevalent CVD, 3-yr mortality	Mortality 50% vs 18% Heart failure 23% vs 7%, p<0.05 OR 4.1 (95% CI 1.8–9.3)
Cardiovascular Health Study (CHS)(Newman *et al.*, 2001)	Secondary analysis Community dwellers	4,735 F=299	Frailty (Fried), prevalent CVD, subclinical CVD, 7-yr mortality	CVD patients are 3 fold likely to be frail Heart failure 14% vs 3%, OR 7.5 (95% CI 4.6–12.1)
Beaver Dam Eye Study(Klein *et al.*, 2005)	Secondary analysis Community dwellers	2,962 F=899	Frailty (Klein), prevalent CVD, 10-yr mortality	One level increase in frailty was associated with 35% increased odds of CVD OR 1.43 (95% CI 1.1–1.8)
Women's Health Initiative-Observational Study (WHI-OS)(Woods *et al.*, 2005)	Secondary analysis Community dwellers	40,657 F=6619	Prevalent frailty (Fried), incident frailty (Fried), prevalent CVD, 5.9-yr mortality	History of CAD 11.6% vs 5.9%, p<0.001 OR 3.36 (95% CI 3.09–3.66)
Women's Health and Aging Studies I and II (WHAS I and II)(Chaves *et al.*, 2005)	Secondary analysis Community dwellers	670 F=94	Frailty (Fried), prevalent CVD, 3-yr mortality	CVD 75.% vs 26%, P<0.001 OR 2.72 (95% CI 1.72–4.30)

CVD- cardiovascular disease, OR- Odds ratio, CI- confidence interval

1.5.5 Frailty and Cardiovascular Outcomes in Community Population

Frail patients with CVD, especially those undergoing invasive procedures or suffering from coronary artery disease and heart failure, are more likely to suffer major cardiovascular events and death compared to their non-frail counterparts.(Afilalo, 2011) Frailty is a powerful predictor of adverse cardiovascular outcomes and hence frailty measures should be routinely used in cardiovascular risk assessment. This is especially of importance in the management of ACS.

Four studies have shown an association between frailty and CVD in community dwelling older adults: Zutphen Elderly Men's Study (OR 4.1; 95% CI 1.8-9.3)(Chin *et al.*, 1999), Cardiovascular Health Study (OR 2.79; 95% CI 2.12-3.67)(Newman *et al.*, 2001), Beaver Dam Eye Study (OR 1.43 per point; 95% CI 1.13-1.82)(Klein *et al.*, 2005), and the Women's Health and Aging Studies (OR 2.72; 95% CI 1.72-4.30).(Chaves *et al.*, 2005) In the Cardiovascular Health Study, there was also an association between frailty and subclinical cardiovascular abnormalities such as left ventricular hypertrophy and carotid intima media thickness (CIMT).(Newman *et al.*, 2001)

The French 3 City Study(Dumurgier *et al.*, 2009) and the Health Aging and Body Composition Study(White *et al.*, 2012) showed that community-dwelling older adults who were frail (as determined by gait speed) were at higher risk of cardiovascular events and mortality. In the French 3 City Study, slow gait speed was associated with a threefold increase in cardiovascular mortality over 5 years (OR 3.00; 95% CI 1.65–5.57).(Dumurgier *et al.*, 2009)

Purser et al.(Purser *et al.*, 2006) showed that, depending on the definition used, 27% to 50% of older patients admitted to hospital and subsequently found to have severe coronary artery disease on coronary angiogram were frail. Tjam et al. showed that frailty was more predictive of mortality than New York Heart Association (NYHA) class in frail older patients with heart failure.(Tjam *et al.*, 2012) Mortality in frail older patients with CVD is displayed in **Table 1.2**.

Table 1.2: Mortality in Frail Older Patients with Severe CVD

Study	Design Population	Number Total, Frail	Key Variables	Mortality
French 3 city Study(Dumurgier *et al.*, 2009)	Prospective cohort Community dwellers	3208 F=1091	Gait speed, CVD events and mortality	10% vs 5% OR 1.64 (95% CI, 1.24-2.57)
Cacciatore et al.(Cacciatore *et al.*, 2005)	Prospective cohort Outpatients with chronic heart failure	1332 F=60	Frailty (Fried), prevalent CVD, 3-yr mortality	88% vs 43% HR 1.62 (95% CI 1.08-2.45)
Purser et al.(Purser *et al.*, 2006)	Prospective cohort In patients with severe coronary artery disease	309 F=84	Frailty (Fried, Rockwood, gait velocity), 6-month mortality	14% vs 9% OR 4.0 (95% CI 1.1-13.8)

CVD- cardiovascular disease, OR-odds ratio, HR-hazard ratio, CI-confidence interval

1.5.6 Frailty and Cardiovascular Outcomes in IHD Patients

1.5.6.1 Frailty in the Setting of ACS

In a study of 307 hospitalised NSTEMI patients ≥75 years between October, 2009 to June,2010; 149 (48.5%) were considered frail by Rockwood(Rockwood *et al.*, 2005) 7 point frailty criteria (1 very fit – robust and active to 7 severely frail – bed ridden). Fewer frail patients underwent coronary angiography compared to non-frail patients (15% vs 46%, p<0.001). Frailty was independently associated with risk of major adverse cardiovascular (death from any cause, myocardial re-infarction, revascularization due to ischemia, hospitalization for any cause, major bleeding, stroke/transient ischemic attack, and need for dialysis) outcomes (45% vs 27%, p=0.0009, OR 2.2; 95% CI 1.3-3.7), in-hospital mortality (11% vs 2%, p=0.003, OR 4.6; 95% CI 1.3-16.8), and 1-month mortality (15% vs 3%, p=0.002, OR 4.7; 95% CI, 1.7-13.0). From this study Ekerstad et al concluded that frailty was strongly and independently associated with in-hospital mortality, one-month mortality and prolonged hospital care.(Ekerstad *et al.*, 2011) Similarly in the 1 year follow up of this study there was increased mortality in frail patients compared with non-frail patients (unadjusted 49% vs 13%, p<0.001, HR 4.3, 95% CI 2.4-7.8).(Ekerstad *et al.*, 2013)

In the above study a very high proportion of patients had type 2 myocardial infarction (n=106/307, 35%) secondary to anaemia, hypoxia and sepsis rather than a primary coronary ischemia. Though type 2 MI was not different between the frail and non-frail groups, significant differences were noted for CCF (38% vs 16%), severe renal impairment (eGFR <30, 38% vs 16%), dementia (28% vs 6%) and anaemia (56% vs 32%). These differences explain why less than a third of patients underwent invasive angiography (30%) The patient group in this study are different from older patients undergoing invasive treatment in the UK.

In a pilot study of 183 patients ≥ 65 years old admitted with ACS frailty was assessed using Edmonton Frailty Scale (EFS). EFS includes assessment of cognition, general health status, functional independence, social support, medications use (5 or more), nutrition, mood, continence and functional performance (timed get up and go test). 30% of patients had EFS score of ≥7 suggestive of frailty. Higher frailty score was associated with increased length of hospital stay (7 days for EFS 0-3, 10 days for EFS 4-6 and 13 days for EFS ≥7, p=0.03) and increased mortality at 1 year (1.6%, 7.7%

and 12.7% respectively, p=0.05).(Graham *et al.*, 2013) Of the 183 recruited patients 18.9% had STEMI, 77% underwent coronary angiogram and 26% underwent PCI. In this study almost 20% of patients had presented with STEMI in which the clinical status and outcomes are different compared to NSTEACS presentation. Though invasive angiogram was performed in a higher proportion of patients, PCI was performed only in about quarter of the patients. Because of this the study did not have enough power to be certain about the benefit or adverse CV outcomes of PCI in frail patients.

1.5.6.2 Frailty in Patients Undergoing PCI

In a prospective cohort study of 628 patients > 65 years, by Singh et al, frailty (as defined by Fried frailty score) (Fried *et al.*, 2001b) was added to conventional cardiovascular risk factors in the Mayo Clinic Risk Score. 18.6% were classified as frail, 47.4% as intermediate frail and 20.6% were non-frail. Frailty was associated with increased long-term (median follow up of 3 years) mortality or myocardial infarction (41% vs 17%, $p<0.05$, HR 2.45; 95% CI 1.33-4.53) among patients undergoing PCI. For mortality alone the difference was 28% vs 6% between frail and non-frail patients. The authors concluded that addition of frailty, co-morbidity and quality of life significantly improves the prognostic ability of Mayo Clinic Risk score.(Singh *et al.*, 2011)

It has to be noted only 41% of eligible patients from the above study, were consented and also the presentations were both stable CAD and acute coronary syndrome. Frailty assessment was done after the PCI procedure and this can have an influence on the frailty status especially if femoral access has been used for the procedure. The proportion of patients who had femoral access has not been discussed.

In a recent study by Murali-Krishnan et al,(Murali-Krishnan *et al.*, 2015) frailty assessed by Rockwood criteria independently predicted 30-day and 1-year mortality in addition to length of hospital stay. In this study 745 patients (mean age 62 years) undergoing PCI for stable CAD and ACS were recruited into the study. 11% were classified as frail. Almost 40% of recruited patients had STEMI and required emergency PCI. At 30 days the mortality was 4.9% in frail and 1.1% in non-frail patients (HR 4.8, 95% CI 1.4 to 16.3, $p=0.01$). At 1 year the mortality was 11.1% in frail and 1.9% in non-frail patients (HR 5.9, 95% CI 2.5 to 13.8, $p<0.001$). Frail patients stayed longer in hospital than non-frail patients (14 days vs 3.5 days, $p<0.001$).

The data collection for the above study was done as a service improvement project. The patients were relatively younger and a high proportion of patients had presented with STEMI. All these factors could have an impact on the outcomes noted.

Older patients constitute a significant group of ACS patients. With increasing life expectancy and advances in medicine the proportion of older patients presenting with ACS will increase. The older high-risk patients who are likely to benefit most from current pharmacotherapy and invasive procedures for ACS are managed conservatively due to the difficulty in risk-benefit assessment. This is a result of a lack of clear evidence due to under representation of this older group in clinical trials. It is important to recognise that chronological age does not always reflect biological age. Frailty, functional status and social aspects are not routinely assessed in older ACS patients. Future trials should enrol a greater proportion of older patients to reflect the real world population needing treatment and assess and report frailty status of trial participants. Standard reporting of age groups across trials and registries is needed to facilitate comparisons and pooling of data. A better understanding and phenotyping of older patients presenting with ACS is required. Prospective trials performed exclusively in the older patients will be of help in assessing the benefits and safety of pharmacotherapy and invasive procedures.

1.5.7 Interpretation of available evidence on frailty and ACS

Frailty is common among older patients both in community and hospitalised patients with CVD. Frailty predicts poor CV outcome in patients with stable CAD and ACS. But it has to be noted that different frailty assessment tools were used in the currently available evidence. There is no consensus on the best frailty measure to be used in CVD patients. Comparing different frailty tools in the same patient cohort with CVD could provide insight into better assessment of frailty status. The underlying presentation was different and varying, between elective procedures for stable angina to emergency procedure for STEMI. This is an important consideration as management and the risk of adverse CV outcomes varies according to the presentation. More importantly the benefit of contemporary invasive management in the specific subset of NSTEACS patients with frailty is not known. In addition to the benefits on improving mortality and adverse CV outcomes in frail older patients, the influence of comorbidity and the impact of quality of life in these patients need to be studied in detail. In the following section comorbidity in the context of ACS and frailty will be reviewed.

1.6 Impact of co-morbidity and cardiovascular outcomes

1.6.1 Co-morbidity

The decision to intervene in older ACS patients need to be balanced against the general health and co-morbidities of these patients.(Tinetti *et al.*, 2004) Old age is not an isolated risk factor especially when age associated conditions such as anaemia, kidney disease, frailty, disability and cognitive dysfunction have an impact on the outcomes of ACS management. In addition, diminished organ reserves and abnormal functional and cognitive status influence the nature of disease presentation, response to treatment, and recovery.(Alexander *et al.*, 2007b) Renal dysfunction is associated with an increased risk of bleeding in older populations.(Moscucci *et al.*, 2003) Patients presenting with ACS have associated chronic comorbidities which can play a major role in short term and long term outcomes.(Alexander *et al.*, 2007a; Alexander *et al.*, 2007b) Although there has been rapid improvements in the management of ACS based on randomised control trials patients with comorbidities are continuing to be excluded from these trials.(Sachdev *et al.*, 2004) Old age related functional and cognitive changes have an impact on disease related risks, which needs to be assessed in the management of older ACS patients.

1.6.2 Influence of Co-morbidity in Research

Co-morbidity can influence disease presentation, diagnosis, treatment offered and prognosis. Hence failure to classify and analyse comorbidities can lead to misrepresentation of statistical results.(Feinstei.Ar, 1970) The important reasons for measuring co-morbidity in research are to improve the internal validity of studies by correcting for confounding factors, to identify effect modification, to use co-morbidity as a predictor of study outcome or natural history and a comprehensive co-morbidity measure is needed for reasons of statistical efficiency.(de Groot *et al.*, 2003)

1.6.3 Charlson Comorbidity Index

There are various measures of co-morbidity. Of these the Charlson Co-morbidity Index (CCI) is the most extensively studied and is a valid and reliable method of co-morbidity measure that can be used in clinical research.(de Groot *et al.*, 2003) Charlson Co-morbidity Index was developed in 1987 as a prognostic index of co-morbid conditions, for patients with multiple medical conditions admitted to general medical wards. The co-morbid conditions on their own or in combination, might alter the risk of short-term mortality for patients enrolled in longitudinal studies.(E, 1987)

There were 19 diseases used in this model and the co-morbidities were weighted by Charlson et al using a point system. One point each for past history of myocardial infarction (MI), heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic lung disease, connective tissue disease, peptic ulcer disease, mild liver disease and diabetes. 2 points were weighted for diabetes with target organ damage, hemiplegia, and moderate to severe renal disease, malignant neoplasm, leukaemia and lymphoma. Moderate to severe liver disease was weighted with 3 points and metastatic solid tumour and Acquired Immunodeficiency Syndrome (stage C) were weighted with 6 points. The point system is displayed in **Table 1.3**.

Table 1.3: Charlson Comorbidity Index Points System

6 points
Metastatic solid tumour
Acquired Immunodeficiency Syndrome (Stage C)
3 points
Moderate to severe liver disease
2 points
Hemiplegia
Diabetes with end organ damage
Moderate to severe renal disease
Malignant neoplasm
Leukaemia
Lymphoma
1 point
Previous myocardial infarction
Heart failure
Peripheral vascular disease
Cerebrovascular disease
Dementia
Chronic lung disease
Connective tissue disease
Peptic ulcer disease
Mild liver disease
Diabetes

CCI was used to test the ability to predict risk of death from co-morbidities by using 1-year mortality data of the primary study population. When CCI was developed, weights were assigned for each co-morbidity based on the relative risks (RR) for 1-year mortality: RR <1.5 were assigned a weight of 1; RR 1.5 to <2.5 a weight of 2; RR ≥2.5 to <3.5 a weight of 3; and metastatic tumours and Acquired Immuno Deficiency Syndrome were assigned a weight of 6. To simplify the system, the conditions with a relative risk below 1.2 were dropped. The RR for each point was 1.39, but in a validation cohort for 10-year mortality the RR for each CCI point increased to 2.3 and was 2.4 for each decade after age 50 years.

1.6.3.1 Validation of Charlson Comorbidity Index in ACS Patients

CCI was used to assess the co-morbidities in AMIS (Acute Myocardial Infarction in Switzerland) Plus prospective multicentre observational registry study in 29,620 patients with acute coronary syndrome from 2002 to 2012.(Radovanovic *et al.*, 2014) The outcome measures were in-hospital and 1-year mortality. 27% were women (mean age 72.1±12.6 years) and 73% were men (64.2±12.9 years). 54.5% had STEMI, 39.1% had NSTEMI and 6.4% had UA. Almost half (48.6%) of the patients had co-morbidities. Patients were grouped into CCI 0 – no comorbidities; CCI 1 – only one co-morbidity weighted as 1; CCI 2 – patients with 2 comorbidities weighted 1 or one co-morbidity weighted 2 and CCI ≥3 patients in which the sum of the weighted points of co-morbidities 3 or above. Most frequent comorbidities were past history of MI (18.0%), diabetes mellitus (14.7%), moderate to severe renal disease (7.1%), cerebrovascular disease (6.0%) and chronic lung disease (6.0%). NSTEACS was more common in patients with higher CCI compared to lower CCI (CCI=0 39.8% vs. CCI ≥3 55.8%, p<0.001).

1.6.3.2 CCI and In-hospital Mortality Following ACS

Based on the impact of single co-morbidity the strongest predictors of in-hospital mortality adjusted for age and gender were heart failure (adjusted OR 1.88; 95% CI 1.57-2.25, p<0.001), metastatic tumours (OR 2.25; 95% CI 1.60-3.19, p<0.001), renal diseases (OR 1.84; 95% CI 1.60-2.11, p<0.001) and diabetes (OR 1.35; 95% CI 1.19-1.54, p<0.001). Based on weighted scoring of co-morbidities in-hospital mortality risk increased with increasing weightage as CCI 1 had an OR of 1.36 (95% CI 1.16-1.60, p=0.001), CCI 2 was 1.65 (95%CI 1.38-1.97, p<0.001) and CCI ≥3 had an OR of 2.20 (95% CI 1.86-2.57,p<0.001).

CCI together with age (Receiver operating characteristic [ROC] curve area=0.756; 95% CI 0.743-0.768) was a better predictor of in-hospital mortality compared to CCI alone (area=0.670; 95% CI 0.656-0.685). CCI together with age and sex (area=0.761; 95% CI 0.748-0.773) did not improve the predictive ability much. In patients >50 years old, each additional 10 years of age, the OR was 1.91 (95% CI 1.82-2.00).

1.6.3.3 CCI and Follow up mortality Following ACS

In 7066 patients followed up (median 386 days [IQR 370 to 409 days]), each CCI point increase was associated with increased incidence of mortality (OR 1.44, 95% CI 1.36-1.53). Each decade increase in age doubled the risk of follow up mortality (OR was 2.08 95% CI 1.81-2.39). ROC area was 0.83, 95% CI 0.80-0.86. There was significant difference in the use of PPCI for STEMI (70% vs 47%, p<0.001) favouring CCI <3. This study confirmed in a real world registry of patients with ACS, co-morbidities were a common occurrence, which had an impact on diagnosis, management and outcomes. In ACS patients CCI is an appropriate predictor of in-hospital and mid-term mortality. The management strategy (invasive or conservative) employed for NSTEACS treatment is not known to relate comorbidity and mortality. Though CCI ≥ 3 was predictor of mortality, treatment strategy was not similar between the patient groups.

1.6.3.4 Simple Comorbidity Index in NSTEACS

Sanchis et al,(Sanchis *et al.*, 2011) developed the simple co-morbidity index (SCI) in a derivation cohort of 1017 patients with NSTEACS using five co-morbid conditions – mild (1 point) to severe (2 points) renal disease, dementia (2 points), peripheral arterial disease (2 points), previous heart failure (2 points) and previous MI (1 point). In addition to SCI, CCI and CAD specific index were calculated. The mean (standard deviation) age of patients was 68(13) years and 34% were women. 71% of patients underwent coronary angiogram while 44% underwent PCI. The patients were followed up for primary outcome of 1 year mortality. Mortality rate increased with increasing points on the SCI; from 3.6% in the lowest co-morbidity category (0 points) to 11% (HR 1.7; 95% CI 1.0-3.1; p=0.06) in the intermediate category (1 or 2 points) and 36% in the high co-morbidity (≥3 points) category (HR 4.8; 95% CI 2.7-8.5; p=0.0001). Invasive management decreased with increased co-morbidity level (83% vs. 67% vs. 36%, p=0.0001). Even after adjustment for management strategy in the predictive tool, invasive management (HR 0.5; 95% CI 0.3-0.8; p=0.01) and SCI (per point: HR 1.5; 95% CI 1.3-1.7; p=0.0001) were predictive of mortality. SCI developed from the above derivation cohort was externally validated on 652 patients with NSTEACS. C-statistic decreased from 0.848 to 0.831 on the validation cohort suggesting lower discriminative ability but the calibration slope was close to 1 and hence did not need shrinkage of the regression coefficients. SCI was independently associated with mortality (per point: HR 1.3; 95% CI 1.1-1.6; p=0.001) and death or MI (per point: HR 1.3; 95% CI 1.1-1.5; p=0.0001). SCI with 5 easily available variables was equivalent to detailed indices such as CCI and CAD specific index but the impact of these indices needs to be studied on therapeutic (revascularisation) effects on prognosis.

1.6.3.5 Predictive Ability of SCI in Patients Undergoing PCI for NSTEACS

Palau et al, (Palau *et al.*, 2012) sought to investigate the predictive ability of SCI on prognostic effect of in-hospital revascularisation in high-risk NSTEACS patients. Between 2002 and 2008, 1017 patients with NSTEACS were recruited. The treatment strategy was at the discretion of cardiologist in charge: early invasive revascularisation or conservative (selective invasive strategy). The indication for revascularisation was based on coronary angiogram performed within 96 (±48 hours). The mean age of the

patient population was 68(±13 years) and 34% were females. The primary endpoint was composite of death from any cause and non-fatal MI. With increasing SCI score of 0, 1, 2 and >2 coronary angiography was performed less frequently 83% vs. 68% vs. 56% vs. 36% (P<0.001) respectively. The trend was similar for performing revascularisation 54% vs. 41% vs. 28% vs. 18% (p<0.001). But the differences were less marked in patients undergoing coronary angiography proceeding to have revascularisation (64.9% vs. 60.6% vs. 52.9% vs. 48.9%, p=0.001). During a median follow up of 16 months, 20% of patients died, 17% suffered MI and 30% had composite endpoints (MI/death). There was no significant difference between non-revascularised patients and revascularised patients with 0 point (1.017 vs. 1.021 per 10 person-year of follow-up, p=0.587) and 1 point (1.812 vs. 2.345 per 10 person-year of follow up, p= 0.497) for rates of the composite end points of death and MI. In comparison, revascularisation significantly reduced the occurrence of the combined end point (0.711 vs. 3.415 per 10 person-year of follow-up, p=0.002 and 2.684 vs. 7.042 per 10 person-year of follow-up, p= 0.028) in those patients with 2 and >2 points respectively. These differential prognostic effects on outcomes were obtained in multivariate analysis with significant risk reduction in revascularised patients with SCI ≥2 (HR 0.51; 95% CI 0.29-0.89, p=0.018). There was no significant benefits from revascularisation in patients with SCI score 0 and 1. Revascularisation benefits were significantly higher in patients with increased co-morbidity burden.

1.6.4 Impact of Co-morbidity on ≥65 year old patients undergoing PCI

Singh et al,(Singh *et al.*, 2011) assessed the prognostic value of frailty, co-morbidity and quality of life over and in addition to the mayo clinic risk score (MCRS) in predicting outcomes of death and death or MI over a median follow up period of almost three years in 628 patients ≥65 year old patients undergoing PCI. 12% of patients died and 22% patients had composite endpoints (death/MI). Univariate analysis showed comorbidity assessed by CCI was associated with mortality (HR 1.10; 95% CI 1.05 - 1.16). Addition of co-morbidity to MCRS increased the predictive ability with increase in C-statistics from 0.628 to 0.671 and from 0.573 to 0.576 for death and death or MI respectively. Addition of frailty, co-morbidity and quality of life significantly increased the prognostic ability of MCRS.

1.6.5 Cardiovascular Comorbidity in Acute Myocardial Infarction

Cardiovascular comorbidities including atrial fibrillation (AF), diabetes, heart failure, hypertension and stroke were examined in 9581 patients with acute myocardial infarction between 1990 and 2007.(McManus *et al.*, 2012) The average age of the participants was 70 years and 43% were females. Patients with two or more cardiovascular co-morbidities were likely to have increased 30 day and 1 year mortality rate. From 1990 to 2007, the proportion of participants in whom no co-morbid illnesses were present almost halved (31% to 16%), but at the other end of the spectrum participants with four or more comorbidities more than doubled (3% to 7%; $p<0.05$). After adjustment for several potentially confounding factors (age, sex and in-hospital complications) of prognostic importance, patients with two or more comorbidities experienced significantly high 30-day (2 co-morbidities: HR 1.49; 95% CI 1.23-1.80; 3 co-morbidities: HR 1.64; 95% CI 1.32–2.03 and co-morbidities ≥4: HR 1.68; 95% CI 1.28–2.21) and 1-year mortality (2 co-morbidities: HR 1.62; 95% CI 1.41-1.87 ; 3 co-morbidities: HR 1.94; 95% CI 1.66-2.26 and co-morbidities ≥4: HR 2.31; 95% CI 1.91-2.78). The risk of 30-day and 1-year mortality was directly related to the number of co-morbidities present. This study has clearly demonstrated the importance of CV co-morbidities on outcomes in patients with MI.

Advanced age is associated with increased comorbidities. It is very common to encounter older patients with multiple co-morbidities presenting with ACS. Co-morbidity burden has a significant impact on CV outcomes, both short and long term. It has been shown that both detailed and simple co-morbidity assessments add to predictive ability of prognosis in patients with ACS. It has also been shown that patients with multiple co-morbidities who are unlikely to be offered early invasive strategy may benefit more from revascularisation. The impact of co-morbidity on CV outcomes in older patients needs to be studied in detail. Also patients with multiple co-morbidities need to be enrolled in clinical trials to confirm findings from observational and registry studies.

1.6.6 Interpretation of available evidence on comorbidity and CVD

Comorbidities are common in older patients with CVD and they influence presentation and management. But older patients with comorbidities are not represented in clinical trials. Also patients with comorbidities do not receive standard guideline based treatment which in turn has an impact on outcomes. Though patients with increased comorbidity are at higher risk of adverse CV outcomes, they stand to benefit from contemporary treatment. Revascularisation benefits were noted to be higher in patients with higher comorbidity burden after NSTEACS. Increased risk of adverse CV outcomes were noted in observational studies compared to randomised trials. This is due to under representation of patients with comorbidities in RCTs. Comorbidity in older patients managed by contemporary NSTEACS treatment need to be assessed in detail.

In previous sections ACS in older patients and their relation to frailty and comorbidity were discussed. In the following sections CVD burden in older patients with non-invasive assessment will be discussed.

1.7 Non-invasive assessment of cardiovascular disease burden

Non-invasive assessment of arterial stiffness, endothelial dysfunction, carotid intima media thickness and left ventricular function will be reviewed. These measures are markers of cardiovascular disease burden. Techniques used in their assessment and its association with CV outcomes will be discussed.

1.7.1 Arterial Stiffness

Atherosclerosis of the arterial system is the key pathological process that results in MI and ischemic stroke, causing considerable morbidity and mortality. Established risk factors for atherosclerosis include hypertension, diabetes, hyperlipidaemia, smoking and a family history of cardiovascular disease (CVD). Increasingly, aging is also considered an independent risk factor for atherosclerosis, and the pathological processes in aging vessels are similar to those seen in atherosclerosis.(O'Rourke and Hashimoto, 2007) The vessel wall is the common end organ on which all deleterious effects of these intermediate risk factors are targeted. Non-invasive assessment of the totality of damage caused to the vessel wall is therefore an attractive method for predicting vascular events and may be more accurate than measurement of any single risk factor alone. Arterial stiffness resulting from vascular remodelling (intimal and medial thickening) and loss of arterial elasticity is now increasingly recognized as a surrogate endpoint for the monitoring of CVD.(Laurent *et al.*, 2006) Indeed, measurement of arterial elastic properties has been suggested as a tool for the assessment of sub-clinical target organ damage by the European Society of Hypertension and the European Society of Cardiology guidelines for the management of arterial hypertension.(Mancia *et al.*, 2007)

1.7.2 Pathophysiology of Arterial Stiffness

The arterial system is made up of large elastic arteries that are rich in elastin and collagen, and smaller, more muscular peripheral arteries. The arterial wall consists of three layers: the tunica adventitia, tunica media and tunica intima. A monolayer of endothelial cells lines the tunica intima between the lumen and vessel wall.

While arterial tone is regulated by the endothelium, arterial elasticity is largely determined by the content of elastin, collagen and smooth muscle in the vessel

wall.(Bank *et al.*, 1996; Bank *et al.*, 1999) Collagen and elastin are the two prominent scaffolding proteins which contribute to the stability, resilience and compliance of the vessel wall. The relative content of these molecules is regulated by a slow but dynamic process of production and degradation. Imbalance in this process, resulting from stimulation of inflammatory cascades, leads to overproduction of abnormal collagen and diminished quantities of normal elastin, with a consequential increase in vascular stiffness.(Fleenor, 2013) Excessive collagen production is also stimulated by hypertension and hypercholesterolemia.(Xu *et al.*, 2000) In aging arteries, these molecular changes are manifested as a 2-3 fold increase in intima-media thickness with associated hypertrophy of the vascular smooth muscle layer.(Zieman *et al.*, 2005) Significant coronary stenosis is associated with increased aortic stiffness which improves after percutaneous coronary intervention.(Kalay *et al.*, 2012)

Endothelial cell signalling and vascular smooth muscle cell tone also influence arterial stiffness. Vascular tone can be modified by cell stretch and changes in calcium signalling.(Ando and Yamamoto, 2013) In addition, vascular tone is influenced by autocrine and paracrine mediators such as angiotensin II,(Dzau, 1986) endothelins,(Yanagisawa *et al.*, 1988) oxidative stress(Gurtner and Burke-Wolin, 1991) and nitric oxide.(Forstermann and Munzel, 2006) Increased expression of the nitric oxide synthase inhibitor, asymmetrical dimethyl arginine, has also been linked to vascular stiffening.(Miyazaki *et al.*, 1999)

Arterial calcification has been associated with traditional atherosclerotic risk factors such as increasing age, hyperlipidaemia, diabetes mellitus and smoking.(Allison *et al.*, 2004), (Post *et al.*, 2007) Aortic calcification, in particular, has been proven to be a predictor of aortic stiffness, and in addition, contributes to isolated systolic hypertension.(McEniery *et al.*, 2009)

Pressure wave is generated by the ejection of blood from the ventricle into the aorta. As this wave travels forward, it gets reflected back along branching points in the arterial tree more from the peripheral branches. The actual pressure waveform is a summation of the forward and reflected waves. In elastic arteries these reflected waves reach the ascending aorta in diastole. But with increasing arterial stiffness they reach the ascending aorta earlier in systole, augmenting systolic pressure and decreasing diastolic pressure.(Safar, 2006)

1.7.3 Importance of Arterial Elasticity

As the largest elastic blood vessel, the aorta is the main determinant of arterial compliance and hence, stiffness. The distensibility of the aorta is responsible for buffering the variation in flow and pressure generated by intermittent cardiac contraction. Loss of elasticity and decreased absorption of this pressure wave by the aorta may increase cardiac after load and impair coronary blood flow.(Nichols and O'Rourke, 2005; Safar and O'Rourke, 2006) The elastic properties of the arterial tree vary with increasing distance from the heart due to differences in the molecular, cellular and histological structure of the vessel wall.(Fischer and Llaurado, 1966; Latham *et al.*, 1985; Bezie *et al.*, 1998; Laurent *et al.*, 2005) Fracture of elastic lamellae is seen in the aorta with aging, and this finding may account for the functional and structural changes.(Virmani *et al.*, 1991)

1.7.4 Effect of Arterial Stiffness on Coronary Perfusion

In older subjects with hypertension, reflected waves travel rapidly back along the arterial tree towards the heart in early systole and are superimposed on the forward wave, increasing systolic pressure. In contrast, blood pressure falls sharply in diastole with reduced diastolic fluctuations.(Laurent *et al.*, 2006) The combined effect of aortic stiffness is thus to increase systolic pressure and decrease diastolic pressure.(Lakatta and Levy, 2003; Nichols and O'Rourke, 2005; Safar and O'Rourke, 2006) The increase in systolic afterload results in LV hypertrophy (LVH) and increases LV oxygen requirements. Additionally, LVH increases the duration of systole while decreasing the length of diastole due to abnormalities in isovolumetric relaxation.(Nichols and O'Rourke, 2005; Safar and O'Rourke, 2006) The increased demands on coronary flow from the hypertrophied ventricle are not met due to decreased aortic pressure throughout diastole and reduced duration of diastole. Thus, coronary blood flow is impaired independent of coronary stenosis and myocardial ischemia results from both increased demand and decreased coronary perfusion.(Ferro *et al.*, 1995) This leads to further impairment of ventricular relaxation and prolongation of the ejection period, all tending to further decrease myocardial perfusion.(Lakatta and Levy, 2003; Nichols and O'Rourke, 2005; Safar and O'Rourke, 2006) This vicious cycle may predispose to

angina in the presence of even minor coronary artery disease (CAD) and to the development of diastolic dysfunction, probably the commonest form of heart failure in the elderly.(Weber *et al.*, 2006)

1.7.5 Measures of Arterial Stiffness

Arterial elasticity in vivo has been assessed by several invasive and non-invasive methodologies. The three most common non-invasive measures (pulse wave velocity [PWV], central pulse wave analysis [PWA] and measurements of changes in arterial diameter to distending pressure) are discussed below.

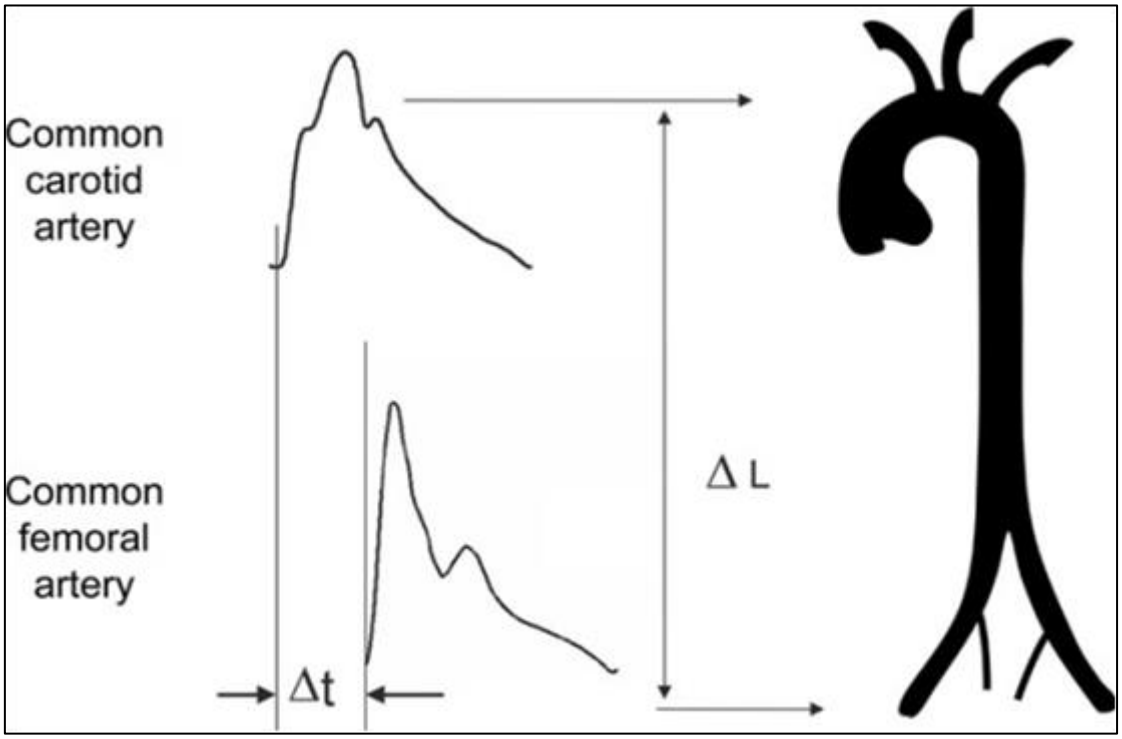
1.7.5.1 Pulse Wave Velocity

Carotid-femoral PWV is generally accepted as the most simple, non-invasive, robust and reproducible method to determine arterial stiffness, and is currently considered the gold-standard measurement.(Laurent *et al.*, 2006) PWV is usually measured by the foot-to-foot velocity method from various waveforms including pressure,(Asmar *et al.*, 1995) distension(van der Heijden-Spek *et al.*, 2000) and Doppler.(Cruickshank *et al.*, 2002) Aortic PWV can also be measured non-invasively using magnetic resonance imaging (MRI).(Mohiaddin *et al.*, 1993) Typically, the arterial PW is recorded at a proximal artery such as the common carotid, and at a distal site such as the femoral artery. The superficial location of these arteries means that their PW-forms are readily measured non-invasively, and between these two sites the PW has to travel through most of the aorta. The foot of the PW occurs at the end of diastole when the steep rise in pressure begins. The time delay between the wave foots at each location is simultaneously measured by continuous Doppler probe (Cruickshank *et al.*, 2002) or by gating to the peak of the R-wave on the ECG.(Millasseau *et al.*, 2000; van der Heijden-Spek *et al.*, 2000)

The measurement of PWV by the foot-to-foot method is illustrated in **Figure 1.4**. PWV is calculated as distance (meters)/transit time (seconds). The transit time is the time of travel of the foot of the wave over a known distance. Distance covered by the PW is defined as the surface distance between the two recording sites. Multiple branches of the aorta with focal atherosclerosis at branching points generate wave reflections and attenuation which can distort the transit time estimation and subsequently affect accurate measurement of PWV.(Stevanov *et al.*, 2001) The measured distance is an estimate of the true distance travelled and may vary according to body habitus and the tortuosity of the abdominal aorta. Aortic tortuosity increases with age, (Wenn and Newman, 1990) potentially leading to an underestimation of PWV. Inaccurate measurement of the distance may therefore adversely affect the absolute value of the PWV.(Chiu *et al.*, 1991) **Figure 1.5** is an example of carotid-femoral PWV measured by the Vicorder device (Skidmore Medical Limited, Bristol, UK). It should be noted that the femoral pressure waveform may be difficult to record accurately in patients with metabolic syndrome, diabetes, obesity and peripheral vascular disease.(Van Bortel *et al.*, 2002) Raised PWV occurs alongside a range of established cardiovascular risk factors,(Lehmann *et al.*, 1998) including age,(Vaitkevicius *et al.*, 1993)

hypercholesterolemia,(Lehmann *et al.*, 1992) type I and II diabetes(Zhang *et al.*, 2011; Theilade *et al.*, 2013) and a sedentary lifestyle.(Vaitkevicius *et al.*, 1993)

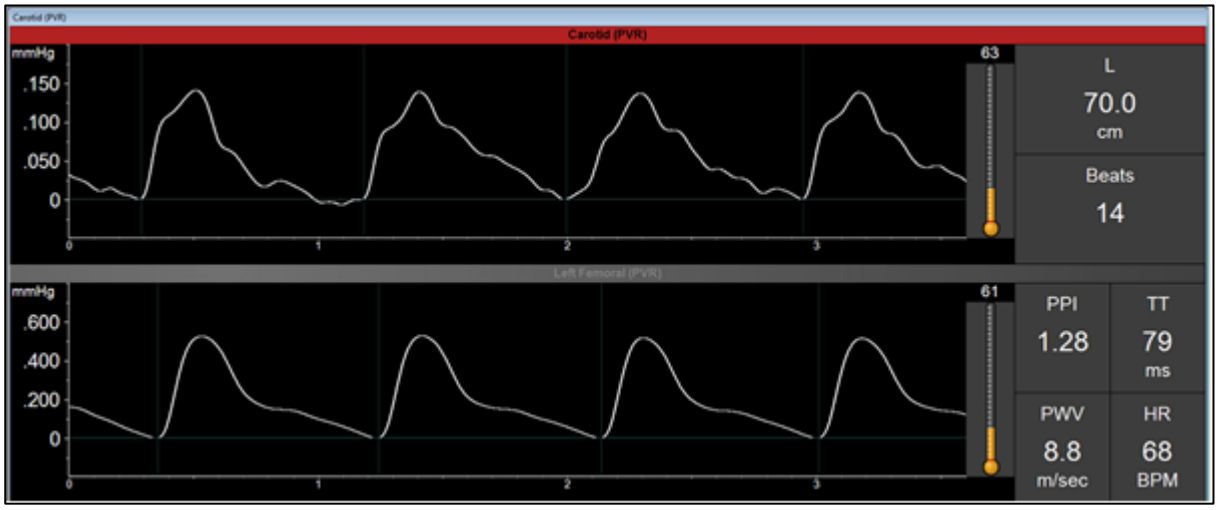
Figure 1.4: Measurement of carotid-femoral PWV with the foot to foot method



The foot of the wave is at the end of diastole, when the steep rise of the wave front begins. The time between the foot of the carotid and femoral pulse waves is used to calculate the PWV. PWV – pulse wave velocity.

Adapted from Laurent et al. European Network for Non-invasive Investigation of Large A. Expert consensus document on arterial stiffness: Methodological issues and clinical applications. European Heart Journal. 2006; 27:2588-2605

Figure 1.5: PWV measurement: A case example



Pulse wave velocity (PWV) measurement from a 75 year old man who had multi-vessel percutaneous coronary intervention for non ST elevation myocardial infarction using Vicorder device (Skidmore Medical Limited, Bristol, UK), which records simultaneous pulse volume at the carotid and femoral artery using pneumatic cuffs. Length travelled by the pulse wave is from the suprasternal notch to the mid cuff in the thigh. PWV is calculated from the distance travelled (L) divided by the transit time (TT). PWV (8.8m/sec) in this patient is normal for his age.

1.7.5.2 Direct Measurement of Arterial Stiffness in Specific Arteries

A direct measure of arterial stiffness may be made by assessing the change in diameter in relation to the distending pressure.(Oliver and Webb, 2003) This is possible in a number of superficial arteries, including the carotid, brachial, and radial arteries, and the aorta. Carotid stiffness may be of particular interest, since atherosclerosis is frequent in carotid arteries.(Laurent *et al.*, 2006) Local arterial stiffness of superficial arteries is most commonly determined using ultrasound devices, although MRI has also been used. Ultrasound measurements, although simpler to perform, are limited in precision due to the need for video-image analysis. More recently, echo tracking devices have been developed to measure diameter at end-diastole and stroke change in diameter with very high precision. These devices use the radiofrequency signal to obtain a resolution 6-10 times higher than video-image systems.(Tardy *et al.*, 1991)

1.7.5.3 Central Pulse Wave Analysis

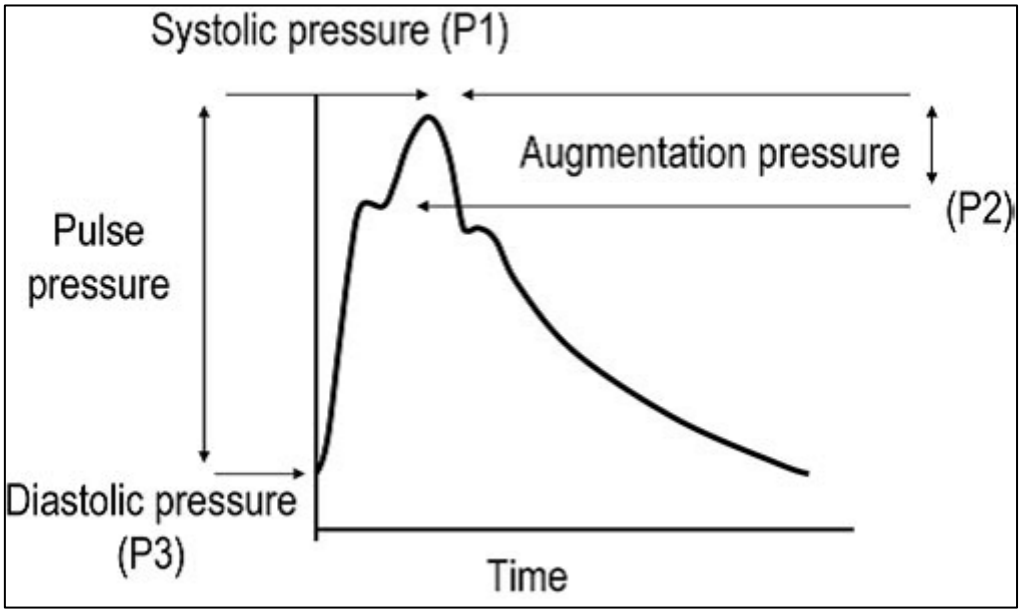
The arterial pressure waveform is a composite of the forward pressure wave created by ventricular contraction and a reflected wave returning from the peripheries. Since the PWV is low in elastic vessels, under normal circumstances the reflected wave reaches the aortic root in diastole. However, as the PWV increases with increasing arterial stiffness, the reflected wave reaches the aortic root earlier, augmenting the forward wave and creating a second, higher peak systolic pressure in the forward wave (**Figure 1.6**). The difference between the first and second systolic peaks is defined as the augmentation pressure. The augmentation index (AI) is defined as the ratio of the augmentation pressure to pulse pressure (PP).(O'Rourke, 1982; London *et al.*, 1992; Mackenzie *et al.*, 2002) PP is calculated as the difference between the systolic blood pressure and diastolic blood pressure. The AI is thus the proportion of central PP that results from arterial wave reflection and is a commonly used measure of arterial stiffness. AI increases with mean arterial pressure (MAP),(Wilkinson *et al.*, 2001) and is inversely related to heart rate(Wilkinson *et al.*, 2000; Gatzka *et al.*, 2001) and body height.(Smulyan *et al.*, 1998)

Ideally, the arterial pressure waveform should be analysed in the ascending aorta, since this represents the true load imposed on the left ventricle and large central arterial walls. Since this is rarely practical in a clinical context, the central aortic

pressure waveform can be estimated from the waveforms measured in the common carotid or radial arteries.(Chen *et al.*, 1996; Chen *et al.*, 1997; Pauca *et al.*, 2001) **Figure 1.7** is an example of PWA measured utilizing the Vicorder device. Because the waveform contour from the radial artery is different from that of the ascending aorta, a transfer function is required to approximate it with the central aortic waveform.(Karamanoglu *et al.*, 1993; Chen *et al.*, 1997) The transfer function is typically built into the computer software for PWA and is calibrated using peripheral blood pressure. However, the transfer function is typically derived from healthy subjects and may not be accurate in different patient populations.(Hope *et al.*, 2004b) Furthermore, issues with methods to calibrate the tonometer to the non-invasively measured blood pressure and reflection waves, which are caused by compression of the peripheral artery by the tonometer, can make estimation of central waveforms unreliable using transfer functions.(Hope *et al.*, 2004a)

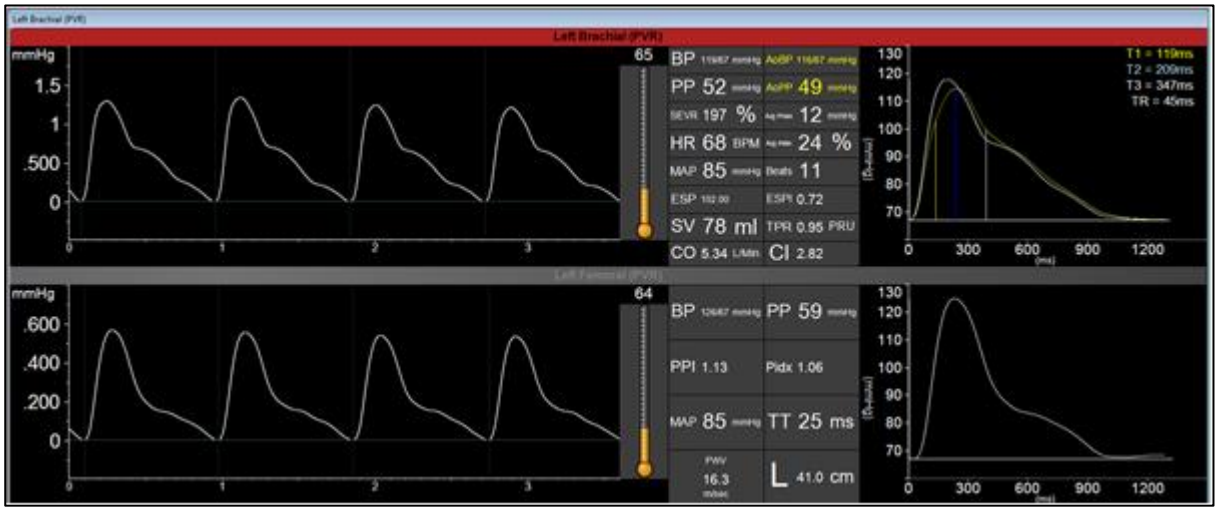
PWA should include central pulse pressure, central systolic pressure and AI.(Laurent *et al.*, 2006) Compared to PWV, which is a direct measure of arterial stiffness, central PP and AI are indirect, surrogate markers of arterial stiffness. Central PWA and aortic PWV determine the contribution of aortic stiffness to wave reflections.(Laurent *et al.*, 2006)

Figure 1.6: Augmentation Index



The height of the late systolic peak (P1) above the inflection (P2) defines the augmentation pressure, and the ratio of augmentation pressure to PP defines the AI (%).

Figure 1.7: Pulse wave analysis: A case example



Pulse wave analysis from a 75 year old man who had multi-vessel PCI for NSTEMI using the Vicorder device (Skidmore Medical Limited, Bristol, UK) at the brachial and femoral artery measured by pneumatic cuffs. In this patient Augmentation Index (24%) is expected for age, with increased PWV (16.3m/sec) suggestive of arterial stiffness

1.7.6 Usefulness of Arterial Stiffness as a Predictor of Cardiovascular Events

The utility of PWV as an additive and independent predictor of cardiovascular events has been tested prospectively in a number of different community and patient populations (**Table 1.4**). These are discussed below.

1.7.6.1 Older Patients

In a report involving patients from the Health Aging and Body Composition (Health ABC) study, aortic PWV was measured at baseline in 2488 generally healthy and community-dwelling older adult participants (mean age±SD, 73.7±2.9 years). Over 4.6 years, 265 deaths occurred, 111 as a result of cardiovascular causes. Results were presented by quartiles because of a threshold effect between the first (lowest) and second aortic PWV quartiles. Higher aortic PWV was associated with both total mortality (relative risk [RR], 1.5, 1.6, and 1.7 for aortic PWV quartiles 2, 3, and 4 vs. quartile 1; p=0.019) and cardiovascular mortality (RR 2.1, 3.0, and 2.3 for quartiles 2, 3, and 4 vs. quartile 1; p=0.004). A higher aortic PWV quartile was also significantly associated with coronary heart disease (p=0.007) and stroke (p=0.001). These associations remained after adjustment for age, gender, race, systolic blood pressure and known CVD.(Sutton-Tyrrell *et al.*, 2005) A further study in the very elderly specifically analysed whether PWV remained an important prognostic indicator for hospital in-patients aged 70 to 100 years. During the 30-month follow-up, 56 patients died, including 27 from cardiovascular causes. While age and loss of autonomy were the strongest predictors of all-cause mortality, aortic PWV was the strongest predictor of cardiovascular mortality (OR 1.19; 95% CI 1.03-1.37, p=0.016).(Meaume *et al.*, 2001)

Table 1.4: Studies Linking Arterial Stiffness to Cardiovascular Outcomes

Study/Year	Number	Mean Age (years)	Mean F/U (years)	Findings
Community Population				
Mitchell et al.(Mitchell *et al.*, 2010) 2010	2232	63	7.8	48% increased CVD risk, 95% CI 1.16-1.91 per SD, *p*=0.002
Wang et al.(Wang *et al.*, 2010) 2010	1272	52	15	Each 1 SD (2.3 m/s in men and 2.5 m/s in women) increase in PWV is associated with increased CV mortality (HR 1.56, 95% CI 1.25-1.94 in men and HR 1.94, 95% CI 1.56-2.42 in women)
Anderson et al.(Anderson *et al.*, 2009) 2009	174	60	19.6	Increased all-cause mortality per 1 m/s increase in PWV, HR 1.15, 95% CI 1.01-1.30
Willum-Hansen et al.(Willum-Hansen *et al.*, 2006) 2006	1678	40-70	9.4	Each 1 SD increment in aortic PWV (3.4 m/s), the risk of an event increased by 16-20%, *p*<0.05
Community Older Population				
Mattace-Raso et al.(Mattace-Raso *et al.*, 2006) 2006	2835	71	4.1	Increased CHD with increased aortic PWV Second tertile HR 1.72; 95% CI 0.91-3.24; Third tertile HR 2.45;95% CI 1.29-4.66
Sutton-Tyrrell et al.(Sutton-Tyrrell *et al.*, 2005) 2005	2488	74	4.6	Higher aortic PWV was associated with all-cause mortality RR, 1.5, 1.6, and 1.7 for aortic PWV quartiles 2, 3, and 4 vs. quartile 1; *p*=0.019 and CV mortality RR 2.1, 3.0, and 2.3 for quartiles 2, 3, and 4 vs. quartile 1; *p*=0.004.
Hospitalised Older Patients				
Meaume et al.(Meaume *et al.*, 2001) 2001	141	87	2.5	Increased PWV predicts CV mortality, OR 1.19, 95% CI 1.03-1.37, *p*=0.018
PCI				
Kaneko et al.(Kaneko *et al.*, 2013) 2013	236	67	0.5-1	Higher brachial ankle PWV (18.3± 3.7 vs. 15.8± 3.1m/s, *p*<0.001) was an independent predictor of PCI to previously non-significant lesions

CVD-Cardio Vascular Disease, CHD-Coronary Heart Disease, PWV-Pulse Wave Velocity, ESRD-End Stage Renal Disease, T2DM-Type 2 Diabetes Mellitus, STEMI-ST Elevation Myocardial Infarction, PCI-Percutaneous Coronary Intervention, SD- Standard Deviation, CI-Confidence Interval, HR-Hazard Ratio, RR- Relative Risk, LV- Left Ventricle

1.7.7 Interpretation of evidence on arterial stiffness and CVD

Arterial stiffness is a measure of atherosclerotic burden in large calibre arteries. Arterial stiffness can be measured by both invasive and non-invasive techniques. Arterial stiffness has been shown to predict adverse CV outcomes. It has been studied in community population but not in patients with established CVD. It has not been studied in older patients with ACS. It can be a risk stratification marker like hypertension.

Similar to arterial stiffness in large calibre arteries, endothelial dysfunction in smaller calibre arteries leads on to adverse CV events. Endothelial dysfunction will be reviewed in the following section.

1.8 Endothelial Dysfunction and Coronary Artery Disease

The endothelium represents the interface between circulating blood and the vascular wall. Through its role in signal transduction and as a source of multiple vasoactive substances, it is a key regulator of vascular homeostasis(Vita and Keaney, 2002). Altered endothelial function precedes the development of morphological atherosclerotic changes. Indeed, endothelial dysfunction is considered the earliest marker of atherosclerosis(Luscher and Barton, 1997) and contributes to lesion development and its later clinical manifestations(Ross, 1993). Cardiovascular risk reduction therapies such as statins and smoking cessation improve endothelial function, whilst the failure of the endothelium to respond to such therapies is associated with higher CV risk (Modena *et al.*, 2002). Endothelial dysfunction is also associated with increased risk of cardiovascular events and its presence has thus been proposed as a marker of heightened CV risk (Schachinger *et al.*, 2000; Suwaidi *et al.*, 2000; Halcox *et al.*, 2002).

1.8.1 Role of Endothelium in Regulation of Vascular Tone

Rather than simply an inert barrier between blood and the vessel wall, the endothelium is a monolayer of cells which respond to physical and chemical signals by the production of multiple autocrine and paracrine vasoactive factors. These factors regulate basal vascular tone, cellular adhesion, thrombogenicity, smooth muscle cell proliferation, and vessel wall inflammation (Luscher and Barton, 1997; Kinlay *et al.*, 2001). Through modulation of vascular tone, the endothelium plays a direct role in maintaining the balance between oxygen supply and demand, and maintaining organ perfusion (Schechter and Gladwin, 2003). Vascular tone is dependent upon the balance between endothelium-derived vasodilators, consisting of Nitric Oxide (NO), prostacyclin, endothelium-derived hyperpolarising factors (EDHF) and C-type naturietic peptide (CNP), and vasoconstrictors, including endothelin-1 (ET-1) and thromboxane.

1.8.2 Endothelial Dysfunction

The mitochondrion is an important source of reactive oxygen species (ROS) and production of ROS and mitochondrial superoxide dismutase (SOD) are carefully balanced during oxidative phosphorylation (Li *et al.*, 1995). This balance may be disturbed during hypoxia, or by obesity-related metabolic disorders and type II diabetes, which are conditions characterized by hyperglycaemia and increased circulating free fatty acids (Li *et al.*, 1995; Evans *et al.*, 2002). Cardiovascular risk factors also modulate expression of chemokines, cytokines, and adhesion molecules by the endothelium. This change in endothelial phenotype likely results from a switch in signalling from NO-mediated inhibition of cellular processes to one of activation by redox signalling, as discussed below. This switch may further lead to interaction with circulating leukocytes and platelets and the initiation of inflammation (Hansson, 2005).

1.8.3 Mechanisms of Endothelial Dysfunction

Sub-endothelial entry and retention of apolipoprotein B–containing lipoproteins plays a central role in the initiation of atherosclerosis by activating the inflammatory process (Tabas *et al.*, 2007). A variety of cardiovascular risk factors including type II diabetes, hypercholesterolaemia, smoking, chronic inflammation and aging are associated with an increase in the expression of nicotinamide adenine dinucleotide phosphate (NADPH)-oxidases in the vessel wall and consequent overproduction of ROS (Griendling *et al.*, 2000; Babior, 2004). Formation of peroxynitrite from the combination of ROS and NO has been proposed as an initial step in the chronic dysregulation of normal NO production by eNOS that characterises endothelial dysfunction (Koppenol *et al.*, 1992; Griendling and FitzGerald, 2003). Central to this change is an increase in monomerisation (‘uncoupling’) of eNOS from its tetrahydrobiopterin (BH4) cofactor. In monomeric form, eNOS produces superoxide, rather than NO. A vicious cycle is initiated, with ROS and superoxide reacting with NO to form peroxynitrite, which in turn oxidises BH4 to a biologically inactive BH3 radical, leading to a further uncoupling of eNOS and further superoxide production (Milstien and Katusic, 1999; Landmesser *et al.*, 2003). Peroxynitrite may have additional direct effects on zinc binding that further promote eNOS uncoupling and is itself a mediator of LDL oxidation, with consequent pro-atherogenic effects (Griendling and FitzGerald, 2003). When uncoupled, eNOS

thus switches from its oxygenase function producing NO to a reductase function producing ROS. The consequent oxidant excess then exerts a deleterious effect on endothelial and vascular function.

Oxidative stress is linked to a pro-inflammatory state of the vessel wall. ROS up regulate expression of adhesion molecules [intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1)] and chemotactic molecules [macrophage chemo attractant peptide-1 (MCP-1)].(Griendling and FitzGerald, 2003) Increased level of C-reactive protein (CRP) has been associated with decreased eNOS activity.(Venugopal *et al.*, 2002; Verma *et al.*, 2002) Other important sources of oxidative stress in the endothelium are NADPH oxidases and xanthine oxidase, which have been shown to have increased activity in the arteries of patients with coronary disease.(Griendling *et al.*, 2000; Spiekermann *et al.*, 2003).

1.8.4 Measures of Endothelial Function

Endothelium dependent vasomotion can be assessed by invasive and non-invasive methods, both in the coronary and peripheral circulation.

1.8.4.1 Assessment of Peripheral Arterial Endothelial Function

1.8.4.1.1 Invasive

Coronary endothelial function has been shown to correlate closely with endothelial function in the brachial artery.(Anderson *et al.*, 1995) Hence, intra-brachial infusion of vasoactive drugs has been used as a surrogate measure of coronary endothelial function.(Anderson *et al.*, 1995; Virdis *et al.*, 2001; Wilkinson and Webb, 2001) Insertion of a cannula into the brachial artery for local drug infusion allows use of doses far lower than would be required to have a biological effect if given systemically. Results are expressed as the ratio of the change in flow between the control and infused forearm and are highly reproducible.(Petrie *et al.*, 1998) The disadvantage of this method is the risk of injury to the brachial artery and median nerve.

1.8.4.1.2 Non-invasive

1.8.4.1.2.1 Flow-mediated Dilatation (FMD)

The vascular endothelium is capable of transducing changes in shear stress to modulate vascular tone. Although the precise mechanism is still debated, an increase in blood flow and shear stress leads to vasodilation. Measurement of flow-mediated vasodilatation (FMD) of the forearm arteries is a widely used technique to assess endothelial function. Forearm blood flow can be measured by venous occlusion plethysmography. Changes in forearm size in response to changes in arterial blood inflow during brief venous occlusion are measured using an external strain gauge, with the contralateral forearm acting as an internal control.(Whitney, 1953; Wilkinson and Webb, 2001) This technique involves baseline ultrasound measurement of brachial artery dimensions and Doppler estimation of flow. After 5 minutes of arterial inflow occlusion, the BP cuff is released and the effect on brachial arterial size of the resultant hyperaemic flow is measured.(Joannides *et al.*, 1995a; Joannides *et al.*, 1995b;

Lieberman *et al.*, 1996) Typically a change of 5% in dilatation can be detected but measurement of such a small change requires reliable and accurate methods.

This technique of measuring FMD is technically difficult and requires extensive training. A number of parameters including study subject preparation, image acquisition and site selection, sphygmomanometer probe position, cuff occlusion time, accurate use of edge-detection software and correct characterization of the FMD response, can have a major impact on results.(Charakida *et al.*, 2010; Harris *et al.*, 2010; Thijssen *et al.*, 2011) Because of this, FMD assessment is limited by inter observer variability and reproducibility. Nevertheless, peripheral endothelial function as assessed by FMD correlates well with coronary artery endothelial function. In a study of 50 patients undergoing cardiac catheterisation, coronary endothelial dysfunction was significantly associated with impaired-flow mediated dilatation in the brachial artery compared to patients with normal coronary endothelial function (4.8 ± 5.5% vs. 10.8 ± 7.6%, $p < 0.01$).(Anderson *et al.*, 1995)

Vasoconstriction of the brachial artery in response to a decrease in blood flow and shear stress induced by a distally placed cuff has been termed low-flow-mediated constriction (LFMC).(Gori *et al.*, 2008; Gori *et al.*, 2010; Gori *et al.*, 2011) The predictive power of a risk factor model based on traditional risk factors for CAD was improved by the addition of LFMC and FMD.(Gori *et al.*, 2012)

1.8.4.1.2.2 Peripheral Arterial Tonometry

Peripheral arterial tonometry (PAT) by finger plethysmography (EndoPAT©; Itamar Medical) is a novel way to measure the peripheral vasodilator response.(Lavie *et al.*, 2000; Kuvin *et al.*, 2003) PAT signal amplitude increases in response to hyperaemia and gives a measure of NO mediated endothelial function.(Noon *et al.*, 1996; Nohria *et al.*, 2006) PAT signals are recorded from the index fingers with pneumatic probes at baseline, during cuff occlusion and during hyperaemia. A measure of endothelial function is calculated from the ratio of PAT signal amplitude at baseline and post-occlusion. The advantages of this technique are that the contralateral arm acts as an internal physiological reference and that the device is easy to use. In a study by Bonetti et al., (Bonetti *et al.*, 2004) of 94 patients without obstructive CAD, digital reactive hyperaemic index was lower in patients with coronary endothelial dysfunction

compared with normal endothelial function (1.27 ± 0.05 vs. 1.78 ± 0.08, $p < 0.001$). In this study coronary endothelial function was assessed by CBF response to intracoronary acetylcholine (ACh).

1.8.5 Association of Endothelial Dysfunction and CV outcomes

Traditional risk factors for the development of atherosclerosis such as hypertension, diabetes, hypercholesterolemia, smoking and a family history of premature cardiovascular disease are associated with endothelial dysfunction.(Vita *et al.*, 1990; John *et al.*, 1998; Schachinger *et al.*, 1999) This has raised the question of whether endothelial dysfunction is an independent predictor of CV events.

1.8.5.1 Studies Using FMD

Several studies have now shown an association between endothelial dysfunction and poor CV outcomes. The Fire fighters and Their Endothelium (FATE)(Anderson *et al.*, 2011b) study recruited 1574 male fire fighters who were clinically free of cardiovascular disease and had a lower incidence of CV risk factors than a general community population. Brachial artery FMD and hyperaemic velocity was measured in each participant. Over a mean follow up of 7 years, FMD corrected for shear stress (HR 1.18 per SD; 95% CI 1.09-1.28; $p<0.001$) and hyperaemic velocity time integral (VTI) (HR 0.52 per SD; 95% CI 0.41-0.66; $p<0.001$) were a significant predictor of CV events (n=111, 7% - non-fatal myocardial infarctions [MI], coronary revascularisations, cerebrovascular disease and peripheral vascular disease). However, FMD alone did not predict CV events (HR 0.92; p=0.54).

In the Cardiovascular Health Study, (Yeboah *et al.*, 2007) FMD was measured in 2792 elderly adults (age range 72 - 98 years). After 5 years, 24% of patients had a CV event and FMD remained a significant predictor of CV events even after adjustment for traditional CV risk factors (HR 0.91; 95% CI 0.83-0.99, p=0.02 per unit SD of FMD).

In the Multi-Ethnic Study of Atherosclerosis (MESA), brachial artery FMD was measured in 3026 adults not known to have history of CVD at recruitment and followed up for 5 years (Yeboah *et al.*, 2009). At follow up 6% of patients had CV events. In univariate analysis adjusted for age and sex, FMD per unit SD was significantly associated with incident CV events including MI, angina, coronary revascularization, stroke, resuscitated cardiac arrest, and CVD death (HR 0.79; 95% CI 0.65-0.97; p=0.01). Similarly in multivariate analysis adjusted for traditional CV risk factors, FMD per unit SD was significantly associated with incident CV events (HR 0.84; 95% CI 0.71-0.99; p=0.04).

1.8.5.2 Studies Using Invasive Techniques

Similar results have been demonstrated when endothelial dysfunction has been measured using invasive techniques. In 308 patients undergoing cardiac catheterisation for investigation of chest pain or abnormal non-invasive cardiac investigations, Halcox et al. (Halcox *et al.*, 2002) measured coronary vascular resistance and epicardial coronary artery diameter to assess endothelium-dependent and independent coronary vasodilation following intracoronary infusions of ACh and sodium nitroprusside, respectively. 11.3% of patients experienced an acute CV event during a follow up period of four years. The study population was divided into tertiles according to the change in coronary vascular resistance (CVR) with ACh and an association between decreased microvascular dilatation and acute CV events (sudden cardiac death, MI, unstable angina and stroke) as measured by CBF (CBF increase of 67 ± 12% versus 114 ± 6%; p=0.007) and CVR (CVR fall of 28 ± 6% versus 46 ± 2%; p=0.007) was demonstrated. Acute CV events were more frequent in patients who had epicardial constriction following IC ACh (13% versus 9.4%, p=0.003 by Kaplan Meir analysis). However, there was no difference in event-free survival when analysed by epicardial artery diameter change in response to sodium nitroprusside (p=0.33). From this it can be inferred that endothelium-dependent vasodilatation abnormalities have prognostic implications but abnormalities of endothelium-independent vasodilatation do not.

Suwaidi et al. (Suwaidi *et al.*, 2000) evaluated coronary flow reserve (CFR) in 157 patients referred for coronary angiography who had minor CAD. Based on CFR, endothelial dysfunction was classified as normal, mild or severe. Over an average follow up period of 2.3 years, 14% of patients with severe endothelial dysfunction experienced cardiac events (MI, revascularisation and or death) whilst there were no events in patients with normal or mild endothelial dysfunction ($p<0.05$). This study suggests that severe endothelial dysfunction may play an important role in the progression of CAD.

In a study by Schachinger et al. (Schachinger *et al.*, 2000) endothelium dependent and independent coronary vasodilatation was assessed in 147 patients undergoing coronary angiography or single vessel percutaneous coronary intervention (PCI). By multivariate Cox regression analysis over a median follow up period of 8 years impaired

coronary endothelial vasoreactivity in response to ACh (p=0.053), cold pressor (p=0.012), increased blood flow (p=0.01) and nitroglycerin (p=0.01) was an independent predictor of CV events.

1.8.5.3 Studies Using PAT

Rubinshtein et al., (Rubinshtein *et al.*, 2010) measured reactive hyperaemia index (RHI) in 270 patients who presented with unexplained chest pain and low-risk findings during stress testing and/or the absence of new obstructive lesions on angiography. During a mean follow up period of 5.8 years adverse cardiac events (CV death/MI/revascularisation or CV hospitalisation) occurred in 86 patients (31%). Adverse events were higher in patients with a natural logarithmic scaled RHI of <0.4 compared with ≥0.4 (48% versus 28%, p=0.03, HR 1.83, 95% CI 1.18-2.81). This finding was mainly driven by increased CV death (3.9% versus 0%, p=0.032) and CV hospitalisations (30.5% versus 18.7%, p=0.018, HR 2.06; 95% CI 1.26-3.38).

1.8.6 Endothelial Dysfunction after PCI

Balloon angioplasty causes coronary endothelial dysfunction, as evidenced by impaired vasodilatation in response to intracoronary ACh, 3-6 months after coronary angioplasty.(Vassanelli *et al.*, 1994) The severity of endothelial dysfunction 6 months after PCI in the left anterior descending artery was worse after PCI with stent compared to PCI with balloon angioplasty or directional atherectomy alone.(Caramori *et al.*, 1999) A differential effect on endothelial dysfunction has also been noted related to the type of drug eluting stents deployed. Coronary vasoconstriction in response to different stimuli (ACh, exercise and pacing) has been noted in multiple studies in the chronic phase following sirolimus-eluting (SES) and paclitaxel-eluting stents (PES), but not with zotarolimus-eluting (ZES) and biolimus-eluting stents (BES), compared with bare-metal stent (BMS).(Minami *et al.*, 2013) The inflammatory response of the vascular wall, stent strut size, the drug eluted and the type of polymer remaining on the stent have each been postulated to influence long-term endothelial function.

1.8.7 Interpretation of evidence on endothelial dysfunction

Endothelial dysfunction predisposes to atherosclerotic changes and plaque development. It can be measured by both invasive and non-invasive techniques. There is a significant association between endothelial dysfunction and adverse CV events. Limited studies have assessed endothelial dysfunction in patients with CAD. It has not been studied in older patients.

Carotid intima media thickness has been extensively studied as a marker of atherosclerotic burden and adverse CV events. This will be reviewed in the next section.

1.9 Carotid Intima Media Thickness

Progression of atherosclerosis results in cardiovascular disease leading to considerable morbidity and mortality, hence direct visualization of the carotid artery quantifying the atherosclerotic burden on the carotid wall can be a useful tool in the cardiovascular and cerebrovascular risk assessment.

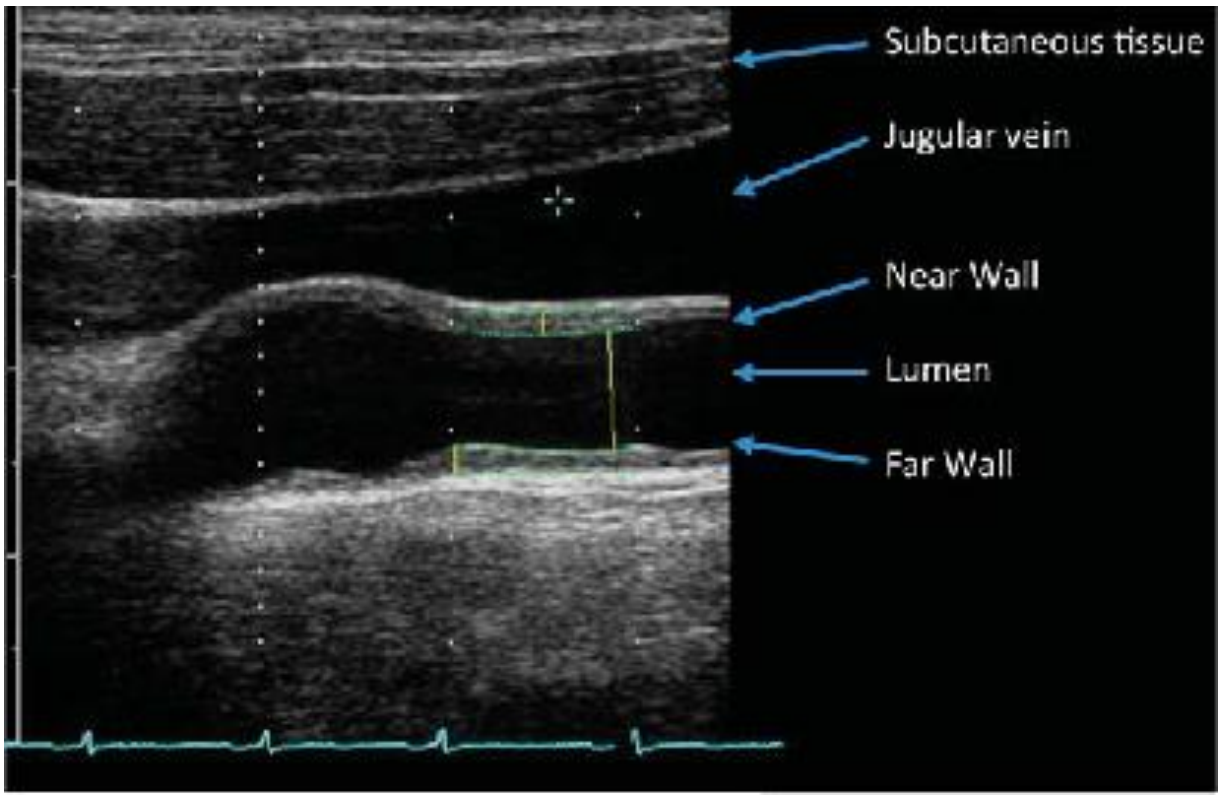
1.9.1 Marker of Subclinical Atherosclerosis

Carotid Intima Media Thickness (CIMT) measurements by non-invasive ultrasound imaging correlated well with measurements from histology specimens.(Pignoli *et al.*, 1986) In this study the authors described a characteristic B-mode image of the arterial wall composed of two parallel echogenic lines separated by a hypo echoic space which was similar to the IMT measured on pathologic examination. The investigators concluded that B-mode imaging could be a useful approach to the measurement of IMT in vivo. The ‘double echo’ pattern shown to represent the combined width of the carotid artery intima and media can be easily accessed for non-invasive imaging by ultrasound. Subsequently CIMT is the most widely used non-invasive measurement of atherosclerosis to quantify the severity of sub-clinical disease.(O'Leary and Bots, 2010)

1.9.2 Carotid Artery Segments and Layers on Ultrasonography

Carotid artery is divided into three segments each approximately 1 cm in length. The proximal segment, immediately prior to the carotid artery bifurcation is the common carotid artery (CCA) which is extra cranial. The mid segment is the carotid bulb formed by the diverging near and far walls with the artery beginning to divide into internal and external branches. The distal margin of the carotid bulb is defined by the tip of the flow divider separating the diverging internal carotid artery (ICA) and external carotid artery (ECA). The final distal segment is the proximal 1 cm of the ICA. The proximal CCA can be readily and reproducibly visualized in nearly all subjects as the carotid artery is superficial, relatively stationary and runs parallel to the neck until bifurcation.(O'Leary and Bots, 2010) The tissue layer lying between the luminal border of the artery and the boundary between the media and adventitia layers forms the intima media portion. In the absence of plaques these layers are distinguished by B-mode ultrasonography as in **Figure 1.8**.

Figure 1.8: Carotid artery segments by B-mode ultrasound



Reproduced from O'Leary et al.(O'Leary and Bots, 2010)

1.9.3 Important Considerations with CIMT Measurements

Intima media thickness need to be differentiated from carotid atherosclerotic plaque. Carotid plaque is defined as a focal structure that encroaches into the lumen of at least 0.5mm or 50% of surrounding IMT value or a thickness >1.5mm from the media adventitia interface to the intima lumen interface.(Touboul *et al.*, 2012) Carotid IMT can vary according to the cardiac cycle by 0.03mm, being thickest at end of diastole and thinnest at peak systole. The CIMT value also varies according to the segment measured, near or far wall measurement and method used for measuring (automated or manual tracing).(Bots *et al.*, 2003)

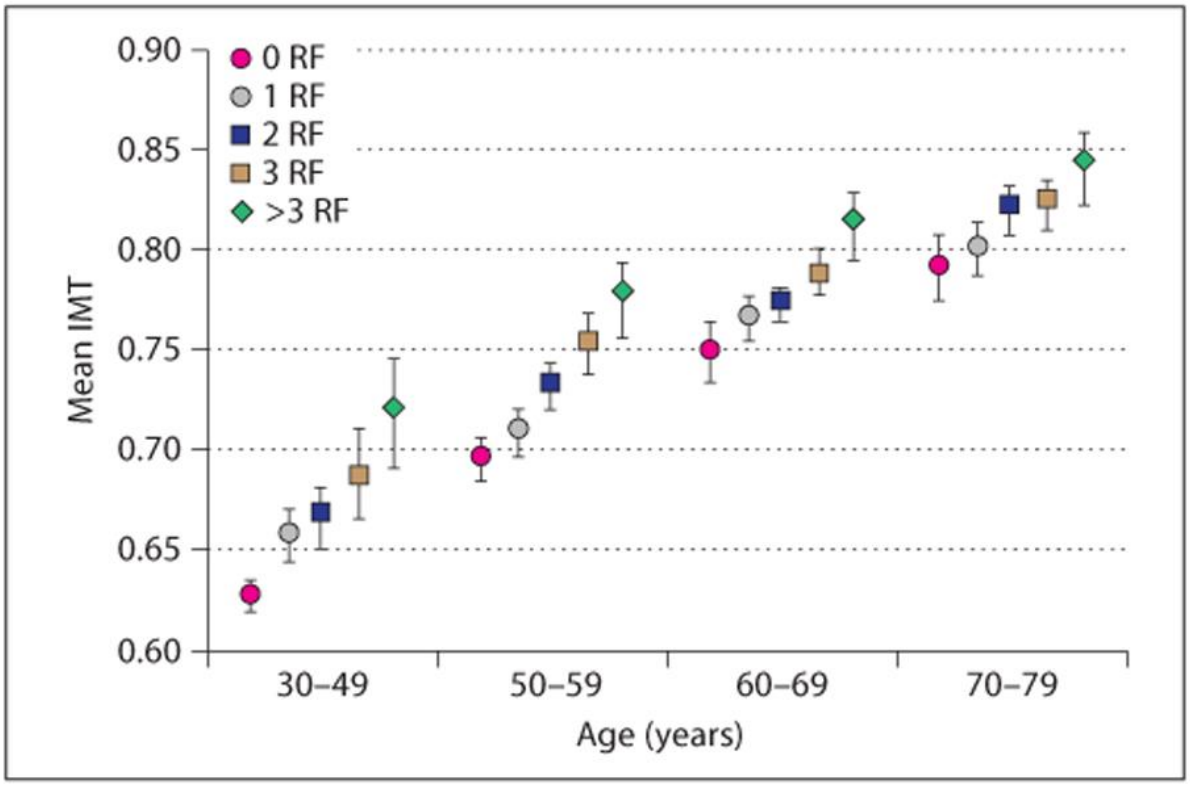
1.9.4 Automated Edge Detection for CIMT Measurements

Automated edge detection programmes reduces the variability in CIMT measures and are designed for measuring far wall CIMT in the CCA. The advantage of this method is that it reduces differences between readers and abolishes reader drift (change in reading behaviour with time).(O'Leary and Bots, 2010) Automated edge detection CIMT measurements are more accurate compared to manual measurements.(Touboul *et al.*, 1992) The manual and semi manual measures are time consuming and require rigorous quality control. It has to be noted that the variation in CIMT values is not only influenced by readers but can also be imaging by differing sonographers. Automated edge detection works well with clear interfaces and would need manual correction if interfaces are not clear.(Tang *et al.*, 2000)

1.9.5 Factors Influencing CIMT

IMT increases with age from 18 years and is associated with CV risk factors. Increased IMT values are associated with multiple CV risk factors like diabetes, hypertension, hyperlipidaemia and smoking.(Heiss *et al.*, 1991; Kuller *et al.*, 1994; Lassila *et al.*, 1997) Reference values varies according to the age, gender, gender, ethnicity and associated risk factors as depicted in **Figure 1.9**. In addition the differing methodologies used in various epidemiological studies makes it difficult to standardise reference values.(Bots *et al.*, 2003) Mannheim consensus on CIMT defines the methods to be used for CIMT assessment in clinical trials and epidemiological studies.(Touboul *et al.*, 2012)

Figure 1.9: CIMT values according to age group and CV risk profile



Reproduced from Touboul et al.(Touboul et al., 2012)

1.9.6 Association of CIMT with CV outcomes

In the prospective ARIC study (Atherosclerosis in Communities) of 15792 healthy subjects (45-65 years), increased mean CIMT at baseline was associated with increased risk of CHD over a follow up period of 4-7 years (HR for men 1.85; 95% CI 1.28-2.69 and HR for women 5.07, 95% CI 3.08-8.36).(Chambless *et al.*, 1997) This is the first major epidemiological study linking CIMT to CV events. Similarly in the Rotterdam study of 7983 patients (>55 years) over a period of 2.7 years, the risk of stroke increased with increasing common CIMT (OR per SD increase in CIMT 1.41, 95% CI 1.25-1.82). In the same way the risk of MI increased 43% per SD increase in common CIMT (OR 1.43; 95% CI 1.16-1.78).(Bots *et al.*, 1997) Excluding the patients with previous stroke or MI increased the OR and adjustment for CV risk factors slightly decreased the OR. In the Cardiovascular Health Study, 4476 older patients (>65 years) without prior CV events were grouped into CIMT quintiles. The risk of MI or stroke (adjusted for age and sex) increased for the quintile with the highest thickness as compared with the lowest quintile (RR 3.87, 95% CI, 2.72-5.51).(O'Leary *et al.*, 1999) There was a stepwise increase in the risk from the lowest to highest quintile groups.

In a meta-analysis of 8 studies by Lorenz et al,(Lorenz *et al.*, 2007) each SD increase in CIMT adjusted for age and sex, increased the risk of MI (RR 1.26, 95% CI 1.21-1.30). Similarly each 0.10 mm increase in CIMT increased the risk of MI (RR 1.15, 95% CI 1.12-1.17). Increased risk of stroke was associated with each SD increase in CIMT (RR 1.32, 95% CI 1.27-1.38) and each 0.10 mm increase in CMT (RR 1.18, 95% CI 1.16-1.21). Variations between the studies were noted for age distribution, carotid segment definition and CIMT measurement protocol. This meta-analysis concluded that CIMT is a strong and independent predictor of vascular events (stroke more than MI).

In a meta-analysis by Costanzo et al, (Costanzo *et al.*, 2010) of 41 trials involving 18307 participants from the general population; CIMT regression at follow up compared to baseline was not related to CV events (CHD: Tau 0.91, p=0.37), Stroke/TIA: Tau -0.32, p=0.75 and all-cause death: Tau -0.41, p=0.69). It was concluded that though there was reduction in CV outcomes due to active treatment, CIMT regression was not related to the CV outcomes.

In another meta-analysis of 16 studies by Lorenz et al,(Lorenz *et al.*, 2012) of 16 studies involving 36984 patients CIMT progression during follow up assessment was

not associated with risk of the combined endpoints of stroke, MI or CV death (HR 0.97, 95% CI 0.94-1.00). But the mean CIMT of the combined baseline and follow up measurements was associated with increased CV events (HR 1.16, 95% CI 1.10-1.22). In the general population there was no association between CIMT progression and CV events.

1.9.7 CIMT in Risk Stratification

A meta-analysis was performed by Den Ruijter et al, (Den Ruijter *et al.*, 2012) adding CIMT to Framingham Risk Assessment for the 10-year CV risk prediction (MI or stroke). There was no difference in the C-statistic of both risk models (0.757, 95% CI 0.749-0.764; and 0.759, 95% CI 0.752-0.766). Addition of CIMT slightly improved the net reclassification (0.8%, 95% CI 0.1%-1.6%). Addition of CIMT to Framingham Risk Score did not alter the clinical importance of the risk prediction. In another meta-analysis by van den Oord et al,(van den Oord *et al.*, 2013) CIMT was added to a risk model based on traditional risk factors for CV risk assessment. There was no statistically significant improvement with the addition of CIMT (AUC of traditional risk model: 0.726, 95% CI 0.700-0.753, compared to addition of CIMT AUC: 0.729, 95% CI 0.700-0.758).

1.9.8 Interpretation of available evidence on CIMT

Increased CIMT was associated with increased risk of future CV events. But CIMT progression or regression was not associated with increased or decreased CV events respectively. Addition of CIMT did not improve the traditional risk models for prediction of CV events. CIMT in patients with established CAD patients, especially older patients is not known.

Arterial stiffness, endothelial dysfunction and CIMT, risk stratification markers of adverse CV events were discussed in previous sections. In patients with established CAD left ventricular function assessment plays a key role in ongoing management to prevent further adverse events. In the following section LV function both systolic and diastolic functions will be reviewed.

1.10 Left ventricular Function

Assessment of LV Systolic and diastolic left ventricular (LV) function by transthoracic echocardiography (TTE) can aid in the risk stratification of patients following ACS by providing prognostic information. Also it can be used to tailor the treatment. The commonly obtained information on TTE assessment are ejection fraction (EF), wall motion score index, ratio of early mitral inflow to myocardial velocity (E/e'), left atrial size, valvular stenosis or regurgitation, right ventricular systolic pressure. Of these ejection fraction and wall score motion index provide a measure of LV systolic function while E/e' and left atrial (LA) size provide information on elevated LV filling pressure (a measure of LV diastolic function).

1.10.1 Physiology of LV function

The two main functions of the left ventricle are being a compliant chamber during diastole allowing the left ventricle to fill even at low LA pressure and alternating into (a stiff chamber with rapidly rising LV pressure in systole to eject the stroke volume at arterial pressures. The key to normal LV function being is dependent on the LV to change between these two states in systole and diastole. Hence routine TTE assessment should include both systolic and diastolic function assessments.(Nagueh *et al.*, 2009)

1.10.2 Left ventricular Systolic Function

1.10.2.1 Simpson's Biplane Method

The most commonly measured marker of LV systolic function is the EF which is the percentage of chamber volume ejected in systole (ratio Stroke volume [SV] to Left Ventricular End Diastolic Volume [LVEDV]). As 2D TTE provides superior spatial resolution for determining left ventricular size and function EF can be evaluated by Simpson's rule which employs a method of disks. This involves correct visualisation of endocardial borders in apical 2 chamber (A2C) and apical 4 chamber views (A4C). The ventricle is divided into disks along the long axis of LV. The ventricular volume is the cumulative total of the volume of each of the disks. EF is calculated from the EDV and End Systolic Volumes (ESV) obtained from this stack of discs method. These calculations are reliant on the accurate tracing of the endocardial borders. Limitations of this method are drop out of myocardium (can be overcome by contrast TTE) and small volumes can be estimated by foreshortening (transducer not at the true apex).

1.10.2.2 Wall Motion Score Index

Left ventricular wall motion is assessed by complete visualisation of all the left ventricular walls in all 2D TTE views. It is important to ensure clear endocardial border definition as this is very crucial in the wall motion assessment. As changes in wall motion are not uniform it is important to obtain different views of the same region. With normal LV contraction, the endocardium moves inwards (endocardial excursion) resulting in diminished LV cavity size. Simultaneously the distance between the endocardium and epicardium increases (wall thickness). Reduction in endocardial excursion together with decrease in the amplitude of wall thickening is noticed in wall motion abnormality. This can be compared to adjacent, normally contracting regions of myocardium. The degree of endocardial thickening is the most reproducible and reliable method of wall motion assessment. Translational and rotational motion of the LV may give a false impression of preserved wall motion.

1.10.3 Left Ventricular Diastolic Function

Diastole starts at the closure of aortic valve and comprises of fall in LV pressure, rapid LV filling, diastasis and atrial contraction.(Brutsaert *et al.*, 1993) Diastolic function is related to the ability of the myocardium to relax and is a passive process modulated by myocardial tone. The process by which the myocardium returns to its unstressed length and force is called myocardial relaxation. Myocardial relaxation is also under the influence of load, inactivation and asynchrony. Dyssynchronous myocardial relaxation leads to delayed LV relaxation and elevated LV filling pressures. Diastolic dysfunction results in elevated filling pressures.(Brutsaert *et al.*, 1993) Increased afterload especially combined with increased preload delays myocardial relaxation resulting in elevating LV filling pressures.(Leite-Moreira *et al.*, 1999) Filling pressures are considered elevated when the mean pulmonary capillary wedge pressure (PCWP) is >12mmHg or when the LV end diastolic pressure (LVEDP) is >16mmHg on invasive pressure measurement.(Paulus *et al.*, 2007) LV filling is determined by LV filling pressures and properties. LV stiffness ($\Delta P/\Delta V$) or the inverse, compliance ($\Delta V/\Delta P$) describe the filing (end diastolic) properties. The extrinsic factors that influence the end diastolic properties are pericardial restraint and ventricular relaxation while the intrinsic factors are myocardial stiffness, tone, LV chamber geometry and LV thickness.(Leite-Moreira, 2006) Practical approach to assess diastolic function is displayed in **Figure 1.10**

1.10.3.1 Assessment of Diastolic Dysfunction

The following are measures of diastolic dysfunction.

1.10.3.1.1 Left Ventricular Hypertrophy

Concentric hypertrophy (increased mass and increased wall thickness) can be observed in patients with diastolic heart failure while patients with depressed EF have eccentric hypertrophy. Hypertension leads to concentric hypertrophy. Hypertensive heart disease is the most common cause of diastolic heart failure and is very common in older patients because of the high prevalence of hypertension in older population.(Nagueh *et al.*, 2009) LV relaxation is delayed in hypertrophied myocardium

resulting in elevated filling pressures. LV mass can be measured but is time consuming.

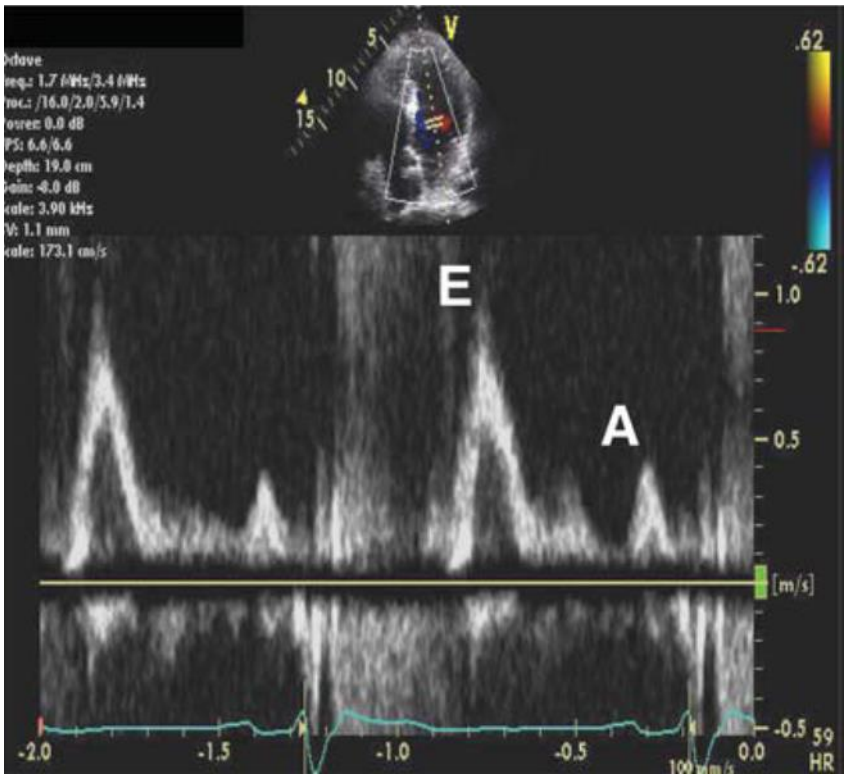
1.10.3.1.2 Left Atrial Volume

LA volume reflects the cumulative effects of elevated filling pressures over a period of time while Doppler velocities indicate filling pressure at the time of assessment. Dilated left atria can be associated with bradycardia, anaemia, atrial arrhythmias, mitral valve disease in the absence of diastolic dysfunction. In the assessment of diastolic dysfunction LA volume needs to be considered in combination with Doppler parameters of LV relaxation.(Nagueh *et al.*, 2009)

1.10.3.1.3 Mitral Inflow

Mitral inflow velocities **(Figure 1.11)** by pulsed-wave (PW) Doppler are obtained in apical 4 chamber (A4C) view for the assessment of LV filling pressures. Peak E (early diastolic) and A (late diastolic) velocities of flow across the mitral valve should be recorded by continuous wave (CW) doppler ensuring maximal velocities are obtained before applying the PW technique. Then 1-3mm sample volume is placed between mitral leaflet tips to record a crisp velocity profile with PW Doppler.(Nagueh *et al.*, 2009) With advancing age, the E velocity and E/A ratio decreases, whereas the A velocity increases. Mitral inflow velocities are affected by heart rate and rhythm, PR interval, cardiac output, mitral annular size and LA function. Older individuals are at higher risk of developing diastolic dysfunction due to age related delayed myocardial relaxation.(Nagueh *et al.*, 2009) Older patients with uncontrolled and longstanding hypertension are associated with abnormal diastolic physiology and filling patterns. Transmitral flow velocities can be used to predict LV filling pressures reliably in patients with systolic dysfunction (EF≤ 50%), but not so in patients with preserved systolic function (EF >50%).(Yamamoto *et al.*, 1997)

Figure 1.11: Mitral Inflow Doppler Velocities

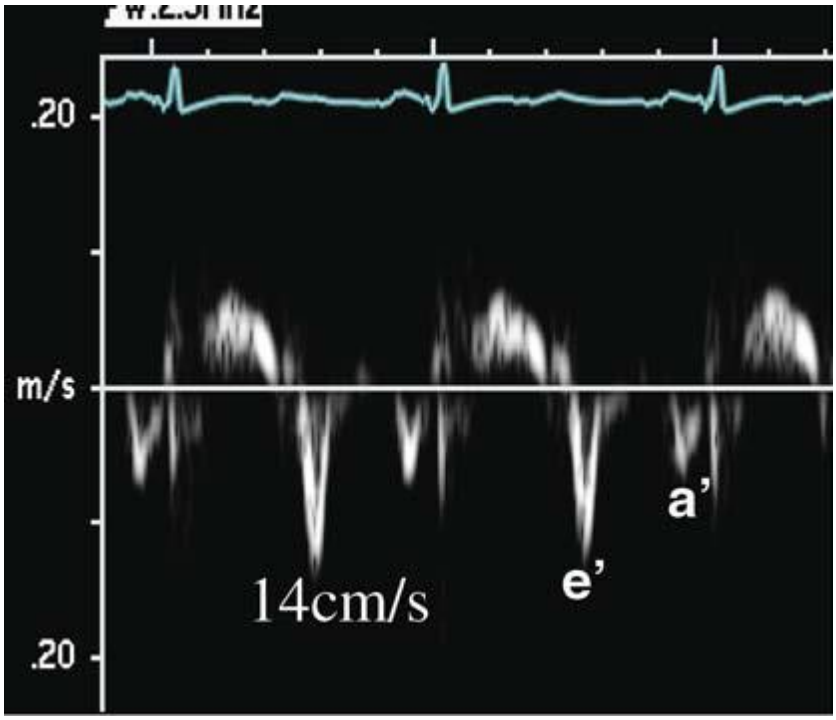


Tissue Doppler Assessment of Mitral Annulus

1.10.3.1.4 Mitral Annulus Tissue Doppler Velocity

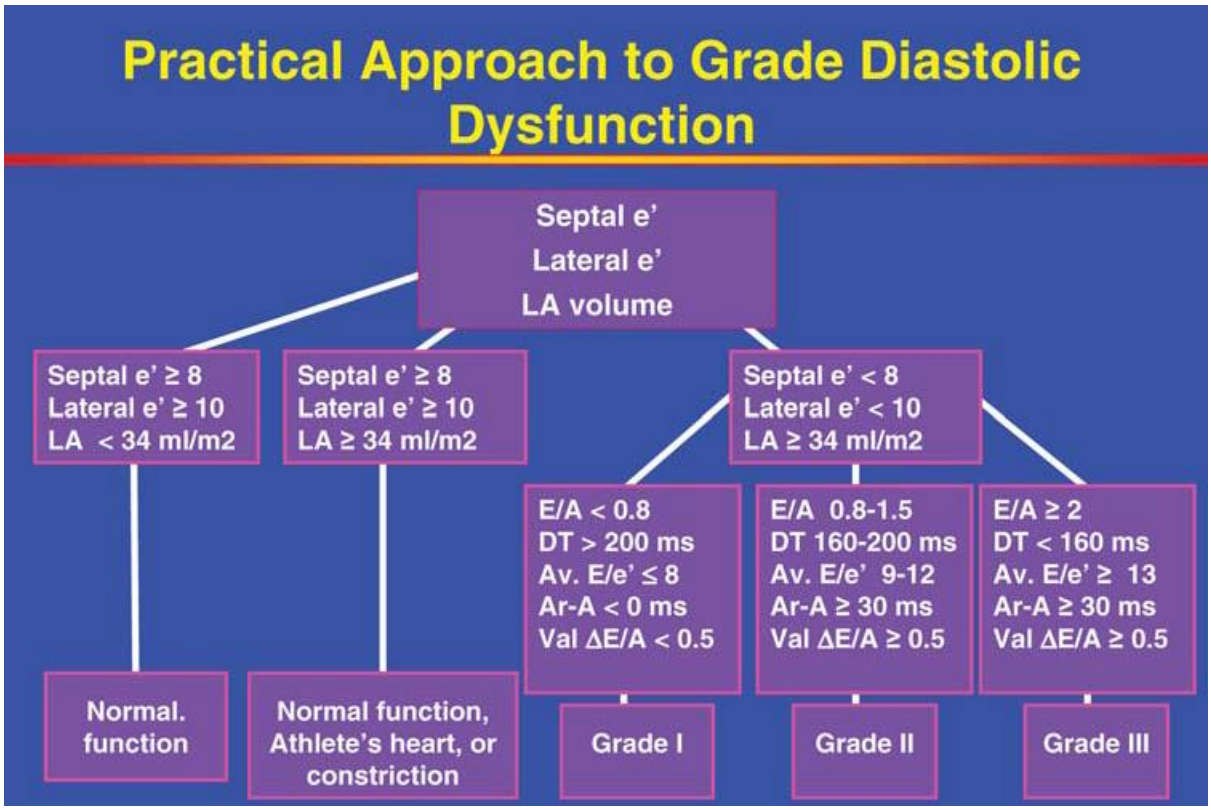
The mitral annular velocity corresponds to LV long axis lengthening rate, as the LV apex remains fixed during cardiac cycle. Peak early diastolic velocity (e') occurs simultaneously with the mitral inflow E-wave.(Masutani *et al.*, 2008) Under normal conditions both E and e' increase in response to exercise and volume load.(Opdahl *et al.*, 2009) The LV filling pressure is determined by the mean LA pressure and elevated LA pressure correlates on TTE are enlarged LA volume, restricted filling pattern with short deceleration time (DT) of E-wave, abnormal pulmonary venous flow pattern and ratio of E to e'. The most commonly used and easy to interpret parameter is E/e'. Mitral inflow E wave is augmented with increased LA to LV pressure gradient and e' is reduced due to slow LV relaxation. Increased E/e' ratio as result of high E and low e' indicates elevated LA pressure.(Little and Oh, 2009) E/e' correlates well with pulmonary capillary wedge pressure.(Nagueh *et al.*, 2009) An E/e' value >15 indicates elevated pulmonary capillary wedge pressure, whereas an E/e' <8 is associated with normal LA pressure.(Ommen *et al.*, 2000) In the intermediate range (E/e' 8-15) other parameters like LA size, LV filling pattern, DT, iso-volumetric relaxation time, and presence of pulmonary hypertension need to be assessed.(Nagueh *et al.*, 2009) E/e' van be obtained either from the medial annular velocity or the lateral annular velocity and the cut off values for elevated LA pressure are 15 and 12 respectively and this difference is due to the increased annular velocity on the lateral annulus compared to the medial annulus. Though an average of the two has been recommended, consistent use of one is adequate in clinical practice.(Nagueh *et al.*, 2009) E/e' may not accurately predict elevated LA pressure in case wall motion abnormalities in the base of the LV, pericardial constriction and significant mitral valvular pathology.(Little and Oh, 2009)

Figure 1.12: Tissue Doppler Velocity of the Mitral Annulus



Reproduced from Nagueh et al.(Nagueh et al., 2009)

Figure 1.10: Approach to assess Diastolic Dysfunction



Av. Average; LA left atrium; Val. Valsalva

Reproduced from Nageuh et al.(Nagueh *et al.*, 2009)

1.10.3.2 Prevalence of Diastolic Dysfunction and CV Outcomes

In 2042 community population (≥ 45 years, mean age 62.8 years [SD 10.6]) of Olmsted county, the prevalence of mild diastolic dysfunction was 20.8% (95% CI 19.0%-22.7%), moderate diastolic dysfunction was 6.6% (95% CI 5.5%-7.8%) and severe diastolic dysfunction was 0.7% (95% CI 0.3%-1.1%). The prevalence of these three grades of diastolic dysfunction in the older subgroup (≥ 75 years) was 52.8%, 14.6% and 3.4% respectively. The overall prevalence of moderate to severe diastolic dysfunction with normal EF was 5.6% (95% CI, 4.5%-6.7%). Both groups of patients with mild diastolic dysfunction (HR 8.31, 95% CI 3.00-23.1, p<0.001) and moderate to severe diastolic dysfunction (HR 10.17 95% CI 3.28-31.0, p<0.001) were higher risk of all-cause mortality after controlling for age, sex and EF.

In a retrospective study of 36261 patients (mean age 58.3, [SD 15.4] years) with normal EF the prevalence of diastolic dysfunction was 65.2% (60.0% mild, 4.8% moderate and 0.4% severe). Patients with diastolic dysfunction were significantly more likely to be males, older (>65 years), obese (BMI >30) and more likely to have CV risk factors and established CV disease. Over a mean follow up period of 6.2 (SD 2.3) years, both moderate (HR 1.58, 95% CI 1.20-2.08, P<0.001) and severe diastolic (HR 1.84; 1.29-2.62, p<0.001 for each function was associated with increased mortality risk.(Halley *et al.*, 2011)

1.10.4 Interpretation of available evidence on LV function

Assessment of LV systolic and diastolic function can add incremental information to the management and risk stratification of patients with ACS. Especially diastolic dysfunction is common among older patients even with normal LV function and no underlying significant CAD. LV function assessment in the context of ACS in older patients managed by contemporary treatment has not been studied in detail.

In addition to preventing adverse CV events in older patients the key management strategy is to improve symptoms and quality of life. In the following section cardiac symptom burden and quality of life measures in patients with CAD will be reviewed.

1.11 Quality of Life and Symptom Burden

1.11.1 Quality of Life

There is no consensus definition of ‘quality of life’ (QoL), but it is deemed to include holistic emphasis on the social, emotional, and physical well-being of patients after treatment.(Greer, 1984) More pertinently it could be the impact of a person's health on his or her ability to lead a fulfilling life.(Bullinger *et al.*, 1993) Health related quality of life (HRQoL) refers to the impact of diseases and their symptoms on individual’s QoL and in the context of health care, HRQoL is preferred over QoL as the focus is on health.(Thompson and Yu, 2003) It can also be an individual's subjective experience related both directly and indirectly to health, disease, disability, and impairment.(Carr *et al.*, 2001) Reducing the impact of disease is expected to increase the quality of life, but severe disease is not always related to poor quality of life.(Evans, 1991) Quality of life in an individual patent is influenced by the expectations and experiences of that patient.(Calman, 1984) Medical management of diseases focus mainly on mortality and morbidity benefits, but equally important is improvement in QoL. QoL needs to be considered as an important outcome of patient management in determining therapeutic benefits.(Mayou and Bryant, 1993; Treasure, 1999) HRQoL can be used as a benchmark to measure the impact of different management strategies on the same disease or impact of different treatment on different diseases.(Thompson and Roebuck, 2001)

Current ACS management strategies are aimed at reduction of mortality, morbidity and the risk of subsequent adverse CV events. QoL outcomes are not routinely taken into consideration in evaluating outcomes of management strategies of ACS. QoL outcomes are increasingly becoming relevant in ACS management due to ageing population and increased life expectancy with advancing medical resources. Especially in older patients QoL outcome is equally if not more important than mortality benefit. It has to be noted that QoL can be influenced by symptoms and anxiety associated with ACS. Though QoL measures are used in clinical research they are rarely used in the clinical setting. QoL measures in the clinical setting helps to focus evaluations and treatment on the patient rather than the disease.(Higginson and Carr, 2001)

1.11.2 Measures of QoL

HRQoL instruments describe or characterize patient experiences (functioning, general health perceptions and overall wellbeing or quality of life) as a result of healthcare and are supplementary to traditional health status assessment of biological measures (mortality and morbidity benefits).(Wilson and Cleary, 1995) QoL measures do not substitute for measures of disease outcomes and may not routinely be the most appropriate patient centred outcome to assess.(Higginson and Carr, 2001) It has to be used in the holistic assessment to address individual patients' expectations. As QoL is influenced by multiple factors an ideal QoL measure needs to include assessment of physical, functional, psychological and social components. There are various QoL measures both generic and disease specific which can be administered in different modes.

1.11.2.1 Generic Measures

1.11.2.1.1 Short Form 36

Short form 36 (SF 36) comprises 36 response items encompassing 8 health domains (physical functioning; role-physical; bodily pain; general health; vitality; social functioning; role-emotional; and mental health).(Ware and Sherbourne, 1992) The first four constitutes the physical health summary measure and the last four the mental health summary measure. The score for each scale ranges from 0 to 100, with a higher score representing a higher HRQoL.(Ware JE, 2000) It is a self-administered instrument to complete responses for the 36 items and takes about 15 minutes to complete all responses. Shortened versions of the SF-36 are the SF-12 and SF-8 which obviously takes less time to complete responses. SF-36 has been proven to be a sensitive instrument for detecting changes in HRQoL among patients with recent MI.(Yu *et al.*, 2003)

1.11.2.1.2 EuroQoL

The EuroQoL comprises EQ-5D and EQ-VAS (Visual Analogue Scale)(Group, 1990) and is a descriptive response system of 5 dimensions of physical and emotional aspects of everyday life including mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each dimension has three different levels of responses as no problem, some problem, or extreme problem. Subjects are asked to choose the level that best describes their current level of function or experience on each dimension.

1.11.2.2 Disease Specific Measures

1.11.2.2.1 Seattle Angina Questionnaire

Seattle angina questionnaire (SAQ) is a disease specific measure designed to assess the functional status of patients with angina.(Spertus *et al.*, 1995) It includes 19 questions that quantify five clinical domains of physical limitation, stability of angina, frequency of angina, treatment satisfaction and disease perception/quality of life. It can be used as a generic HRQoL measure as 7 of its 19 items assess emotional health.

1.11.2.2.2 Myocardial Infarction Dimensional Assessment Scale

Myocardial Infarction Dimensional Assessment Scale (MIDAS) is a patient reported outcome measure of the health status after a MI.(Thompson *et al.*, 2002) It comprises measures of 35 items on seven dimensions (physical activity; insecurity; emotional reaction; dependency; diet; concerns over medication; side effects). It addresses concerns specifically related to patients with recent MI. Each dimension is scored separately using a simple scoring system to indicate the extent of ill health in each of the seven domains assessed.(Thompson and Watson, 2011)

1.11.3 Symptom Burden

Cardiac symptoms of angina and dyspnoea can have an impact on health status and HRQoL. This can be assessed by New York Heart Association (NYHA) dyspnoea severity scale (1-4) as in **Table 1.5** and Canadian Cardiovascular Society (CCS) angina severity scale (0-5) as in **Table 1.6**.

Table 1.5: New York Heart Association Dyspnoea Classification

I	No symptoms and no limitation in ordinary physical activity
II	Mild symptoms (mild shortness of breath) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

Table 1.6: Canadian Cardiovascular Society Angina Scale

0	No Angina
I	Angina only during strenuous or prolonged physical activity
II	Slight limitation, with angina only during vigorous physical activity
III	Symptoms with everyday living activities, i.e., moderate limitation
IV	Inability to perform any activity without angina or angina at rest, i.e., severe limitation

1.11.4 Quality of Life and Symptom Burden in Relation to Clinical Outcomes

In a prospective cohort study of CAD patients in outpatient department, prognostic utility of SAQ was evaluated. 5558 patients completed the SAQ and were followed up for 1 year. SAQ physical limitation was the strongest predictor of health status and patients with severe limitations had a relative odds of mortality of 6.2 during follow up (95% CI 3.8-10.5). Patients with a significant deterioration in angina over the preceding month had a 1-year mortality rate of 11.4% compared with 4.9% for the rest of the population. Also patients with severe angina were three (95% CI 1.7-5.3) times more likely suffer from ACS than those reporting minimal angina. Inclusion of SAQ domains in risk models significantly increased the model *c*-statistics for both the mortality (0.69 to 0.72, p=0.004) and ACS (0.69 to 0.73, p=0.003) models.

The third Randomized Intervention Trial of unstable Angina (RITA-3) evaluated early intervention strategy (IS, n=895) versus conservative strategy (CS, n=915) in patients with NSTEACS.(Fox *et al.*, 2002) Health status of the patients was assessed using EuroQoL, SF36 and SAQ at four months and one year of follow up in addition to EQ5D being done at baseline. Baseline EQ-VAS scores were comparable between IS and CS patients. Though there was significant improvement in EQ-VAS scores in both groups improvement at four months (mean difference of 3.0, 95% CI 1.3-4.7; p<0.001) and 1 year (mean difference of 2.3, 95% CI 0.6-4.1; p<0.01) was significantly greater in the IS group compared with the CS group. As regards to EQ-5D during both follow-up times, more proportion of patients in the CS group had a worsening of HRQoL related to performing usual daily activities. The change in the EQ-5D global utility score was significantly better among patients in the IS group at four months (treatment mean difference of 0.036, p=0.005), but this difference was reduced at one year (treatment mean difference of 0.016, p=0.20). Patients in the IS group had a higher mean SF-36 component scores compared to patients in the IS group. The biggest gain in HRQoL were made with regard to physical role function and general health and was found significant at 4 months and 1 year. Patients in the IS group had significantly better mean SAQ component scores compared to patients in the CS group. Though there was attenuation of treatment differences at one-year follow-up compared with the four-month results both remained highly significant. Stability of angina, frequency of angina, and disease perception domains had the largest gains in HRQoL.(Kim *et al.*, 2005)

The authors conclude that in patients with NSTEACS, an early IS provided improvement in HRQOL mainly due to improvements in angina symptoms.

In 200 Chinese patients with CAD administration of SF-36 HRQoL measure reported a poorer HRQoL compared to patients in western countries.(Wang *et al.*, 2014) Older age, co-morbidity with heart failure or hypertension, and smoking status were significant predictors of poor physical health status by multiple regression analysis. Co-morbidity with heart failure and perceived social support were predictors of poor mental health status. Health status and social support needs to be addressed to HRQoL in patients with CAD.

HRQoL was evaluated in 3220 patients after acute coronary syndrome treated with clopidogrel at baseline, two months and four months of follow up.(Chudek *et al.*, 2014) 38% had STEMI and 62% had experienced NSTEACS. The management strategy was medical management (7.2%), thrombolysis (2.4%) and PCI (90.4%). Women reported lower levels of HRQoL compared to men across all domains of health status ($p<0.001$ for each health status domain) during the first follow up visit. Patients older than 60 years and patients managed by non-invasive strategy had reported the lowest quality of life. During subsequent follow up visits, all aspects of health status improved irrespective of the treatment strategy. Also health status differences between the treatment groups decreased as time progressed. In the immediate period after ACS, invasive treatment strategy especially in older patients had better HRQoL outcomes.

In 257 patients with ACS, HRQoL was assessed using SF-36 at baseline, 1 year and at 3 years to evaluate the effect of ACS trigger on HRQoL.(Bhattacharyya *et al.*, 2010) At follow up 76% patients were reassessed at 12 months, and 62% at 36 months. Management strategy was medical (36%), PCI (54%) and CABG (10%). Of the patients followed up at one year, acute emotional distress was experienced prior to ACS onset in 37% and physical exertion in 6% while 3% of patients reported combined physical exertion and emotional stress. There was a significant association between emotional trigger at ACS onset and poor mental health at one year independent of age, gender, social deprivation, GRACE risk score, and ACS type ($\beta=-0.175$, S.E. 0.072, $p=0.016$) at 12 months. Mean adjusted scores were 68±22 in the emotional trigger and 75±20 in the no trigger patients. Physical health status at 12 months reflected physical activity levels before ACS (mean scores of 58.7, 68.7 and 72.3 for inactive, low activity and high activity groups respectively, adjusted for age and gender, $p=0.011$). Patients with

physical exertion at the time of ACS onset had significantly lower physical health status scores at 3 years (adjusted means 32±12) than those who had not been physically active (mean 50±21, p=0.019). ACS triggers had an impact on both physical and mental components of HRQoL in the short and medium term after ACS irrespective of management strategy.

1.11.5 HRQoL in Older Patients with CAD

Health status was evaluated by use of SAQ in 21573 patients undergoing cardiac catheterisation and followed up at one year and at three years.(Graham *et al.*, 2006) Of these, 15392 patients were <70 years of age, 5198 patients were 70-79 years, and 983 patients were ≥ 80 years of age. Responses at one year were available in 7883, 2940 and 439 patients respectively in the three age groups. Patients >70 years managed by revascularisation strategy had better SAQ scores compared to medical therapy after risk adjustment. In all the three age groups patients managed by CABG scored better compared to PCI with the exception of exercise capacity in the two older age groups (p<0.001 for all PCI vs. CABG comparisons). At three years responses were available for 6612 patients of >70 years, 2185 patients of 70–79 years, and 261 patients of ≥80 years of age. The risk-adjusted SAQ scores were better for patients managed by revascularisation compared to medical therapy especially in patients aged >70 years, and those 70–79 years of age. Patient who underwent CABG in ≥80 years scored higher than PCI patients in all dimensions except exercise capacity.

In 624 patients admitted with ACS, SF-36 was administered to evaluate HRQoL outcomes at baseline and 6-months of follow up.(Li *et al.*, 2012) Of these 46% underwent PCI, 6% underwent CABG and 48% were treated conservatively. At 6 months' follow up 82% of enrolled patients responded. Patients treated with PCI had higher scores at 6 months in all 8 domains than those treated conservatively especially with significant differences in physical functioning, general health, social functioning and vitality (p<0.05 for each domain). After risk adjustment, physical health status including physical functioning, bodily pain and the physical component summary were significantly better for patients aged 60–79 years and >80 years with PCI than medical therapy. The biggest increase in score was noted in patients aged >80 years. By multivariable analyses PCI (OR 1.79, 95% CI 1.10–2.92) and age (per ten years increase, OR=1.27, 95% CI 1.02–1.57) were independent predictors of better PCS

scores. Elderly patients received the greatest benefit from PCI in terms of improvement in HRQoL by its impact on physical functioning.

In a prospective cohort of 651 patients who underwent PCI HRQoL was reported using SF-36 at 6 months, 1 year and 3 years.(Panasewicz *et al.*, 2013) Patients were categorised into two groups of <70 years (74%) and ≥70 years (26%). Older patients experienced poor scores which were significant on all four physical domains ($p<0.05$ for each domain) whereas of the four mental health domains only vitality and role emotional functioning had significantly poor scores in older patients ($p<0.05$ for each). Over increasing follow up periods HRQoL improved in younger patients and worsened in older patients. At 36 months follow up, there was a decrease in SF-36 scores in all domains and was significant for five domains of physical functioning (–6.42; p=0.003), general health (–4.93; P=0.01), social functioning (–7.55; p=0.01), mental health (–4.13; P=0.02) and vitality (–5.73; p=0.01). In a further subgroup analysis by four different age groups (<60 years, 60-70 years, 70-80 years, and ≥80 years) older patients (70-80 years or ≥80 years) reported to experience poor HRQoL than the younger patients (<60 years or 60-70 years). Thus over a period of three years, older patients reported poor HRQoL after PCI compared to younger patients.

In a systematic review of 700 octogenarians (mean age 82.9 years) identified from 11 studies (published between 1993 and 2012) who underwent PCI HRQoL improved as much as in younger patients.(Johnman *et al.*, 2013) Octogenarians gained improvement in the areas of physical functioning and improved angina status. The benefits are greatest in the early post PCI period (6 months) and continued long term (up to 3 years).

1.11.6 Interpretation of available evidence on quality of life

Quality of life encompasses physical, emotional and social well-being. In patients managed by revascularisation for CAD significant improvement in physical and functional domains were noted. In older patients the improvement was more in the short term, but deteriorated in the long term. In older patients with CAD, quality of life improves with PCI, mainly due to improvement in physical functioning and improvement in angina status. Quality of life has not been studied with contemporary management of CAD in older patients, especially in the context of frailty status. Older age is a predictor of poor CV outcomes after ACS and or PCI. Frailty and co-morbidity independently have been proven to be predictors of adverse CV outcomes after ACS and or PCI. Impact of older age, frailty and co-morbidity on HRQoL after PCI for ACS has not been studied. Better understanding of this will help in improving the management of older patients with ACS.

1.12 Cognitive Impairment

Mild cognitive impairment is the intermediate stage between normal cognitive aging and dementia. Mild cognitive impairment is detectable by clinical criteria, but not producing impairment in daily functioning whereas dementia, a chronic progressive disease is characterized by disturbance of cognitive function in association with impairment in functional, emotional and social behaviours. The most common causes of dementia are neuro-degenerative dementia (Alzheimer's dementia) and vascular dementia and the uncommon causes are frontotemporal dementia and Lewy body dementia.(Knopman *et al.*, 2003).

In a population based prospective cohort study carotid atherosclerosis was associated with an increased risk of dementia during a mean follow up period of 9 years, supporting the hypothesis of the role of atherosclerosis in the pathogenesis of dementia and Alzheimer's disease.(van Oijen *et al.*, 2007) A systematic review showed coronary artery disease was associated with general cognitive deficits and reduced ejection fraction and cardiac output was associated with impairment in executive function.(Eggermont *et al.*, 2012)

In another population based prospective cohort study (614 patients), cognitive outcomes assessed by mini mental state examination (MMSE, maximum score 30) were worse at 1 year in patients with ACS compared to patients with TIA (mean MMSE 26.6 SD 2.7 vs. 27.6 SD 2.5, $p<0.0001$) and ACS was associated with moderate/severe cognitive impairment (OR 2.14, 95% CI 1.11-4.13).(Volonghi *et al.*, 2013)

A systematic review concluded that frailty increased the risk of cognitive impairment and similarly cognitive impairment increased the risk of frailty, implying a common causal pathway for cognitive impairment and frailty, associated with ageing.(Robertson *et al.*, 2013)

It is important to understand the prevalence of sub clinical cognitive impairment in older patients with acute coronary syndrome, especially managed by contemporary treatment and its association with frailty.

1.13 Summary of Introduction Chapters

With eradication of communicable diseases in the last century and better primary prevention measures with cardiovascular disease, the proportion of people in the later decades of life are increasing as never before all over the world, more so in the developed countries. IHD is a leading cause of morbidity and mortality along with dementia and cancer in older patients. Limited evidence available currently in the management of these older cohort of patients. Current management of older patients with ACS is mostly based on extrapolation from evidence available from research studies with couple of decade younger patients. Older patients were under represented in clinical trials.

Older age is associated with frailty and comorbidities. There are different frailty assessment tools available. Frailty has been identified as an independent risk factor for adverse CV outcomes in patients with acute coronary syndrome. But not the same frailty assessment tool was used and patient cohort had differing presentations with CAD. Not all these patients were treated with contemporary treatment strategies. Frailty in a specific subset of patients like NSTEACS with both Fried and Rockwood frailty assessment tools has not been studied in patients managed with contemporary treatment strategies.

Comorbidities play a vital role in older age due to their impact on clinical presentation, diagnosis and treatment strategies. As stated earlier older patients are underrepresented in clinical trials and even the very small proportion of older patients were highly selected with no or few comorbidities. Comorbidities also play a role in the development of frailty syndrome. Comorbidities have an impact on adverse CV outcomes but has not been studied along with frailty in patients managed with contemporary treatment strategy. In every day clinical practice lot of older patients with frailty and comorbidities are seen with challenging decisions on management to be made.

Arterial stiffness, endothelial dysfunction, carotid intima media thickness and LV function are markers of underlying CV disease burden. They have been shown to impact CV outcomes in community population and have been note as risk factors in predicting CV outcomes. They have not been studied in older patients with established

CV disease. Understanding CV disease burden with these measures in older patients in relation to frailty can be useful.

Treatment strategies for younger patients were aimed at improving mortality and morbidity. In older patients in addition to these outcomes quality of life needs to be an important consideration. Frailty and comorbidity could influence quality of life even prior to a CV event and hence it is important to consider quality of life prior to invasive treatment strategies. Quality of life measures should include physical, mental and social wellbeing. Impact of contemporary treatment needs to be studied in relation to quality of life in addition to adverse CV outcomes.

Cognitive impairment is a major cause of morbidity and institutionalisation in older patients. Subclinical cognitive impairment in older patients with NSTEACS in the context of frailty has not been studied.

From the above review the hypothesis and aims of this study are stated in the following page.

1.14 Hypothesis

1. Frailty status varies according to the assessment tool used
2. Frailty is associated with adverse CV outcomes even in patients managed by contemporary invasive treatment for NSTEACS
3. Frailty is associated with the cardiovascular disease burden of older NSTEACS patients
4. Increased comorbidity burden is associated with frailty and adverse CV outcomes
5. Frailty is associated with increased cardiac symptom burden and poor quality of life
6. Older NSTEACS patients have subclinical cognitive impairment

1.15 Aims

1. To determine the prevalence of frailty and compare frailty status by Fried and Rockwood Frailty scales
2. To assess adverse CV outcomes at one month according to frailty status in older NSTEACS patients managed by invasive strategy
3. To assess cardiovascular disease burden in relation to frailty status
4. To assess comorbidity burden according to frailty status and asses its relation to adverse CV outcomes at one month
5. To evaluate cardiac symptom burden and the quality of life in older NSTEACS patients managed by invasive strategy
6. Assess cognitive function in older NSTEACS patients and its association with frailty

CHAPTER 2: METHODS

2.1 Study Design and Protocol

2.1.1 Study Design

The study was designed as a prospective observational study of older patients aged ≥75 years undergoing invasive management (coronary angiography with a view to revascularisation) for NSTEACS in a tertiary interventional cardiology centre. The data collected for my thesis was part of a larger study - A Study to **I**mprove **C**ardiovascular **O**utcomes in High Risk Patie**N**ts with Acute Coronary Syndrome (ICON1 study). All the data presented in this thesis were collected by me. My role in the study as the primary researcher is detailed in the following section. The data collected for the thesis included frailty status, comorbidity, CV disease burden, quality of life measures and cognitive status. The tools and measures used for the data collection are detailed in the following section. The larger ICON1 study involved collection of intracoronary imaging data (not part of my thesis) in addition to all the data presented in this thesis. The lead sponsors for the study were Newcastle University and Newcastle upon Tyne NHS Hospitals Foundation Trust. Approval was obtained from the local research and development Newcastle Joint research Office and the National Research Ethics Service committee for North East of England based at Sunderland with Regional Ethical Committee reference number 12/NE/0160. The UK Clinical Research Network registration number was 12742.

2.1.2 Study Setting

This observational study was conducted in Freeman Hospital, Newcastle upon Tyne, in the North-East of England. The Freeman Hospital, is a tertiary cardiac centre providing advanced cardiac services to a population of 2 million. Approximately 3000 PCIs are performed per year. The study participants were recruited from patients referred to this hospital from the neighbouring district general hospitals for invasive treatment of NSTEACS. Patients were transferred the day before or on the day of procedure to the tertiary hospital. Suitable patients were identified from the electronic referral system and on arrival to the tertiary hospital were approached for recruitment into the study. I explained the study to the patient and a patient information sheet was provided. If the patient agrees to take part in the study, written informed consent was obtained. All patients screened for the study were entered in a screening log with details regarding the patients consented, declined, consented but not recruited (due to alternative diagnosis following coronary angiography).

2.1.3 My Role in the Study

I was working on the project as a clinical research associate. I identified potential patients on the electronic referral system and approached them to take part in the study on arrival to Freeman Hospital. I explained the study and gave patient information sheet to patients as per the inclusion and exclusion criteria. If suitable patients agree to take part in the study I obtained written consent. Frailty assessment was performed by me prior to the invasive procedure in the ward and the operator for angiogram and PCI was blinded to the finding. Similarly all non-invasive investigations were performed prior to the patient undergoing invasive procedure. This was strictly adhered to by me, to make sure the invasive procedure did not have any impact on the non-invasive test findings. When I was on leave, my colleague recruited 10 patients. My colleague was appropriately trained. Standard treatment protocol was followed in the clinical care as per the instructions from the consultant Interventionist in the lab and the on-call team under the supervision of the consultant in the ward.

I collected the baseline demographics, angiogram and PCI details on the case report form. I was independent in performing and reporting transthoracic echocardiogram and have been signed off for the same during my 3 years of general cardiology training. I had appropriate training in doing the non-invasive investigations which were done as per the Standard Operating Procedure (SOP) in the appendix. Quality of life data was collected on the questionnaire completed by the patient prior to discharge. If the patient had difficulty reading, I read the questions and marked the patient chosen answer. All relevant data were collected in the paper case report form. The data was transferred to a password protected excel spreadsheet. I collected the follow up data at one month from the hospital patient record, summary care record and information faxed from GP surgery.

Overall I was solely responsible for the recruitment of patients, performing non-invasive investigations as described in subsequent sections, cognitive assessment, quality of life measures, entry of data in the database and also collection of follow up data.

2.1.4 Power Calculation

My thesis is based on an observational study for a holistic assessment of older patients undergoing invasive treatment strategy for NSTEACS. Though clinical outcomes at one month were collected this was to understand how older patients did based on frailty status after invasive procedure, rather than to show clinically relevant difference. It has to be noted outcome data in a similar cohort of patients as in my thesis, for sample size calculation was not available. With outcomes from Global Registry of Acute Coronary Events (GRACE) study mainly based on age (30%), rough estimate level of significance of 5% and a power of 80%, a sample size of about 300 patients was chosen. My thesis is based on the 240 patients I was involved with recruitment and data collection during the two years of my dedicated clinical research period. With relatively small number of patients like in my thesis, I do understand the results are more likely to be hypothesis generating, than to be definitive of clinical significance in the findings and results. Also with contemporary management lower rate of adverse CV outcomes, will result in the study being under powered to show significant difference between the patient groups for adverse clinical outcomes. I have written this thesis from the data collected from my work on 240 patients, to explore and describe the observations made.

2.1.5 Inclusion and Exclusion Criteria

Inclusion and exclusion criteria are displayed in Table 2.2.

Table 2.2: Inclusion and exclusion criteria for ICON1 study

Inclusion Criteria
≥ 65 years old
Non ST Elevation Acute Coronary Syndrome
Planned for CA or PCI
Exclusion Criteria
Cardiogenic shock
Primary Arrhythmias
Significant valvular heart disease
Malignancy with life expectancy <1 year
Active Infection
Urinary Tract Infection
Pneumonia
Sepsis
Alternative diagnosis after CA (excluded after consent)
Pulmonary embolism
Takotsubo cardiomyopathy
Myocarditis
Coronary vasospasm
Unable to consent
Known Dementia
Language barrier
Visual impairment
Lack of capacity

CA-Coronary Angiogram, PCI-Percutaneous Coronary Intervention

2.1.6 Treatment Protocol

Contemporary treatment of NSTEACS as felt appropriate by the treating interventional cardiologist was offered to the patient.(Hamm *et al.*, 2011) According to standard practice, patients were revascularised by PCI or coronary artery bypass graft (CABG) surgery. Patients may also be managed medically if deemed not appropriate for either of the revascularisation strategies at the discretion of the operating cardiologist.

2.1.7 Data Collection

Data were collected on standardised case report forms by members of the research team. The data collected include demographics, baseline characteristics, and details of coronary angiography and or PCI. Peri-procedural complications and in-hospital complications were recorded. Further data were collected on the cardiovascular status, Canadian Cardiovascular Society (CCS) angina grade, New York Heart Association (NYHA) dyspnoea grade, frailty category, functional health status, quality of life and cognitive status. The assessments done as part of the study are in **Table 2.3**.

Table 2.3: Assessments Tools

Cardiovascular Status
Arterial Stiffness
Peripheral Arterial Tonometry
Carotid Intima Media Thickness
Trans-thoracic Echocardiogram
Cardiac Symptoms
New York Heart Association Dyspnoea
Canadian Cardiovascular Society Angina
Frailty Assessment
Fried Frailty Index
Rockwood Frailty Index
Quality of Life
SF-36, Euro QoL - 5D (EQ-5D™)
Cognitive Status
Montreal Cognitive Assessment (MoCA©)
Co-morbidity
Charlson Co-morbidity Index

2.2 Frailty and Comorbidity Assessments

Frailty was assessed by Fried Frailty Index derived from Cardiovascular Health Study(Fried *et al.*, 2001b) and Rockwood Frailty Index derived from Canadian Study of Health and Aging.(Rockwood *et al.*, 2005) Fried frailty index is based on assessing 5 criteria by both subjective answers from the patient (weight loss, physical energy, physical activity) and objective assessment (hand grip strength, walking speed). A score of 0 was categorised robust, 1 or 2 as intermediate frail or pre-frail and 3 or more as frail. Rockwood criteria was based on assessment by the researcher into categories 1 to 7 from very fit to severely frail depending on functional status and independence/dependence on others for activities of daily living. See appendix for Fried and Rockwood tools.

In addition, the Charlson co-morbidity index,(E, 1987) a method of predicting mortality based on weighted index of the number and seriousness of co-morbid conditions is evaluated for each patient. Charlson co-morbidity index has been demonstrated to be an appropriate indicator of in-hospital and one-year outcomes in the setting of ACS.(Radovanovic *et al.*, 2014)

2.3 Functional Status and Quality of Life Measures

Short form - 36 standard (SF-36® Standard) health survey was completed by each patient prior to discharge from the hospital and at one-year follow-up to assess functional health and quality of life. The responses will be used to obtain physical component summary and mental component summary scores.(Ware and Sherbourne, 1992) SF-36 survey was used with permission (License number QM033917) from the RAND Corporation. Copyright © the RAND Corporation. RAND's permission to reproduce the survey is not an endorsement of the products, services, or other uses in which the survey appeared or was applied in this study .In addition EQ-5D™-3L questionnaire was used to assess health outcome of each patient at discharge.(Group, 1990; R, 1996) See SF-36 and EQ5D-3L in appendix.

2.4 Cognitive Status Assessment

Atherosclerosis is associated with increased risk of cognitive impairment in older patients.(van Oijen *et al.*, 2007) To assess the cognitive status of patients during admission, the Montreal Cognitive Assessment (MoCA©) (Nasreddine *et al.*, 2005) test was utilised (Permission obtained from MoCA Clinic and Institute on behalf of Dr Ziad Nasreddine, copyright owner of MoCA) as given in appendix. The MoCA test has been shown to have high sensitivity in screening patients with known CV disease for mild cognitive impairment even in a non-memory clinic setting.(McLennan *et al.*, 2011)

2.5 Non-Invasive Assessments of Cardiovascular Status

2.5.1 Arterial Stiffness

Carotid-femoral PWV was assessed by the Vicorder device (Skidmore Medical Limited, Bristol, UK). In addition brachio-femoral PWV, pulse wave analysis (includes pulse pressure, augmentation pressure and augmentation index) was also assessed. This device has been validated for these measurements.

2.5.2 Endothelial Function

Endothelial function was measured by EndoPAT^{TM} (Itamar Medical, Caesarea, Israel). PAT signals are recorded from the index fingers with pneumatic probes at baseline, during cuff occlusion and during hyperaemia. A measure of endothelial function is calculated from the ratio of PAT signal amplitude at baseline and post-occlusion.

2.5.3 Carotid Intima Medial Thickness

CIMT was assessed using vivid I GE machine with a vascular probe. CIMT measurement is obtained by the semi-automated measurement software which uses edge detection technique. CIMT values will be analysed for prediction of adverse outcomes and will be incorporated in the risk model.

2.5.4 Trans-thoracic Echocardiogram

Trans-thoracic echocardiogram was performed using Vivid i GE echo machine, according to the British Society of Echocardiography guidelines to assess systolic function, diastolic function and valvular heart disease.(Gill Wharton, 2012) Systolic and diastolic function will be analysed for prediction of adverse CV outcomes.

Standard Operating Procedure (SOP) followed in performing the above non-invasive tests are in appendix.

2.6 Outcome Measures

Procedural complications and in-hospital adverse outcomes were followed up until discharge. One-month outcomes were recorded from the hospital electronic patient record, summary care record and general practitioner summary obtained from the patients' general practice surgeries. Outcome measures were death, myocardial infarction,(Thygesen *et al.*, 2007) stroke, unplanned revascularisation and BARC (Bleeding Academic Research Consortium)(Mehran *et al.*, 2011) defined bleeding in-hospital and at 30-days as per definitions in appendix.

2.7 Statistical Methods

All the statistical analysis presented in this thesis are done by me using IBM® SPSS® (version 22, 2013). I had attended appropriate courses for basic and advanced use of SPSS run by Newcastle University. I received statistical guidance on one-one basis from the University appointed guide for statistics for post-graduate students (see acknowledgment).

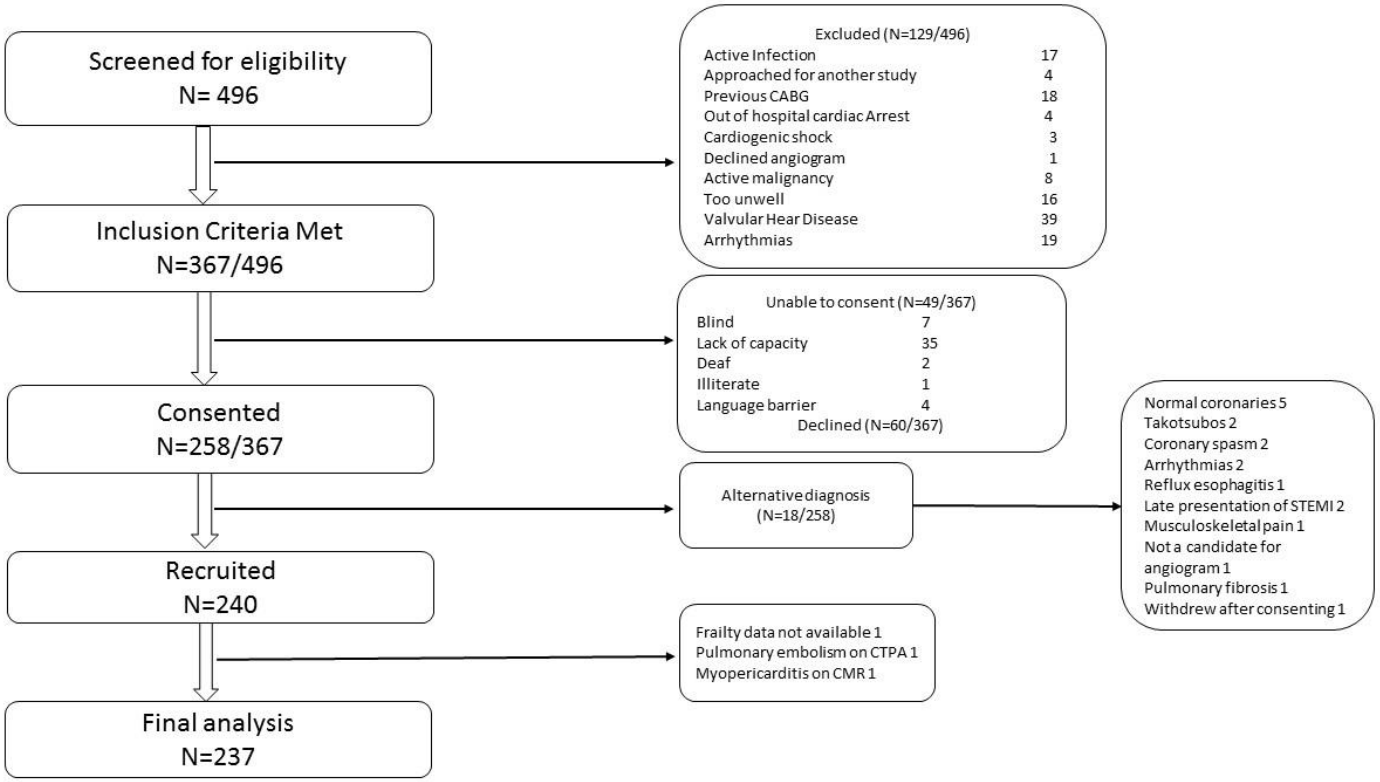
Frequency of categorical data are presented as number and percentage. Normally distributed continuous data is presented as mean and standard deviation. Non-normally distributed data is presented as median and range or interquartile range. Differences between groups were assessed by t-tests (normally distributed continuous data), Wilcoxon-Mann-Whitney U tests (non-normally distributed continuous data) and chi-squared tests (categorical data). The p values are two sided with bonferroni correction applied for multiple testing as appropriate. Missing values are excluded from analysis (number of missing data are reported). Regression analysis (binary logistic and ordinal) model were used for prediction of dependent variable from related independent variables.

CHAPTER 3: RESULTS

3.1 Recruitment

A screening log was maintained to keep record of patients with NSTEACS who were screened and recruited into ICON1 study from November 2012 to December 2014. A total of 496 patients were screened. **Figure 3.1** depicts the patient recruitment. Of these 129 were excluded as they did not meet the eligibility criteria. Of the remaining patients, 49 patients could not be recruited due to consent issues and 60 patients declined to take part in the study. So 258 patients were consented of which 18 had to be excluded after coronary angiography as they had an alternative diagnosis. Of the 240 patients recruited into the study further 3 patients could not continue in the study leaving 237 patients whose data was analysed.

Figure 3.1: Flow chart detailing patient recruitment



CABG Coronary Artery Bypass Surgery, CTPA Computed Tomography Pulmonary Angiogram, CMR Cardiac Magnetic Resonance imaging

3.2 Baseline Characteristics of Patient Cohort at Recruitment

The number of patients recruited into the study from November 2012 to December 2014 was 237 patients. Of these 89 (37.6%) were females. The mean age of the patient cohort was 80.3 years (SD 4.9). The oldest was 93.6 years and the youngest was 66.2 years old. Patients belonged to the age group 65-80 years (108, 45.6 %) and >80 years (129, 54.4%). Most of the patients were ≥ 75 years old (218, 92.5%) and only 18 (7.5%) were between the age group 65-74 years. The final diagnosis prior to invasive treatment was NSTEMI (196, 82.7%) and UA (41, 17.3%). Baseline characteristics are displayed in **Table 3.1**.

The cardiovascular risk factor profile of the patient cohort was hypertension (182, 76.8%), diabetes (61, 25.7%), current smoker (19, 8.0%), ex-smoker (116, 48.9%), hypercholesterolemia (146, 61.6%), peripheral vascular disease (22, 9.3%) and previous cerebrovascular disease with either stroke or transient ischemic attack (41, 17.3%).

Cardiac history included previous MI (81, 34.2%), previous angina (94, 39.7%), previous PCI (45, 19.0%), previous CABG (12, 5.1%), previous AF/PAF (30, 12.7%) and CCF (18, 7.6%).

Other medical history of significance were renal impairment (40, 16.9%), peptic ulcer disease (10, 4.2%), bleeding problems (6, 2.5%), anaemia (20, 8.4%), COPD (47, 19.8%), previous malignancy (23, 9.7%) and osteoarthritis (77, 32.5%). There were no patients with known dementia or active malignancy as these were exclusion criteria.

Table 3.1: Baseline characteristics of patient cohort

Variable	Number of patients N=237	% of total patients
Male	148	62.4
Female	89	37.6
Age in years mean (SD)	80.3 (4.9)	
> 80 years	129	54.4
65-80 years	108	45.6
< 75 years	18	7.5
NSTEMI	196	82.7
UA	41	17.3
Hypertension	182	76.8
Diabetes mellitus	61	25.7
Current smoker	19	8.0
Ex-smoker	116	48.9
Never smoked	102	43.1
Hypercholesterolemia	146	61.6
Peripheral vascular disease	22	9.3
Cerebrovascular disease	41	17.3
Myocardial infarction	81	34.2
Angina	94	39.7
CABG	12	5.1
AF/PAF	30	12.7
CCF	18	7.6
Renal impairment	40	16.9
Anaemia	20	8.4
Major bleeding problems	6	2.5
COPD	47	19.8
Previous malignancy	23	9.7
Osteoarthritis	77	32.5

AF/PAF Atrial Fibrillation/Paroxysmal AF, CABG Coronary Artery Bypass Surgery, CCF Congestive Cardiac Failure, COPD Chronic Obstructive Pulmonary disease, NSTEMI Non ST Elevation Myocardial Infarction, UA Unstable Angina

3.3 Frailty Classification

As per FFC, there are three groups – Frail, Pre-frail and Frail. RFC categorises the patients in 7 grades of which 1-4 are non-frail and 5-7 describe the frail patients (**Table 3.2**). The analysis in the following sections are done as Frail, Pre-Frail and Robust groups and also as Frail and Non-Frail groups for easier comparison between the two criteria. Fried criteria was made in to frail and non-frail (combining robust and pre-frail groups together). Similarly Rockwood was divided into three groups by describing the non-frail as robust 1-2 and pre-frail 3-4; with frail group comprising categories 5-7.

Table 3.2: Frailty Groups Classification

Three Groups by Fried and Rockwood Criteria	Fried Frailty Score	Rockwood Frailty Category	Two Groups by Fried and Rockwood Criteria
Robust	0	1 2	Non-Frail
Pre-Frail	1-2	3 4	
Frail	3-5	5 6 7	Frail

3.3.1 Frailty status

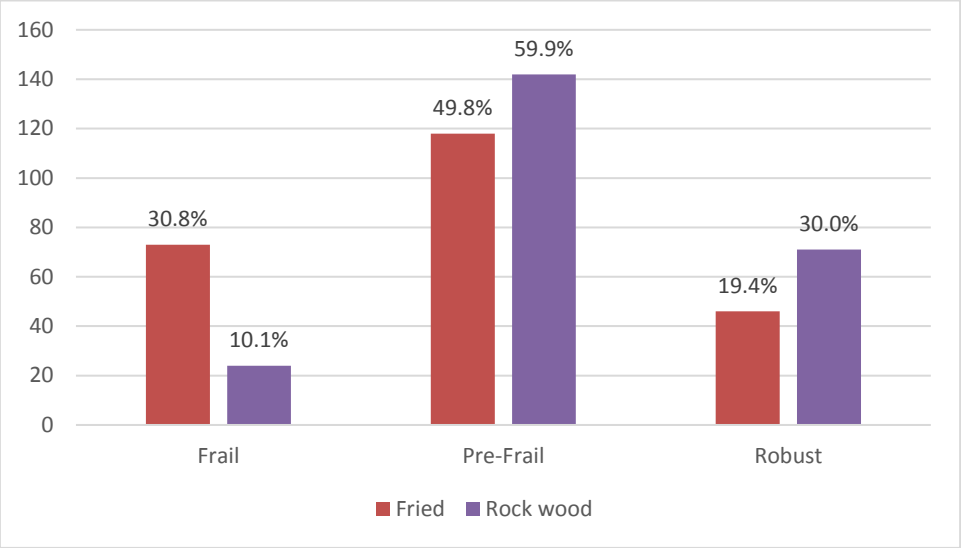
3.3.1.1 Fried Criteria

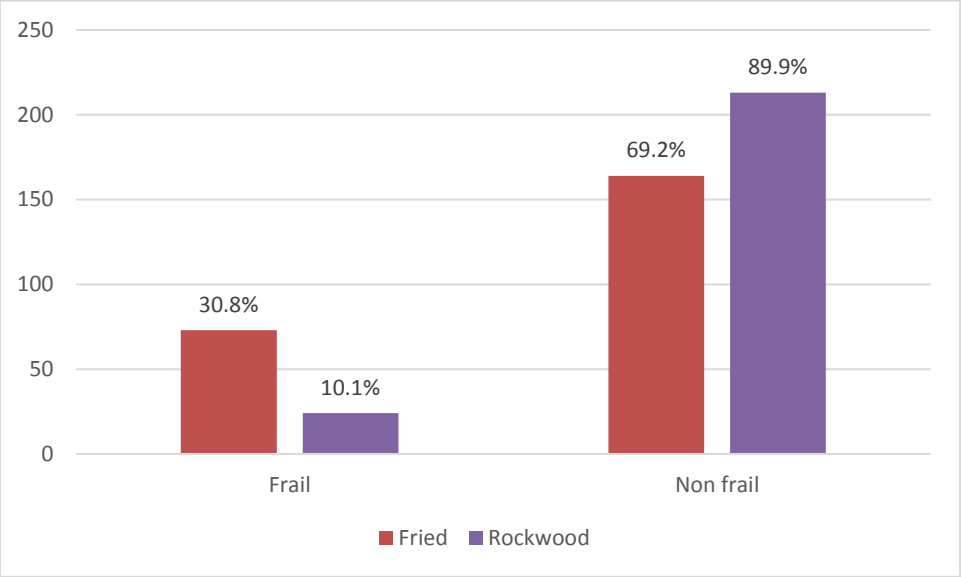
As per FFC, patients are grouped into frail, pre-frail and robust groups. The prevalence of these three groups of patients in the study were 30.8% (n=73), 49.8% (n=118) and 19.4% (n=46) respectively. But when classified as frail and non-frail groups, 69.2% (n=164) patients were non-frail.

3.3.1.2 Rockwood Criteria

As per RFC, the frail and non-frail groups of patients are 10.1% (n=24) and 89.9% (n=213) respectively. When the non-frail patients were further sub classified to equate with Fried frailty status groups, 59.9% (n=142) were pre-frail and 30.0% (n=71) belonged to robust group.

Figure 3.2: Frailty Groups as per Fried and Rockwood Criteria





3.3.2 Frailty status variation between the two frailty tools

Frailty status by the two assessment tools vary significantly. As has been depicted in the previous bar charts (**Figure 3.2**) 30.8% of patients are classified as frail by the Fried criteria while only 10.1% of the patients are frail by the Rockwood classification. The frailty status determined by Rockwood group compared to Fried frailty status was similar in 26% of frail, 66.1% of pre-frail and 73.9% of robust patients (**Table 3.3**). When classified as two groups of frail and non-frail only 26% of patients were classified similarly as frail by the two criteria but this increases to 97% when classifying non-frail groups (**Table 3.4**).

Since there was variation in the frailty status depending on the frailty assessment tool, subsequent results are analysed for frailty status for both Fried and Rockwood frailty status separately.

Table 3.3: Prevalence of Frail, Pre-Frail and Robust Groups by Fried and Rockwood Criteria

		Fried Frailty Groups				
		Frail	Pre-Frail	Robust	Total	p value
Rockwood Frailty Groups	Frail	19 (26.0%)	4 (3.4%)	1 (2.2%)	24	<0.0001
	Pre-Frail	53 (72.6%)	78 (66.1%)	11 (23.9%)	142	
	Robust	1 (1.4%)	36 (30.5%)	34 (73.9%)	71	
	Total	73	118	46	237	

Table 3.4: Prevalence of Frail and Non-Frail Groups by Fried and Rockwood Criteria

		Fried Frailty Groups			
		Frail	Non-Frail	Total	p value
Rockwood Frailty Groups	Frail	19 (26.0%)	5 (3.0%)	24	<0.0001
	Non-Frail	54 (74.0%)	159 (97.0%)	213	
	Total	73	164	237	

3.4 Variables Determining Frailty Status by Fried Variables

Fried frailty status assessment is based on five variables; three of which are subjective responses from patients (weight loss, physical endurance and physical activity) and two are objective assessments (handgrip strength and walking speed). The order of prevalence of these variables in the frail group are weakness by hand grip strength (91.8%), low physical activity (83.6%), poor physical endurance (71.2%), weight loss in the last year (64.4%) and slow walking speed (34.7%). In the pre-frail group the prevalence of these variables are weakness by handgrip strength (70.1%), weight loss in the last year (22.9%), low physical activity (24.6%), poor physical endurance (19.5%) and slow walking speed (4.3%). These are displayed in **Table 3.5 and Figure 3.3**.

In the frail group a score of 3 was most common (61.6%), followed by score of 4 (30.1%) and score 5 (8.2%). In the pre-frail group the prevalence of score 2 was 42.2% and score 1 was 57.8%.

When these variables were assessed for Rockwood frailty groups the prevalence of these Fried variables in the frail group, weakness by handgrip strength 87.5%, low physical activity 75.0%, poor physical endurance 66.7%, weight loss 45.8% and slow walking speed 45.5%, the pre-frail group 71.1%, 50.0%, 38.0%, 38.7% and 13.4% respectively and robust group 38.6%, 1.4%, 7.0%, 11.3% and 1.4% respectively were significantly different between the groups. These are displayed in **Table 3.6 and Figure 3.4**.

Table 3.5: Frequency of Fried Frailty Status Variables

Fried Criteria Scoring variables	Frail	Pre-Frail	Robust	p value
Weight Loss in the last year	64.4%	22.9%	0%	<0.0001
Poor Physical Endurance	71.2%	19.5%	0%	<0.0001
Low Physical Activity	83.6%	24.6%	0%	<0.0001
Weakness by Handgrip strength	91.8%	70.1%	0%	<0.0001
Slow walking speed	34.7%	4.3%	0%	<0.0001

Figure 3.3: Fried Frailty Groups and Fried Score

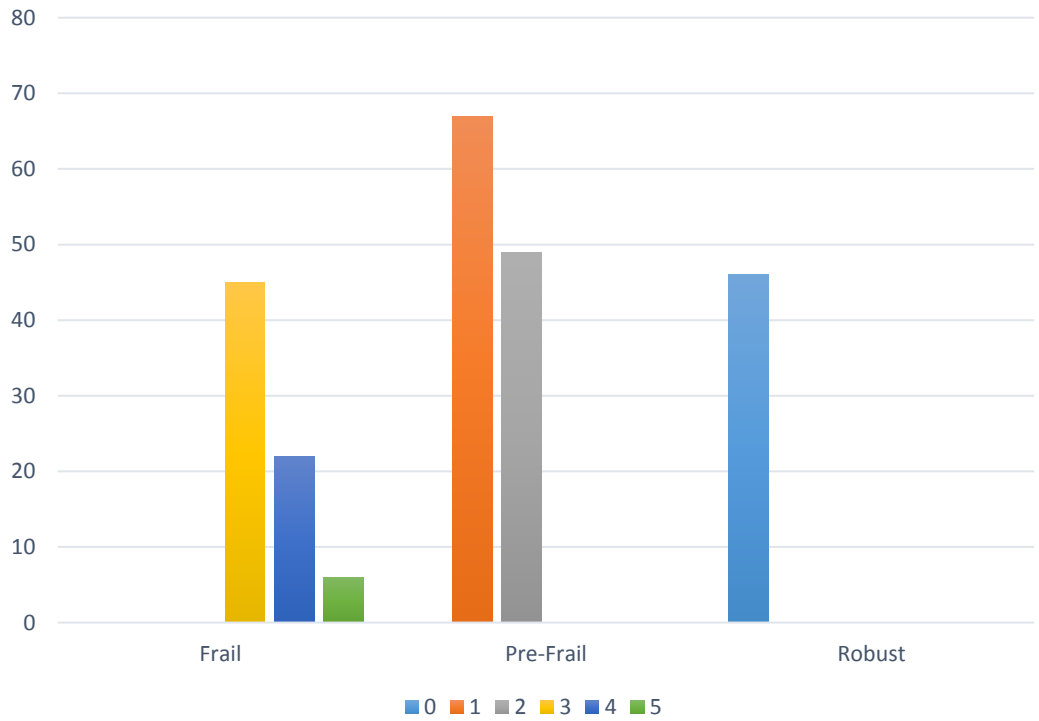
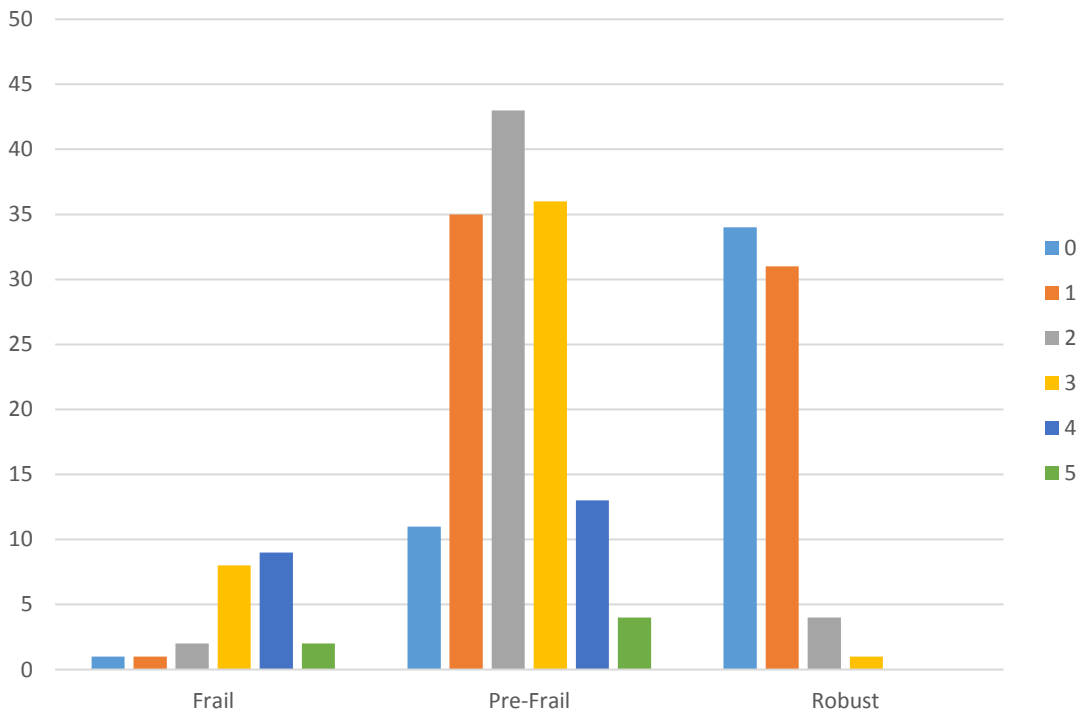


Table 3.6: Rockwood Frailty Status and Frequency of Fried Scoring Variables

Fried Criteria Scoring variables	Frail	Pre-Frail	Robust	p value
Weight Loss in the last year	45.8%	38.7%	11.3%	<0.0001
Physical Endurance	66.7%	38.0%	7.0%	<0.0001
Low Physical Activity	75.0%	50.0%	1.4%	<0.0001
Weakness by Handgrip strength	87.5%	71.1%	38.6%	<0.0001
Slow walking speed	45.5%	13.4%	1.4%	<0.0001

Figure 3.4: Rockwood Frailty Groups and Fried Scores



3.5 Baseline Characteristics of Patients by Frailty Status

3.5.1 Demographics, CV Risk Factors, CV Disease Profile and Comorbidities

3.5.1.1.1 Fried Frailty Status

The mean age of robust patients was 78.3 (SD 4.9) years compared to 80.8 (4.9) years of frail and 80.8 (4.7) years of pre-frail group of patients (p=0.007). The mean age was not significantly different when compared as frail and non-frail groups (80.8 vs. 80.1, p=0.301). Though the proportion of females were not significantly different between the three groups, females comprised more of the frail status compared to non-frail status (47.9% vs. 32.9%, p=0.030). **Table 3.7** displays the baseline characteristics by Fried frailty status.

Cardiac risk factor profile was similar between the groups but history of cardiovascular disease with previous MI (46.6% vs. 28.7%, p=0.011), previous angina (49.3% vs. 35.4%, p=0.046), previous PCI (27.4% vs. 15.2%, p=0.032), previous cerebrovascular disease (26.0% vs. 13.4%, p=0.025) and congestive cardiac failure (15.1% vs. 4.3%, p=0.007) was significantly more prevalent in the frail patients compared to non-frail patients. There was no significant difference in the prevalence of AF/PAF and PVD.

From non-cardiac perspective, history of arthritis (43.8% vs. 27.4%, p=0.010) and COPD (28.85 vs. 15.9%, p=0.007) was more common among frail patients than non-frail patients. There was no significant difference in the prevalence of previous malignancy, previous major bleeding problems or anaemia.

Table 3.7: Baseline Characteristics by Fried Frailty Status

Baseline variables	Total N=237	Frail (F) N=73	Pre-Frail (PF) N=118	Robust (R) N=46	p value F v PF v R	Non Frail (R +PF) N=164	p value F v NF
Age mean±SD	80.3 (4.9)	80.8 (4.9)	80.8 (4.7)	78.3 (4.9)	0.007*	80.1 (4.9)	0.301
Female n (%)	89 (37.6)	35 (47.9)	41 (34.7)	13 (28.3)	0.065	54 (32.9)	0.030*
Height mean (SD) in cm	165.5 (10.0)	163.3 (10.0)	166.2 (10.0)	167.2 (9.4)	0.070	166.5 (9.8)	0.026*
Weight mean (SD) in kg	75.0 (14.5)	72.5 (15.4)	75.3 (14.9)	78.2 (11.4)	0.111	76.1 (14.0)	0.076
BMI mean (SD)	27.4 (4.7)	27.0 (4.8)	27.4 (4.9)	27.9 (3.7)	0.577	27.6 (4.6)	0.393
Hypertension n (%)	182 (77.1)	59 (80.8)	89 (75.4)	34 (75.6)	0.663	123 (75.5)	0.406
Diabetes n (%)	61 (25.7)	21 (28.8)	33 (28.0)	7 (15.2)	0.190	40 (24.4)	0.521
Current smoker n (%)	19 (8.0)	7 (9.6)	9 (7.6)	3 (6.5)	0.815	12 (7.3)	0.607
Ex-smoker n (%)	116 (48.9)	43 (58.9)	52 (44.1)	21 (45.7)	0.121	73 (44.5)	0.049*
Hyperlipidaemia n (%)	146 (61.6)	49 (67.1)	66 (55.9)	31 (67.4)	0.202	97 (59.1)	0.252
Renal Impairment n (%)	40 (16.9)	16 (21.9)	21 (17.8)	3 (6.5)	0.086	24 (14.6)	0.190
Previous MI n (%)	81 (34.2)	34 (46.6)	37 (31.4)	10 (21.7)	0.014*	47 (28.7)	0.011*
Previous Angina n (%)	94 (39.7)	36 (49.3)	47 (39.8)	11 (23.9)	0.022*	58 (35.4)	0.046*
Previous PCI n (%)	45 (19.0)	20 (27.4)	20 (16.9)	5 (10.9)	0.059	25 (15.2)	0.032*
Previous CABG n (%)	12 (5.1)	5 (6.8)	4 (3.4)	3 (6.5)	0.503	7 (4.3)	0.521
AF/PAF n (%)	30 (12.7)	14 (19.2)	11 (9.3)	5 (10.9)	0.127	16 (9.8)	0.056
PVD n (%)	22 (9.3)	8 (11.0)	11 (9.3)	3 (6.5)	0.719	14 (8.5)	0.629
Previous TIA/Stroke n (%)	41 (17.3)	19 (26.0)	19 (16.1)	3 (6.5)	0.021*	22 (13.4)	0.025*
Arthritis n (%)	77 (32.5)	32 (43.8)	39 (33.1)	6 (13.0)	0.002*	45 (27.4)	0.010*
COPD n (%)	47 (19.8)	21 (28.8)	20 (16.9)	6 (13.0)	0.060	26 (15.9)	0.033*
Previous Malignancy n (%)	23 (9.7)	6 (8.2)	12 (10.2)	5 (10.9)	0.868	17 (10.4)	0.813
Congestive cardiac failure n (%)	18 (7.6)	11 (15.1)	6 (5.1)	1 (2.2)	0.012*	7 (4.3)	0.007*
Previous major bleeding problems n (%)	6 (2.5)	3 (4.1)	3 (2.5)	0 (0)	0.381	3 (1.8)	0.375
Anaemia n (%)	20 (8.4)	9 (12.3)	11 (9.3)	0 (0)	0.055	11 (6.7)	0.204

AF/PAF Atrial Fibrillation/ Paroxysmal AF, BMI Body Mass Index, CABG Coronary Artery Bypass Surgery, COPD Chronic Obstructive Pulmonary Disease, MI Myocardial Infarction, PCI Percutaneous Coronary Intervention, PVD Peripheral vascular Disease, SD Standard Deviation

3.5.1.1.2 Rockwood Frailty Status

The mean age of frail patients was 83.1 (4.7) years compared to 79.1 (SD 5.2) years of robust and 80.5 (4.5) years of pre-frail group of patients (p=0.002). Similarly frail patients were older by 3 years compared to non-frail patients (p=0.004). Frail patients were more likely to be females when compared as three groups (62.5% vs. 42.3% vs. 19.7%, p=<0.001) or two groups (62.5% vs. 34.7%, p =0.0130). **Table 3.8** displays the baseline characteristics by Rockwood frailty status.

When compared as frail, pre-frail and robust groups, regarding the CV risk profile significant difference was noted in the prevalence of diabetes (16.7% vs. 35.2% vs. 9.9%, p = <0.001) and hypertension (87.5% vs. 80.3% vs. 67.1%, p=0.045). But when compared as frail and non-frail groups there was no significant difference in the CV risk profile.

IHD was more prevalent in the frail patients with previous MI (70.8%), previous angina (66.7%), previous PCI (37.5%) and previous CABG (16.7%) when compared either as three or two groups. Similarly previous cerebrovascular disease (33.3%) was more common in frail patients when compared either as three or two groups but CCF (7.6%) was more prevalent in frail patients only when compared as three groups. There was no significant difference in the prevalence of AF/PAF and PVD.

From non-cardiac comorbidities arthritis (54.2%) and anaemia (25.0%) was more prevalent in the frail patients when compared to either as three or two groups. COPD (25.0%) was more common in frail patients only when compared as three groups but not as two groups. There was no significant difference in the prevalence of previous malignancy and previous major bleeding problems.

Table 3.8: Baseline Characteristics by Rockwood Frailty Status

Baseline variables	Total N=237	Frail (F) N=24	Pre-Frail (PF) N=142	Robust (R) N=71	p value F v PF v R	Non Frail (R +I) N=213	p value F v NF
Age mean±SD	80.3 (4.9)	83.1 (4.7)	80.5 (4.5)	79.1 (5.2)	0.002*	80.0 (4.8)	0.004*
Female n (%)	89 (37.6)	15 (62.5)	60 (42.3)	14 (19.7)	<0.001*	74 (34.7)	0.013*
Height mean (SD) in cm	165.5 (10.0)	160.1 (12.1)	164.8 (9.8)	168.8 (8.3)	<0.001*	166.1 (9.5)	0.005*
Weight mean (SD) in kg	75.0 (14.5)	70.6 (15.2)	75.4 (15.8)	75.6 (11.0)	0.302	75.5 (14.4)	0.122
BMI mean (SD)	27.4 (4.7)	27.4 (5.1)	27.8 (5.2)	75.6 (11.0)	0.131	27.4 (4.7)	0.954
Hypertension n (%)	182 (77.1)	21 (87.5)	114 (80.3)	47 (67.1)	0.045*	161 (75.9)	0.304
Diabetes n (%)	61 (25.7)	4 (16.7)	50 (35.2)	7 (9.9)	<0.001	57 (26.8)	0.335
Current smoker n (%)	19 (8.0)	1 (4.2)	15 (10.6)	3 (4.2)	0.211	18 (8.5)	0.702
Ex-smoker n (%)	116 (48.9)	14 (58.3)	74 (52.1)	28 (39.4)	0.136	102 (47.9)	0.392
Hyperlipidaemia n (%)	146 (61.6)	18 (75.0)	86 (60.6)	42 (59.2)	0.356	128 (60.1)	0.187
Renal Impairment n (%)	40 (16.9)	7 (29.2)	16 (18.3)	7 (9.9)	0.071	33 (15.5)	0.145
Previous MI n (%)	81 (34.2)	17 (70.8)	52 (36.6)	12 (16.9)	<0.001*	64 (30.0)	<0.001*
Previous Angina n (%)	94 (39.7)	16 (66.7)	64 (45.1)	14 (19.7)	<0.001	78 (36.6)	0.007*
Previous PCI n (%)	45 (19.0)	9 (37.5)	29 (20.4)	7 (9.9)	0.009	36 (16.9)	0.025*
Previous CABG n (%)	12 (5.1)	4 (16.7)	4 (2.8)	4 (5.6)	0.016*	8 (3.8)	0.023*
AF/PAF n (%)	30 (12.7)	5 (20.8)	20 (14.1)	5 (7.0)	0.154	25 (11.7)	0.201
PVD n (%)	22 (9.3)	2 (8.3)	17 (12.0)	3 (4.2)	0.183	20 (9.4)	1.000
Previous TIA/Stroke n (%)	41 (17.3)	8 (33.3)	26 (18.3)	7 (9.9)	0.028*	33 (15.5)	0.043*
Arthritis n (%)	77 (32.5)	13 (54.2)	52 (36.6)	12 (16.9)	0.001*	64 (30.0)	0.022*
COPD n (%)	47 (19.8)	6 (25.0)	37 (26.1)	4 (5.6)	0.002*	41 (19.2)	0.588
Previous Malignancy n (%)	23 (9.7)	3 (12.5)	13 (9.2)	7 (9.9)	0.876	20 (9.4)	0.713
Congestive cardiac failure n (%)	18 (7.6)	4 (16.7)	14 (9.9)	0 (0)	0.008*	14 (6.6)	0.094
Previous major bleeding problems n (%)	6 (2.5)	2 (8.3)	4 (2.8)	0 (0)	0.076	4 (1.9)	0.115
Anaemia n (%)	20 (8.4)	6 (25.0)	13 (9.2)	1 (1.4)	0.001*	14 (6.6)	0.008*

AF/PAF Atrial Fibrillation/ Paroxysmal AF, BMI Body Mass Index, CABG Coronary Artery Bypass Surgery, COPD Chronic Obstructive Pulmonary Disease, MI Myocardial Infarction, PCI Percutaneous Coronary Intervention, PVD Peripheral vascular Disease, SD Standard Deviation

3.5.2 Blood Results Prior to Invasive Management

Baseline blood results are displayed in **Table 3.9** for Fried Frailty status and in **Table 3.10** for Rockwood Frailty status.

3.5.2.1.1 Fried Frailty Status

The mean haemoglobin level was 13.1 (SD 1.7) g/dl in the 235 patients the result was available. The mean level in the frail, pre-frail and robust patients was 12.6 (SD 1.6), 13.0 (SD 1.7) and 14.1 (SD 1.6) respectively (p=<0.001). When compared as frail and non-frail patients this was 12.6 (SD 1.6) and 13.1 (SD 1.7) respectively (p=0.003). There was no significant difference in the mean white cell count (8.4 vs. 8.4 vs. 7.7 and 8.4 vs. 8.2 $x10^3$/microlitre) or median platelet counts (235 vs. 243 vs. 235 and 235 vs. 229 $x10^3$/microlitre) according to the three or two groups of frailty status classification.

The median creatinine was not significantly different between the 3 groups: 92 µmol/L in frail, 93 µmol/L in pre-frail and 103 µmol/L in robust patients. The levels when compared as frail and non-frail patients were 92 µmol/L and 94 µmol/L respectively. The median GFR (ml/min) was not significantly different between the three groups (49.0 vs. 51.4 vs. 56.3) or two groups (49.0 vs. 50.9).

The mean serum glucose and cholesterol levels were not significantly different between the groups. It has to be noted that results were available for 178 and 184 patients respectively. Clotting profile of PT, APTT and fibrinogen were similar between the patient groups.

The median high sensitivity troponin level was 86 ng/L in frail, 119 ng/L in pre-frail and 153 ng/L in robust patients and this was not significant between the groups. Similarly there was no significant difference in median high sensitivity CRP levels between the three groups (4.4 vs. 4.1 vs. 2.7, p=0.368).

Though the frail patients had lower median serum vitamin D levels of 25 nmol/L compared to pre-frail (29.5 nmol/L) and robust (43.0 nmol/L), this was not statistically significant. Parathormone levels were measured in 142 patients and there was no significant difference of median levels between the three groups (6.4 nmol/L vs. 6.0 nmol/L vs. 5.2 nmol/L, p=0.139).

3.5.2.1.2 Rockwood Frailty Status

Similar to the difference noted in the fried frailty groups mean haemoglobin was lower in the frail (12.2 g/dL, SD 1.8) compared to pre-frail (12.8 g/dL, SD 1.6) and robust (13.9 g/dL, SD 1.7) patients with statistical significance ($p < 0.001$). This remained significant when compared as frail and non-frail groups (12.2 g/dL, SD 1.8 vs. 13.2 g/dL, SD 1.7, $p=0.010$).

Though there was no significant difference between the groups for median creatinine values but the median GFR values (ml/min) were significantly lower in the frail patients compared to pre-frail and robust patients (46.0 vs. 50.9 vs. 56.6, $p=0.004$). This difference persisted even when compared as frail and non-frail patients (46.0 vs. 52.2, $p=0.001$).

There was no difference noted in the mean serum glucose level, total cholesterol level, clotting profile, troponin and HS CRP levels, similar to the fried frailty groups.

The median vitamin D level was significantly lower in the frail group when compared as three groups (25.5 nmol/L vs. 26.0 vs. 39.0, $p=0.014$) but not when compared as two groups (25.5 vs. 30.5, $p=0.721$). Conversely median parathormone level was higher in frail patents when compared as three groups (96.2 nmol/L vs. 6.1 v vs. 5.5 nmol/L, $p=0.013$) but not when compared as two groups (96.2 nmol/L vs. 5.9 nmol/L, $p=0.416$).

Table 3.9: Baseline Blood Results by Fried Frailty Status

	Number	Normal lab reference	Total	Frail (F)	Pre-Frail (PF)	Robust (R)	p value F v PF v R	Non-Frail (R + PF)	p value F v NF
Haemoglobin g/dL	235	11.5 - 16.5	13.1 (1.7)	12.6 (1.6)	13.0 (1.7)	14.1 (1.6)	<0.001*	13.1 (1.7)	0.003*
White cell count	235	4 - 11	8.3 (2.7)	8.4 (2.8)	8.4 (2.8)	7.7 (1.9)	0.244	8.2 (2.6)	0.714
Platelet count median (range)	234	15 - 450	229 (550)	235 (308)	243 (498)	235 (481)	0.691	229 (550)	0.573
Creatinine median (range) µmol/L	235	70 - 145	93 (258)	92 (258)	93 (164)	103 (94)	0.943	94 (165)	0.930
GFR median (range)	235		50.9 (125.8)	49.0 (125.4)	51.4 (103.8)	56.3 (78.0)	0.223	50.9 (125.8)	0.228
Glucose mmol/L	178		7.3 (2.8)	7.5 (2.5)	7.2 (3.0)	7.0 (2.8)	0.714	7.1 (2.9)	0.433
Total Cholesterol mmol/L	184		4.1 (1.0)	4.1 (1.1)	4.1 (1.0)	4.3 (1.0)	0.746	4.2 (1.0)	0.729
PT s	232	10-13	11.6 (2.3)	11.6 (1.5)	11.5 (2.3)	12.0 (3.2)	0.466	11.7 (2.6)	0.746
APTT median (range) s	226	25-37	31 (207)	31 (61)	31 (207)	32 (25)	0.416	31 (207)	0.414
Fibrinogen g/L	232	2.1-4.8	4.9 (1.2)	4.9 (1.1)	5.0 (1.2)	4.8 (1.0)	0.579	4.9 (1.2)	0.827
Peak Troponin (HS) median (range) ng/L	235	<12	118 (9874)	86 (9874)	119 (5244)	153 (2999)	0.925	147 (5244)	0.933
HS CRP median (range) mg/L	234	0-5	3.9 (295)	4.4 (98.5)	4.1 (295)	2.7 (66.8)	0.368	3.9 (295)	0.881
Vitamin D median (range) nmol/L	234	>50	28.5 (123)	25 (110)	29.5 (123)	43.0 (85)	0.245	32.0 (123)	0.152
Parathormone median (range) pmol/L	142	1.1 - 6.4	6.0 (18.1)	6.4 (18.1)	6.0 (11.0)	5.2 (11.5)	0.139	6.0 (18.1)	0.136

GFR Glomerular Filtration Rate by Cockcroft Gault formula, PT Prothrombin Time, APTT Activated Partial Thromboplastin Time, HS High sensitive, CRP C-Reactive Protein

Table 3.10: Baseline Blood Results by Rockwood Frailty Status

	N	Normal lab ref.	Total	Frail (F)	Pre-Frail (PF)	Robust (R)	p value F v PF v R	Non-Frail (R + PF)	p value F v NF
Haemoglobin g/dL	235	11.5 - 16.5	13.1 (1.7)	12.2 (1.8)	12.8 (1.6)	13,9 (1.7)	<0.001 *	13.2 (1.7)	0.010*
White cell count	235	4 - 11	8.3 (2.7)	8.8 (3.6)	8,2 (2.2)	8.2 (3.1)	0.641	8.2 (2.6)	0.348
Platelet count median (range)	234	15 - 450	229 (550)	249 (340)	229 (451)	224 (482)	0.879	249 (340)	0.723
Creatinine median (range) µmol/L	235	70 - 145	93 (258)	105 (160)	91 (258)	94 (110)	0.335	93 (258)	0.168
GFR median (range)	235		50.9 (125.8)	46.0 (51.8)	50.9 (125.8)	56.6 (86.5)	0.004*	52.2 (125.8)	0.001*
Glucose mmol/L	178		7.3 (2.8)	7.5 (2.1)	7.4 (3.0)	6.8 (2.6)	0.363	7.2 (2.9)	0.669
Total Cholesterol mmol/L	184		4.1 (1.0)	3.9 (0.9)	4.1 (1.1)	4.3 (1.0)	0.329	4.2 (1.1)	0.437
PT s	232	10-13	11.6 (2.3)	12.2 (3.2)	11.5 (2.3)	11.7 (2.0)	0.420	11.6 (2.2)	0.213
APTT median (range) s	226	25-37	31 (207)	33 (18)	31 (203)	31.5 (63)	0.579	31 (207)	0.566
Fibrinogen g/L	232	2.1-4.8	4.9 (1.2)	4.8 (1.0)	5.0 (1.2)	4.7 (1.1)	0.253	4.8 (1.0)	0.713
Peak Troponin (HS) median (range) ng/L	235	<12	118 (9874)	67.5 (1070)	107 (9874)	147.5 (3000)	0.106	121 (9874)	0.135
HS CRP median (range) mg/L	234	0-5	3.9 (295)	4.7 (66.6)	4.6 (295)	2.3 (118)	0.588	3.7 (295)	0.934
Vitamin D median (range) nmol/L	234	>50	28.5 (123)	25.5 (110)	26.0 (123)	39.0 (112)	0.014*	30.5 (123)	0.721
Parathormone median (range) pmol/L	142	1.1 - 6.4	6.0 (18.1)	6.2 (8.9)	6.1 (18.1)	5.5 (11.5)	0.013*	5.9 (18.1)	0.416

GFR Glomerular Filtration Rate by Cockcroft Gault formula, PT Prothrombin Time, APTT Activated Partial Thromboplastin Time, HS High sensitive, CRP C-Reactive Protein

3.6 Type of NSTEACS and Management Strategy

These are displayed in **Tables 3.11 and 3.12** as per frailty classifications.

3.6.1 Arterial access and management strategy

3.6.1.1 Fried Frailty Status

There was no significant difference in the presentation with NSTEMI between frail, pre-frail and robust groups (80.8% vs. 82.2% vs. 87.0%, p=0.676) and also between frail and non-frail groups (80.8% vs. 83.5%, p=0.710). Similarly UA presentation was not significantly different between the frailty status groups (19.2% vs. 17.8% vs. 13.0% for F vs. PF vs. R and 19.2% vs. 16.5% for F vs. NF).

Frail patients were less likely to have coronary angiogram by radial access compared to the other groups (76.7% vs. 91.5% vs. 91.3%, p=0.008 and 76.7% vs. 91.5%, p=0.003). Conversely femoral access was more used in frail patients (23.3% vs. 8.5% vs. 8.7%, p=0.008 and 23.3% vs. 8.5%, p=0.003).

In terms of the final management strategy of revascularisation there was no significant difference in the use of PCI (87.7% vs. 83.9% vs. 82.6%, p=0.700 and 87.7% vs. 83.5%, p=0.2) and CABG (4.1% vs. 4.2% vs. 4.3%, p=0.9 and 4.1% vs 4.3%, p=1.0). Similarly medical management after coronary angiogram was not different between the groups (8.2% vs. 11.9% vs. 13.0%, p=0.649 and 8.2% vs. 12.2%, p=0.5).

Table 3.11: Type of NSTEACS and Management Strategy by Fried Frailty Status

	Total N=237	Frail (F) N=73	Pre-Frail (PF) N=118	Robust (R) N=46	p value F v PF v R	Non Frail (R +PF) N=164	p value F v NF
NSTEMI n (%)	196 (82.7)	59 (80.8)	97 (82.2)	40 (87.0)	0.676	137 (83.5)	0.710
UA n (%)	41 (17.3)	14 (19.2)	21 (17.8)	6 (13.0)	0.676	27 (16.5)	0.710
PCI n (%)	201 (84.8)	64 (87.7)	99 (83.9)	38 (82.6)	0.700	137 (83.5)	0.557
CABG n (%)	10 (4.2)	3 (4.1)	5 (4.2)	2 (4.3)	0.998	7 (4.3)	1.000
Conservative n (%)	26 (11.0)	6 (8.2)	14 (11.9)	6 (13.0)	0.649	20 (12.2)	0.500
Radial access n (%)	206 (86.9)	56 (76.7)	108 (91.5)	42 (91.3)	0.008*	150 (91.5)	0.003*
Femoral access n (%)	31 (13.1)	17 (23.3)	10 (8.5)	4 (8.7)	0.008*	14 (8.5)	0.003*
Time from presentation in days mean (SD)	5.5 (3.1)	5.7 (3.4)	5.4 (2.9)	5.6 (3.1)	0.895	5.5 (2.9)	0.713
Length of stay in days median (IQR)	6 (4)	7 (5)	6 (4)	6 (3)	0.391	6 (3)	0.172
Length of stay in days median (IQR) PCI	6.0 (4)	7.0 (6)	6.0 (4)	6.0 (3)	0.551	6.0 (3)	0.284
Length of stay in days median (IQR) CABG	28.5 (26)	34 (-)	21 (24)	18 (-)	0.056	21 (22)	0.016*
Length of stay in days median (range) conservative	6 (4)	6 (1)	5 (5)	6 (8)	0.771	5 (8)	0.756

NSTEMI Non ST Elevation Myocardial Infarction, PCI percutaneous Coronary Intervention, CABG Coronary Artery Bypass Graft, SD Standard Deviation, IQR Inter Quartile Range, UA Unstable Angina

3.6.1.2 Rockwood Frailty Status

There was no significant difference in the presentation with NSTEMI between frail, pre-frail and robust groups (83.3% vs. 81% vs. 85.9%, p=0.666) and also between frail and non-frail groups (83.3% vs. 82.6%, p=1.000). Similarly UA presentation was not significantly different between the frailty status groups (16.7% vs. 19.0% vs. 14.1% for F vs. PF vs. R and 16.7% vs. 17.4% for F vs. NF).

There was no significant difference in the arterial access for angiography procedure between the patient groups for radial access (79.2% vs. 88% vs. 87.3 for F vs. PF vs. R and 79.2% vs. 87.8% for F vs. NF). Though femoral access was more used in frail patients (20.8% vs. 12.0% vs. 12.7%, p=0.489 and 20.8% vs. 12.2%, p=0.216) this difference was not statistically significant.

In terms of the final management strategy of revascularisation there was no significant difference in the use of PCI (75.0% vs. 86.6% vs. 84.5%, p=0.34 and 75% vs. 85.9%, p=0.2) and CABG (4.2% vs. 4.2% vs. 4.2%, p=1.0 and 4.2% vs. 4.2%, p=1.0). Though medical management after coronary angiography was used more commonly in frail patients (20.8% vs. 8.5% vs. 12.7%, p=0.172 and 20.8% vs. 11.0%, p=0.157), this did not meet statistical significance.

3.6.1.3 Predictors of Femoral Access

A binary logistic regression analysis was conducted to predict use of femoral access for PCI using age, sex, previous CABG, previous PCI, PVD, weakness by grip strength, fried and rockwood frailty categories (as frail and non-frail groups). The regression model was statistically significant with chi-square 31.1 ($p < 0.001$). The model explained 23% (Nagelkerke R2) of the variance of use of femoral access and classified 88% of cases correctly with Hosmer and Lemeshow fit of 0.412. Patient with previous CABG were 21 times more likely to have femoral access. Femoral access is commonly used for clinical reason to access the left internal mammary artery used as a graft to LAD, though left radial access can be used for the same reason. Previous PCI, PVD and rock wood frailty predicted femoral access but not sex or weakness by grip strength.

Table 3.12: Type of NSTEACS and Management Strategy by Rockwood Frailty Status

	Total N=237	Frail (F) N=24	Pre-Frail (PF) N=142	Robust (R) N=71	p value F v PF v R	Non Frail (R +I) N=213	p value F v NF
NSTEMI n (%)	196 (82.7)	20 (83.3)	115 (81.0)	61 (85.9)	0.666	176 (82.6)	1.000
UA n (%)	41 (17.3)	4 (16.7)	27 (19.0)	10 (14.1)	0.666	37 (17.4)	1.000
PCI n (%)	201 (84.8)	18 (75.0)	123 (86.6)	60 (84.5)	0.340	183 (85.9)	0.224
CABG n (%)	10 (4.2)	1 (4.2)	6 (4.2)	3 (4.2)	1.000	9 (4.2)	1.000
Conservative n (%)	26 (11.0)	5 (20.8)	12 (8.5)	9 (12.7)	0.172	26 (11.0)	0.157
Radial access n (%)	206 (86.9)	19 (79.2)	125 (88.0)	62 (87.3)	0.489	187 (87.8)	0.216
Femoral access n (%)	31 (13.1)	5 (20.8)	17 (12.0)	9 (12.7)	0.489	26 (12.2)	0.216
Time from presentation in days mean (SD)	5.5 (3.1)	6.2 (2.7)	5.6 (3.2)	5.2 (2.9)	0.358	5.5 (3.1)	0.244
Length of stay in days median (IQR)	6 (4)	7.0 (5)	6.0 (4)	6.0 (4)	0.049*	6.0 (4)	0.092
Length of stay in days median (IQR) PCI	6.0 (4)	7.5 (5)	6.0 (4)	6.0 (4)	0.070	6 (3)	0.063
Length of stay in days median (IQR) CABG	28.5 (26)	34 (0)	29.5 (18)	7 (-)	0.283	28 (25)	0.222
Length of stay in days median (IQR) conservative	6 (4)	6 (4)	6 (2)	3 (5)	0.464	6.0 (8)	0.715

NSTEMI Non ST Elevation Myocardial Infarction, PCI percutaneous Coronary Intervention, CABG Coronary Artery Bypass Graft, SD Standard Deviation, IQR Inter Quartile Range, UA Unstable Angina

3.6.2 Revascularisation by Percutaneous Coronary Intervention Strategy

PCI details by frailty status are displayed in **Tables 3.13 and 3.14**

3.6.2.1 Fried Frailty Status

Of the 201 patients revascularised by PCI, radial access was used less in frail patients compared to other groups of patients (75% vs. 91.8% vs. 92.1%, p=0.005 in F vs. PF vs. R and 75% vs. 92%, p=0.002 in F vs. NF respectively). This in turn resulted in more use of femoral access in frail patients (25% vs. 8.1% vs. 7.9% and 25% vs. 8%). Almost a third of patients (72.6%) had single vessel PCI and just more than a quarter of the patients (27.4%) had multi vessel PCI but there was no significant difference in single vessel or multi vessel PCI in the patient groups by frailty status. The volume of contrast used for PCI was not significantly different between the patient groups. PCI was performed most in left anterior descending artery. But there was no significant difference in the coronary artery in which PCI was performed by frailty status. Though left main stem PCI was performed more in frail patients (12.5% vs. 8.1% vs. 2.6%, p=0.219) this did not reach statistical significance.

Table 3.13: PCI details by Fried Frailty Status

	Total N=201	Frail (F)	Pre-Frail (PF)	Robust (R)	p value F v PF v R	Non Frail (R +PF)	p value F v NF
Radial access PCI n **(%)**	174 (86.6)	48 (75.0)	91 (91.9)	35 (92.1)	0.005*	126 (92.0)	0.002*
Femoral access PCI n (%)	27 (13.4)	16 (25.0)	8 (8.1)	3 (7.9)	0.005*	11 (8.0)	0.002*
Single Vessel PCI n (%)	146 (72.6)	47 (73.4)	70 (70.7)	29 (76.3)	0.793	99 (72.3)	1.000
Multi Vessel PCI n (%)	55 (27.4)	17 (26.6)	29 (29.3)	9 (23.7)	0.793	38 (27.7)	1.000
Number of stents median (range)	1(6)	1 (6)	1 (5)	2 (3)	0.530	2 (5)	0.419
Contrast volume ml median (range)	170 (380)	155 (320)	170 (380)	160 (280)	0.648	170 (380)	0.396
LMS n (%)	17 (8.5)	8 (12.5)	8 (8.1)	1 (2.6)	0.219	9 (6.6)	0.179
LAD n (%)	115 (57.2)	38 (59.4)	59 (59.6)	18 (47.4)	0.395	77 (56.2)	0.760
LCx n (%)	67 (33.3)	24 (37.5)	31 (31.3)	12 (31.6)	0.693	43 (31.4)	0.424
RCA n (%)	66 (32.8)	16 (25.0)	35 (35.4)	15 (39.5)	0.243	50 (36.5)	0.111
Graft n (%)	2 (1.0)	1 (1.6)	0 (0)	1 (2.6)	0.327	1 (0.7)	0.537
Length of hospital stay median (range) in days	6 (27)	7 (27)	6 (18)	6 (18)	0.193	6 (18)	0.075

PCI Percutaneous Coronary Intervention, LMS Left Main Stem, LAD Left Anterior Descending, LCx Left Circumflex, RCA Right Coronary Artery

3.6.2.2 Rockwood Frailty Status

Though radial access was used less in frail patients this difference was not statistically significant (72.2% vs. 87.8% vs. 88.3%, p=0.173 and 72.2% vs. 88%, p=0.074). Similarly more use of femoral access in frail patients was not statistically significant either. The proportion of single vessel and multi vessel PCI was not different between the frailty groups. More LMS PCI (22.2% vs. 8.2% vs. 5.0%, p=0.252 and 22.2% vs. 7.2%, p=0.051) and less RCA PCI in frail patients (22.2% vs. 29.3% vs. 43.3%, p=0.099 and 22.2% vs. 33.9%, p=0.433) did not reach statistical significance. When compared as three frailty status groups volume of contrast used was no different statistically (median 140 ml vs. 160 ml vs. 170 ml, p=0.083) but this was significantly different. Less contrast used in frail patients when compared as frail and non-frail patients groups (140 ml vs. 170 ml, p=0.046).

Table 3.14: PCI details by Rockwood Frailty Status

	Total N=201	Frail (F)	Pre-Frail (PF)	Robust (R)	p value F v PF v R	Non Frail (R +PF)	p value F v NF
Radial access PCI n (%)	174 (86.6)	13 (72.2)	108 (87.8)	53 (88.3)	0.173	161 (88.0)	0.074
Femoral access PCI n (%)	27 (13.4)	5 (27.8)	15 (12.2)	7 (11.7)	0.173	22 (12	0.074
Single Vessel PCI n (%)	146 (72.6)	13 (72.2)	91 (74.0)	42 (70.0)	0.851	133 (72.7)	1.000
Multi Vessel PCI n (%)	55 (27.4)	5 (27.8)	32 (26.0)	18 (30.0)	0.851	50 (27.3)	1.000
Number of stents median (range)	1(6)	1.5 (3)	1 (6)	2 (5)	0.505	1 (6)	0.721
Contrast volume ml median (range)	170 (380)	140 (240)	160 (380)	170 (300)	0.083	170 (380)	0.046*
LMS n (%)	17 (8.5)	4 (22.2)	10 (8.1)	3 (5.0)	0.069	13 (7.1)	0.051
LAD n (%)	115 (57.2)	11 (61.1)	75 (61.0)	29 (48.3)	0.252	104 (56.8)	0.807
LCx n (%)	67 (33.3)	6 (33.3)	40 (32.5)	21 (35.0)	0.946	61 (33.3)	1.000
RCA n (%)	66 (32.8)	4 (22.2)	36 (29.3)	26 (43.3)	0.099	62 (33.9)	0.433
Graft n (%)	2 (1.0)	0 (0)	1 (0.8)	1 (1.7)	0.780	2 (1.1)	1.000
Length of hospital stay median (range) in days	6 (27)	7 (11)	6 (26)	6 (18)	0.350	6 (26)	0.609

PCI Percutaneous Coronary Intervention, LMS Left Main Stem, LAD Left Anterior Descending, LCx Left Circumflex, RCA Right Coronary Artery

3.6.3 Revascularisation by Coronary Artery Bypass Strategy

Only ten patients (4.2%) were revascularised by CABG.

3.6.3.1 Fried Frailty Status

There was no difference in the proportion of patients revascularised by CABG (4.1% vs. 4.2% vs. 4.3% in F vs. PF vs. R, p=0.9 and 4.1% vs. 4.3% in F vs. NF, p=1.0).

3.6.3.2 Rockwood Frailty Status

Similar to comparison by fried frailty status, there was no difference in the proportion of patients revascularised by CABG in rockwood frailty status as well (4.2% vs. 4.2% vs. 4.2%, p=1.0 and 4.2% vs. 4.2%, p=1.0).

3.6.4 Medical Management Strategy

Twenty six patients (11.0%) were managed by medical treatment only as revascularisation was deemed too high risk or the coronary artery anatomy was not suitable for PCI as decided by the interventional cardiologist.

3.6.4.1 Fried Frailty Status

There was no significant difference in the proportion of patients managed by medical treatment between the frailty groups (8.2% vs. 11.9% vs. 13.0%, p=0.649 and 8.2% vs. 12.2%, p=0.5).

3.6.4.2 Rockwood Frailty Status

Although more frail patients were managed medically this did not reach statistical significance either by three frailty groups (20.8% vs. 8.5% vs. 12.7%, p=0.17) or two groups 20.8% vs. 11.0%, p=0.16)

3.6.5 Time from presentation to invasive treatment and Length of Hospital stay

3.6.5.1 Time from presentation to invasive treatment

3.6.5.1.1 Fried Frailty Status

Days from initial admission to local hospital with NSTEACS to invasive treatment with coronary angiography and or PCI at Freeman hospital was not significantly different between either the three groups of frailty status (F vs. PF vs. R respectively of 5.7 days vs. 5.4 days vs. 5.6 days, p=0.8) or the two groups (F vs. NF respectively of 5.7 days vs. 5.5 days, p=0.7).

3.6.5.1.2 Rockwood Frailty Status

Time from initial admission to local hospital with NSTEACS to the day of invasive treatment with coronary angiogram and or PCI at Freeman hospital was not significantly different between either the three groups of frailty status (F vs. PF vs. R respectively of 6.2 days vs. 5.8 days vs. 5.2 days, p=0.36) or the two groups (F vs. NF respectively of 6.2 days vs. 5.5 days, p=0.24).

3.6.5.2 Length of Hospital stay

3.6.5.2.1 Fried Frailty Status

The median length of stay for all patients was 6 days (IQR of days). There was no difference in the median length of stay between the frailty groups (7 vs. 6 vs. 6 days, p=0.55 and 7 vs. 6, p=0.17). When the length of stay was compared depending on management strategy there was no significant difference for PCI and medical management. The difference was noted for management by CABG when compared as frail and non-frail patients (34 vs. 21 days, p=0.016) but not as three frailty groups (34 vs. 21 vs. 18, p=0.056 for F vs. PF vs. NF).

3.6.5.2.2 Rockwood Frailty Status

The difference between the lengths of stay of all patients was significant with frail patients staying a day longer compared to pre-frail and non-frail patients (7 vs. 6 vs. 6. p=0.049) but this difference was not significant when compared as frail and non-frail patients (7 vs. 6, p=0.092). There was no difference in the length of stay in hospital when compared separately by management strategy.

3.6.6 Secondary Prevention Medications at Discharge

Medications were prescribed as per the established guidelines for secondary prevention.(Hamm *et al.*, 2011) The routine secondary prevention medications were aspirin long term and either clopidogrel, ticagerlor or prasugrel as second antiplatelet (usually for 1 year), beta-blocker, angiotensin converting enzyme inhibitor (ACEi) and statin. The discharge medications relevant to CV disease are displayed in **Tables 3.15 and 3.16**. There was high use of these medications in all patients irrespective of the frailty status at the time of discharge. Oral anticoagulants (either warfarin or novel oral anticoagulant) were used in 6.8% of patients for stoke prophylaxis though 12.7% had AF/PAF. The lesser use of oral anticoagulants than indicated was probably due to the need for concurrent use of antiplatelet, which can increase the risk of bleeding. Nearly 42% of patients were discharged on proton pump inhibitor, as there was increased risk of upper gastrointestinal bleeding with dual antiplatelets.

Though only just over a quarter of patients were prescribed Isosorbide Mono Nitrate, an anti-angina medication, this was significantly higher in frail patients both by FFC (35.6% in F vs. 26.3% in PF vs. 13.0% in R, p=0.025) and RFC (54.2% in vs 23.5% in NF, p=0.003). Similarly use of another anti-angina medication, Nicorandil was higher in Frail patients by both FFC (20.5% vs 15.3% vs 2.2%, p=0.019) and RFC (37.5% vs. 11.4%, p=0.003).

Table 3.15: Fried frailty and medications at discharge

Medication n (%)	Total N=237	Frail (F) N=73	Pre-Frail (PF) N=118	Robust (R) N=46	p value F v PF v R	Non Frail (R +PF) N=164	p value F v NF
Aspirin	236 (99.6)	73 (100)	117 (99.2)	46 (100)	0.603	163 (99.4)	1.000
Clopidogrel	146 (61.6)	46 (63.0)	70 (59.3)	30 (65.2)	0.750	100 (61.0)	0.885
Prasugrel	2 (0.8)	1 (1.4)	1 (0.8)	0 (0)	0.729	1 (0.6)	0.522
Ticagrelor	83 (35.0)	23 (31.5)	46 (39.0)	14 (30.4)	0.441	60 (36.6)	0.466
Beta-blocker	192 (81.0)	55 (75.3)	102 (86.4)	35 (76.1)	0.105	137 (83.5)	0.153
Warfarin	12 (5.1)	4 (5.5)	6 (5.1)	2 (4.3)	0.963	8 (4.9)	1.0
NOAC	4 (1.7)	2 (2.7)	2 (1.7)	0 (0)	0.528	2 (1.2)	0.589
Angiotensin converting enzyme inhibitor	211 (89.0)	63 (86.3)	105 (89.0)	43 (93.5)	0.475	148 (90.2)	0.375
Statin	228 (96.2)	72 (98.6)	113 (95.8)	43 (93.5)	0.337	156 (95.1)	0.281
Calcium channel blocker	78 (32.9)	23 (31.5)	40 (33.9)	15 (32.6)	0.942	55 (33.5)	0.881
Isosorbide mononitrate	63 (26.6)	26 (35.6)	31 (26.3)	6 (13.0)	0.025*	37 (22.6)	0.040*
Nicorandil	34 (14.3)	15 (20.5)	18 (15.3)	1 (2.2)	0.019*	19 (11.6)	0.074
Proton pump inhibitor	98 (41.4)	31 (42.5)	51 (43.2)	16 (34.8)	0.599	67 (40.9)	0.887

Table 3.16: Rockwood Frailty and medications at discharge

Medication n (%)	Total N=237	Frail (F) N=24	Pre-Frail (PF) N=142	Robust (R) N=71	p value F v PF v R	Non Frail (R +I) N=213	p value F v NF
Aspirin	236 (99.6)	24 (100)	141 (99.3)	71 (100)	0.715	212 (99.5)	1.0
Clopidogrel	146 (61.6)	18 (75.0)	82 (57.7)	46 (64.8)	0.221	128 (60.1)	0.187
Prasugrel	2 (0.8)	0 (0)	2 (1.4)	0 (0)	0.509	2 (0.9)	1.0
Ticagrelor	83 (35.0)	5 (20.8)	54 (38.0)	24 (33.8)	0.255	78 (36.6)	0.175
Beta-blocker	192 (81.0)	18 (75.0)	113 (79.6)	61 (85.9)	0.394	174 (81.7)	0.417
Warfarin	12 (5.1)	1 (4.2)	8 (5.6)	3 (4.2)	0.887	11 (5.2)	1.0
NOAC	4 (1.7)	0 (0)	4 (2.8)	0 (0)	0.256	4 (1.9)	1.0
Angiotensin converting enzyme inhibitor	211 (89.0)	20 (83.3)	123 (86.6)	68 (95.8)	0.084	191 (89.7)	0.313
Statin	228 (96.2)	24 (100)	136 (95.8)	68 (95.8)	0.590	204 (95.8)	0.604
Calcium channel blocker	78 (32.9)	11 (45.8)	47 (33.1)	20 (28.2)	0.281	67 (31.5)	0.173
Isosorbide mononitrate	63 (26.6)	13 (54.2)	40 (28.2)	10 (14.1)	<0.001	50 (23.5)	0.003*
Nicorandil	34 (14.3)	9 (37.5)	23 (16.2)	2 (2.8)	<0.001	25 (11.7)	0.003*
Proton pump inhibitor	98 (41.4)	12 (50.0)	64 (45.1)	22 (31.0)	0.096	86 (40.4)	0.388

3.7 Frailty Status and Major Adverse Cardiovascular Outcomes

Adverse CV outcomes were classified under procedural complications, in- hospital complications and outcomes at 30 days. Procedural complications and in-hospital complications were collected from hospital medical notes, PCI database and discharge summary. Outcomes at 30 days were collected from GP surgery records faxed to the research team at Freeman Hospital. Adverse outcomes as per frailty status are displayed from **Tables 3.17 to 3.22**.

3.7.1 Procedural complications

There were 4 (1.7%) procedural complications. They were LAD perforation, two cardiogenic shock and 1 cardiac arrest requiring shock treatment.

The incidence of procedural complications both by Fried frailty status (F vs. PF vs. R of 1.4% vs. 1.7% vs. 2.2%, p=0.95 and F vs. NF of 1.4% vs. 1.8%, p=1.0 respectively) and Rockwood frailty status (0% vs. 2.1% vs. 1.4%, p=0.74 and 0% vs. 1.9%, p=1.0) was not significantly different between the frailty groups.

3.7.2 In-hospital complications

There were 13 (5.5%) in hospital complications. They were 1 (0.4%) death, 2 (0.8%) unplanned revascularisation, 5 (2.1%) major bleeding problems, 2 (0.8%) stroke and 3 (1.3%) contrast induced nephropathy. The procedural complications were not included in the in-hospital complications. Contrast induced nephropathy were managed medically and did not need renal replacement treatment. There was no significant difference in these events either by Fried or Rockwood frailty status classification.

3.7.3 30 day MACE rate

The total number of major adverse events at 30 days were 23 (9.7%) in 17 (7.2%) patients. The events were 1 (0.4%) death, 4 (1.7%) acute coronary syndrome, 3 (1.3%) unplanned revascularisation, 9 (3.8%) major bleeding, 3 (1.3%) stroke and 3 (1.3%) contrast nephropathy. There was no significant difference in the incidence of these events when compared by both Fried and Rockwood frailty statuses in comparison based either on three groups or two groups. The composite outcomes based on number of patients did not show any difference.

Table 3.17: Procedural, In hospital and one month primary outcomes by Fried Frailty Status

	Total N=237	Frail (F) N=73	Pre-Frail (PF) N=118	Robust (R) N=46	p value F v PF v R	Non Frail (R +PF) N=164	p value F v NF
Procedural complication n (%)	4 (1.7)	1 (1.4)	2 (1.7)	1 (2.2)	0.946	3 (1.8)	1.000
In hospital n (%)	13 (5.5)	7 (9.6)	5 (4.2)	1 (2.2)	0.157	6 (3.7)	0.117
Composite MACE at 30-day n (%)	17 (7.2)	8 (11.0)	7 (5.9)	2 (4.3)	0.302	9 (5.5)	0.172

Table 3.18: In-hospital major adverse cardiovascular events by Fried frailty status

	Total N=237	Frail (F) N=73	Pre-Frail (PF) N=118	Robust (R) N=46	p value F v PF v R	Non Frail (R +PF) N=164	p value F v NF
Death n (%)	1 (0.4)	1 (1.4)	0 (0)	0 (0)	0.324	0 (0)	0.308
Acute coronary syndrome n (%)	0 (0)	0 (0)	0 (0)	0 (0)	-	0 (0)	-
Unplanned revascularisation n (%)	2 (0.8)	1 (1.4)	1 (0.8)	0 (0)	0.729	1 (0.6)	0.522
Major bleeding n (%)	5 (2.1)	2 (2.7)	3 (2.5)	0 (0)	0.538	3 (1.8)	0.645
Stroke n (%)	2 (0.8)	1 (1.4)	0 (0)	1 (2.2)	0.330	1 (0.6)	0.522
Contrast nephropathy/Renal replacement n (%)	3 (1.3)	2 (2.7)	1 (0.8)	0 (0)	0.364	1 (0.6)	0.225

Table 3.19: 30-day major adverse cardiovascular events by Fried frailty status

	Total N=237	Frail (F) N=73	Pre-Frail (PF) N=118	Robust (R) N=46	p value F v PF v R	Non Frail (R +PF) N=164	p value F v NF
Death n (%)	1 (0.4)	1 (1.4)	0 (0)	0 (0)	0.324	0 (0)	0.308
Acute coronary syndrome n (%)	4 (1.7)	1 (1.4)	2 (1.7)	1 (2.2)	0.946	3 (1.8)	1.000
Unplanned revascularisation n (%)	3 (1.3)	1 (1.4)	1 (0.8)	1 (2.2)	0.789	2 (1.2)	1.000
Major bleeding n (%)	9 (3.8)	5 (6.8)	4 (3.4)	0 (0)	0.155	4 (2.4)	0.139
Stroke n (%)	3 (1.3)	1 (1.4)	1 (0.8)	1 (2.2)	0.789	2 (1.2)	1.000
Contrast nephropathy/Renal replacement n (%)	3 (1.3)	2 (2.7)	1 (0.8)	0 (0)	0.364	1 (0.6)	0.225

Table 3.20: Procedural, In hospital and one month primary outcomes by Rockwood status

	Total N=237	Frail (F) N=24	Pre-Frail (PF) N=142	Robust (R) N=71	p value F v PF v R	Non Frail (R +I) N=213	p value F v NF
Procedural complication n (%)	4 (1.7)	0 (0)	3 (2.1)	1 (1.4)	0.741	4 (1.9)	1.000
In hospital n (%)	13 (5.5)	1 (4.2)	9 (6.3)	3 (4.2)	0.780	12 (5.6)	1.000
Composite MACE at 30-day n (%)	17 (7.2)	2 (8.3)	11 (7.7)	24 (5.6)	0.831	15 (7.0)	0.685

Table 3.21: In-hospital major adverse cardiovascular events by Rockwood status

	Total N=237	Frail (F) N=24	Pre-Frail (PF) N=142	Robust (R) N=71	p value F v PF v R	Non Frail (R +I) N=213	p value F v NF
Death n (%)	1 (0.4)	0 (0)	1 (0.7)	0 (0)	0.715	1 (0.5)	1.000
Acute coronary syndrome n (%)	0 (0)	0 (0)	0 (0)	0 (0)	-	0 (0)	-
Unplanned revascularisation n (%)	2 (0.8)	0 (0)	1 (0.7)	1 (1.4)	0.776	2 (0.9)	1.000
Major bleeding n (%)	5 (2.1)	0 (0)	5 (3.5)	0 (0)	0.181	5 (2.3)	1.000
Stroke n (%)	2 (0.8)	0 (0)	1 (0.7)	1 (1.4)	0.776	2 (0.9)	1.000
Contrast nephropathy/Renal replacement n (%)	3 (1.3)	1 (4.2)	2 (1.4)	0 (0)	0.280	2 (0.9)	0.275

Table 3.22: 30-day major adverse cardiovascular events by Rockwood status

	Total N=237	Frail (F) N=24	Pre-Frail (PF) N=142	Robust (R) N=71	p value F v PF v R	Non Frail (R +I) N=213	p value F v NF
Death n (%)	1 (0.4)	0 (0)	1 (0.7)	0 (0)	0.715	1 (0.5)	1.000
Acute coronary syndrome n (%)	4 (1.7)	0 (0)	2 (1.4)	2 (2.8)	0.599	4 (1.9)	1.000
Unplanned revascularisation n (%)	3 (1.3)	0 (0)	1 (0.7)	2 (2.8)	0.362	3 (1.3)	1.000
Major bleeding n (%)	9 (3.8)	1 (4.2)	6 (4.2)	2 (2.8)	0.875	8 (3.8)	1.000
Stroke n (%)	3 (1.3)	0 (0)	2 (1.4)	1 (1.4)	0.843	3 (1.4)	1.000
Contrast nephropathy/Renal replacement n (%)	3 (1.3)	1 (4.2)	2 (1.4)	0 (0)	0.280	2 (0.9)	0.275

3.8 Frailty and Cardiovascular Status

3.8.1 Arterial Stiffness Measures by Vicorder in Fried Frailty Status

The mean peripheral systolic BP was not significantly different between the three groups of patients with SBP of 130 mmHg in frail, 134 mmHg in pre-frail and 131 mmHg in robust patients. Similarly there was no difference in peripheral DBP between the three groups (63 mmHg, 65 mmHg and 64 mmHg respectively). The peripheral pulse pressure was 67 mmHg in frail, 68 mmHg in pre-frail and 67 mmHg in robust patients. The peripheral MAP was not significantly different (90 mmHg, 93 mmHg and 92 mmHg respectively). Aortic SBP and DBP were similar between the three groups. All the above were not significant when compared as frail and non-frail patient groups.

Carotid femoral PWV, a direct measure of arterial stiffness was 9.1 m/s in frail, 9.4 m/s in pre-frail and 9.6 m/s in robust patients (p=0.346). Similarly there was no significant difference when compared as frail and non-frail groups (9.1 m/s vs 9.5 m/s, p=0.186). Aortic PP and augmentation index are the surrogate markers of arterial stiffness. Aortic PP was not significantly different between the three groups (63 mmHg vs 66 mmHg vs 64 mmHg, p=0.447). Augmentation index was 25.8 in frail, 26.6 in pre-frail and 24.9 in robust patients (p=0.440). There was no difference noted when compared as frail and non-frail groups. There was no difference noted when compared as frail and non-frail groups. There was a significant correlation between carotid femoral PWV which is a marker of aortic stiffness and brachial femoral PWV (r=0.552, p<0.0001). The Vicorder measures by Fried Frailty status are displayed in **Table 3.23**.

Table 3.23: Fried Frailty Status and Vicorder Measures

	Number	Total	Frail (F)	Pre-Frail (PF)	Robust (R)	p value F v PF v R	Non-Frail	p value F v NF
Peripheral SBP mmHg	224	132.7 (17.6)	130.6 (16.0)	134.5 (19.3)	131.7 (15.4)	0.323	133.7 (18.2)	0.224
Peripheral DBP mmHg	224	64.7 (8.8)	63.8 (9.2)	65.5 (9.1)	64.4 (7.3)	0.425	65.2 (8.6)	0.273
Peripheral Pulse Pressure mmHg	224	67.7 (14.3)	67.0 (12.1)	68.4 (16.5)	67.3 (11.9)	0.799	68.1 (15.3)	0.601
Peripheral MAP mmHg	224	92.2 (12.9)	90.3 (11.4)	93.1 (12.2)	92.8 (16.4)	0.339	93.0 (13.5)	0.143
Stroke Volume ml	224	105.5 (31.4)	101.7 (32.4)	108.7 (32.1)	103.7 (27.7)	0.325	107.2 (30.9)	0.226
Cardiac Output l/min	224	6.5 (2.0)	6.6 (6.1)	6.6 (1.9)	6.3 (1.9)	0.791	6.5 (1.9)	0.824
Cardiac Index	224	3.7 (1.3)	3.8 (1.4)	3.7 (1.4)	3.4 (1.0)	0.307	3.7 (1.3)	0.355
Aortic SBP mmHg	224	129.3 (18.5)	127.2 (15.3)	130.9 (21.5)	128.7 (15.2)	0.426	130.2 (19.9)	0.257
Aortic DBP mmHg	224	64.7 (8.7)	64.0 (9.3)	65.2 (8.8)	64.6 (7.4)	0.638	65.0 (8.4)	0.391
Aortic Pulse Pressure mmHg	224	65.1 (13.7)	63.5 (11.5)	66.4 (15.5)	64.3 (11.8)	0.368	65.8 (14.6)	0.256
Augmentation Pressure mmHg	224	17.2 (7.0)	16.5 (6.4)	17.8 (6.9)	16.9 (8.3)	0.447	17.6 (7.3)	0.308
Augmentation Index	224	26.0 (7.5)	25.8 (6.4)	26.6 (7.2)	24.9 (7.0)	0.440	26.1 (7.2)	0.772
Pressure Index	222	1.09 (0.07)	1.07 (0.07)	1.10 (0.07)	1.12 (0.08)	0.003*	1.10 (0.07)	0.002*
Pulse Pressure Index	222	1.19 (0.15)	1.14 (0.15)	1.20 (0.14)	1.24 (0.16)	0.005*	1.21 (0.15)	0.003*
Sternal notch to umbilicus length in cm	223	35.0 (3.8)	35.0 (3.8)	35.0 (3.9)	34.9 (3.5)	0.977	35.0 (3.8)	0.952
Transit time in milliseconds (Brachio Femoral)	221	21.6 (11.6)	24.2 (16.6)	20.1 (8.0)	21.4 (9.0)	0.079	20.5 (8.3)	0.030*
Brachial femoral PWV m/s	221	20.2 (11.7)	18.9 (12.1)	21.3 (12.5)	19.4 (8.4)	0.388	20.7 (11.5)	0.286
Sternal notch to mid femoral cuff in cm	213	61.5 (5.8)	60.9 (5.7)	61.6 (5.8)	62.3 (5.7)	0.504	61.8 (5.8)	0.325
Transit time in milliseconds (Carotid Femoral)	212	67.7 (17.3)	71.4 (25.5)	65.8 (11.3)	66.1 (11.1)	0.098	65.9 (11.2)	0.031
Carotid femoral PWV m/s	212	9.4 (1.7)	9.1 (2.1)	9.4 (1.4)	9.6 (1.5)	0.346	9.5 (1.4)	0.186
Ankle brachial index	218	1.15 (0.18)	1.13 (0.19)	1.15 (0.17)	1.15 (0.21)	0.806	1.15 (0.18)	0.517

DBP Diastolic Blood Pressure, MAP Mean Arterial Pressure, PWV Pulse Wave Velocity, SBP Systolic Blood Pressure

3.8.2 Arterial Stiffness measures by Vicorder in Rockwood Frailty Status

The mean peripheral SBP was 132 mmHg in frail, 134 mmHg in pre-frail and 130 mmHg in robust patients (p=0.382). The mean peripheral DBP was not significantly different between the three groups (63 vs 64 vs 65, p=0.683). The peripheral PP (69 vs 68 vs 65, p=0.230) and MAP (90 vs 93 vs 90, p=0.383) was similar between the three groups. Aortic SBP and DBP were similar between the three groups. All the above were not significant even when compared as frail and non-frail patient groups.

The mean carotid femoral PWV was 9.5 m/s in frail, 9.4 m/s in pre-frail and 9.3 m/s in robust patients (p=0.859). There was no significant difference in the surrogate markers of arterial stiffness with aortic PP of 65 mmHg, 66 mmHg and 62 mmHg respectively (p=0.178) and augmentation index of 26, 25 and 26 respectively p=0.846) between the three groups. Similarly there was no significant difference noted when compared as frail and non-frail groups. **Table 3.24** displays Rockwood frailty status and Vicorder measures.

Table 3.24: Rockwood Frailty Status and Vicorder Measures

	Number	Total	Frail (F)	Pre-Frail (PF)	Robust (R)	p value F v PF v R	Non-Frail	p value F v NF
Peripheral SBP mmHg	224	132.7 (17.6)	132.6 (19.0)	134.0 (18.4)	130.3 (15.1)	0.382	132.7 (17.4)	0.965
Peripheral DBP mmHg	224	64.7 (8.8)	63.2 (7.5)	64.8 (9.6)	65.0 (7.5)	0.683	64.9 (8.9)	0.389
Peripheral Pulse Pressure mmHg	224	67.7 (14.3)	69.4 (13.9)	68.7 (15.5)	65.2 (11.6)	0.230	67.5 (14.4)	0.548
Peripheral MAP mmHg	224	92.2 (12.9)	90.6 (12.0)	93.2 (13.7)	90.8 (11.5)	0.383	92.4 (13.0)	0.527
Stroke Volume ml	224	105.5 (31.4)	106.3 (34.1)	106.8 (34.1)	102.6 (24.4)	0.655	105.4 (31.2)	0.896
Cardiac Output l/min	224	6.5 (2.0)	6.9 (1.7)	6.8 (2.1)	6.0 (1.6)	0.021*	6.5 (2.0)	0.374
Cardiac Index	224	3.7 (1.3)	4.2 (1.4)	3.8 (1.4)	3.3 (1.0)	0.003*	3.7 (1.3)	0.063
Aortic SBP mmHg	224	129.3 (18.5)	128.6 (17.5)	130.9 (18.2)	126.4 (19.5)	0.270	129.3 (18.7)	0.864
Aortic DBP mmHg	224	64.7 (8.7)	64.3 (8.0)	64.5 (9.4)	65.2 (7.5)	0.860	64.8 (8.8)	0.797
Aortic Pulse Pressure mmHg	224	65.1 (13.7)	65.4 (13.1)	66.3 (14.7)	62.5 (11.3)	0.178	65.0 (13.8)	0.904
Augmentation Pressure mmHg	224	17.2 (7.0)	17.4 (7.4)	17.3 (6.8)	17.0 (7.4)	0.931	17.2 (7.0)	0.915
Augmentation Index	224	26.0 (7.5)	26.1 (8.5)	25.8 (7.3)	26.4 (7.6)	0.846	26.0 (7.4)	0.924
Pressure Index	222	1.09 (0.07)	1.06 (0.07)	1.09 (0.07)	1.11 (0.07)	0.032*	1.1 (0.07)	0.053
Pulse Pressure Index	222	1.19 (0.15)	1.13 (0.13)	1.18 (0.15)	1.23 (0.16)	0.018*	1.2 (0.15)	0.042*
Sternal notch to umbilicus length in cm	223	35.0 (3.8)	33.9 (4.0)	35.2 (3.8)	35.0 (3.6)	0.316	35.1 (3.7)	0.142
Transit time in milliseconds (BF)	221	21.6 (11.6)	20.0 (6.7)	21.7 (13.3)	22.0 (9.2)	0.792	21.8 (12.0)	0.503
Brachial femoral PWV m/s	221	20.2 (11.7)	19.9 (9.8)	20.3 (12.4)	19.9 (11.0)	0.968	20.2 (11.9)	0.906
Sternal notch to mid femoral cuff in cm	213	61.5 (5.8)	58.7 (4.2)	61.4 (6.2)	62.7 (4.9)	0.023*	61.8 (5.8)	0.018*
Transit time in milliseconds (CF)	212	67.7 (17.3)	63.8 (12.3)	67.9 (20.7)	68.5 (8.8)	0.544	68.1 (17.7)	0.279
Carotid femoral PWV m/s	212	9.4 (1.7)	9.5 (1.8)	9.4 (1.8)	9.3 (1.4)	0.859	9.3 (1.7)	0.786
Ankle brachial index	218	1.15 (0.18)	1.12 (0.14)	1.13 (0.18)	1.18 (0.19)	0.188	1.15 (0.19)	0.555

DBP Diastolic Blood Pressure, MAP Mean Arterial Pressure, PWV Pulse Wave Velocity, SBP Systolic Blood Pressure

3.8.3 Age and Arterial Stiffness

There was a positive correlation between age and arterial stiffness measures of carotid femoral pulse wave velocity (r=0.199, p=0.004) and pulse pressure (r=0.209, p=0.002) as displayed in **Figures 3.5 and 3.6**. There was significant correlation between carotid and Brachio femoral PWV as displayed in **Figure 3.7**.

Figure 3.5: Age and Carotid Femoral Pulse Wave Velocity

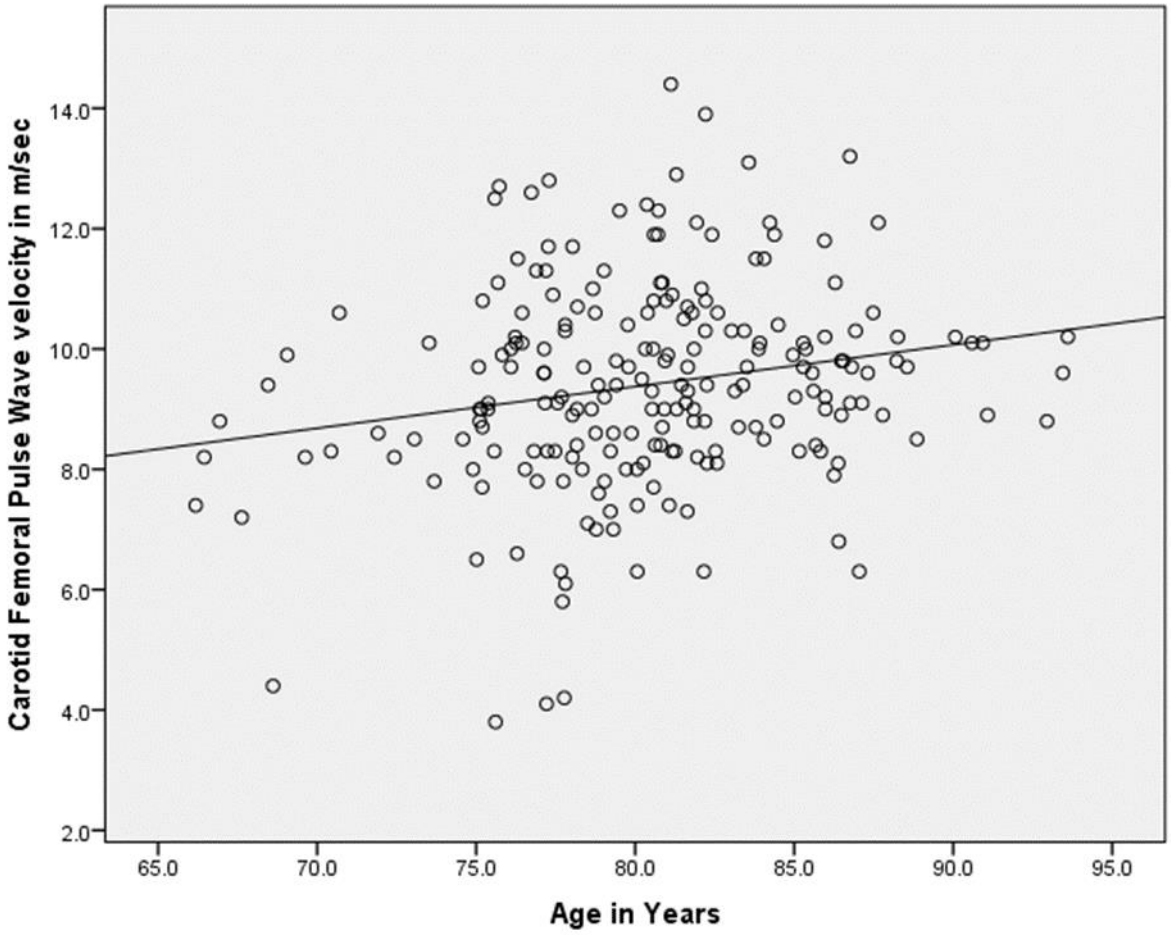


Figure 3.6: Age and Aortic Pulse Pressure

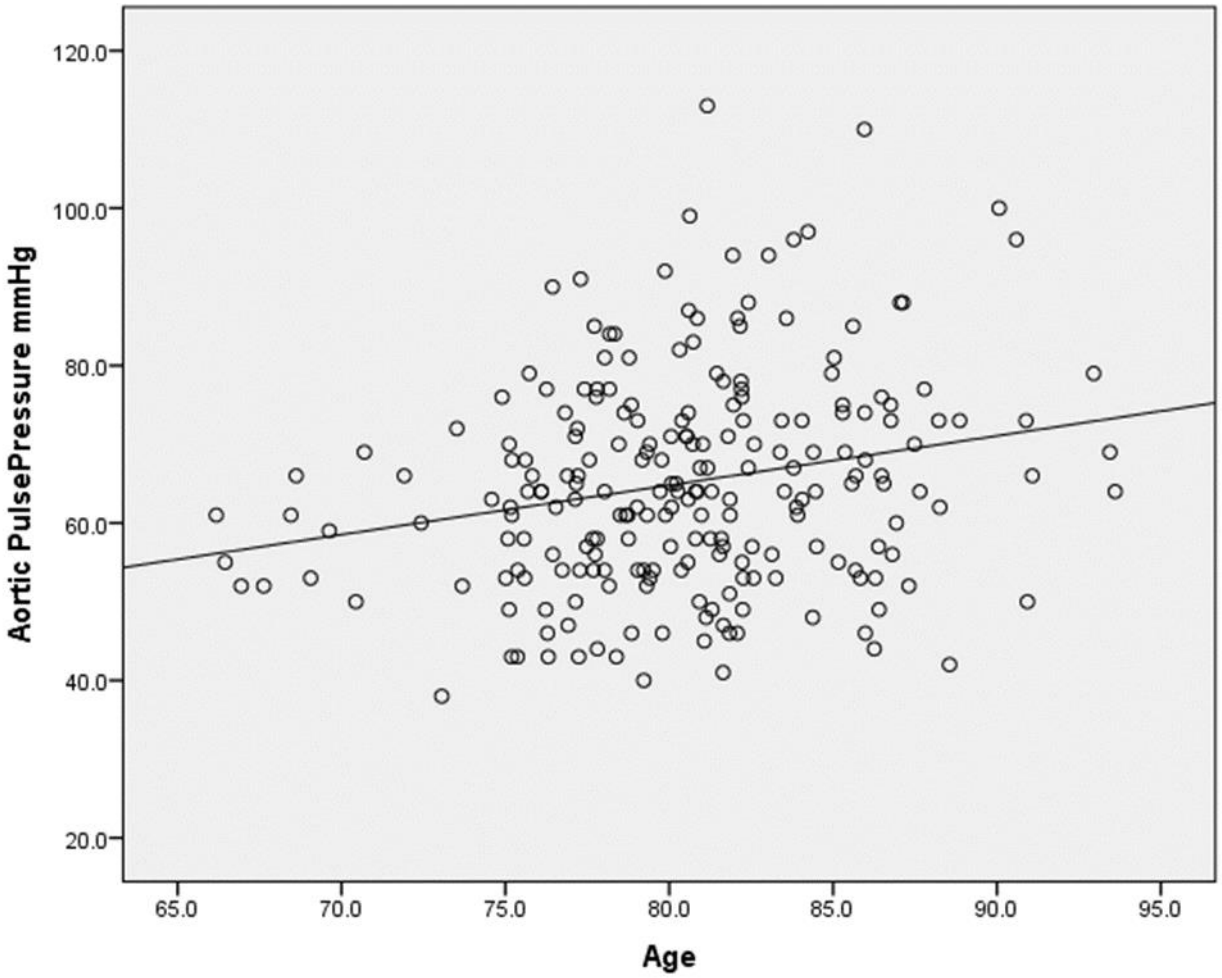
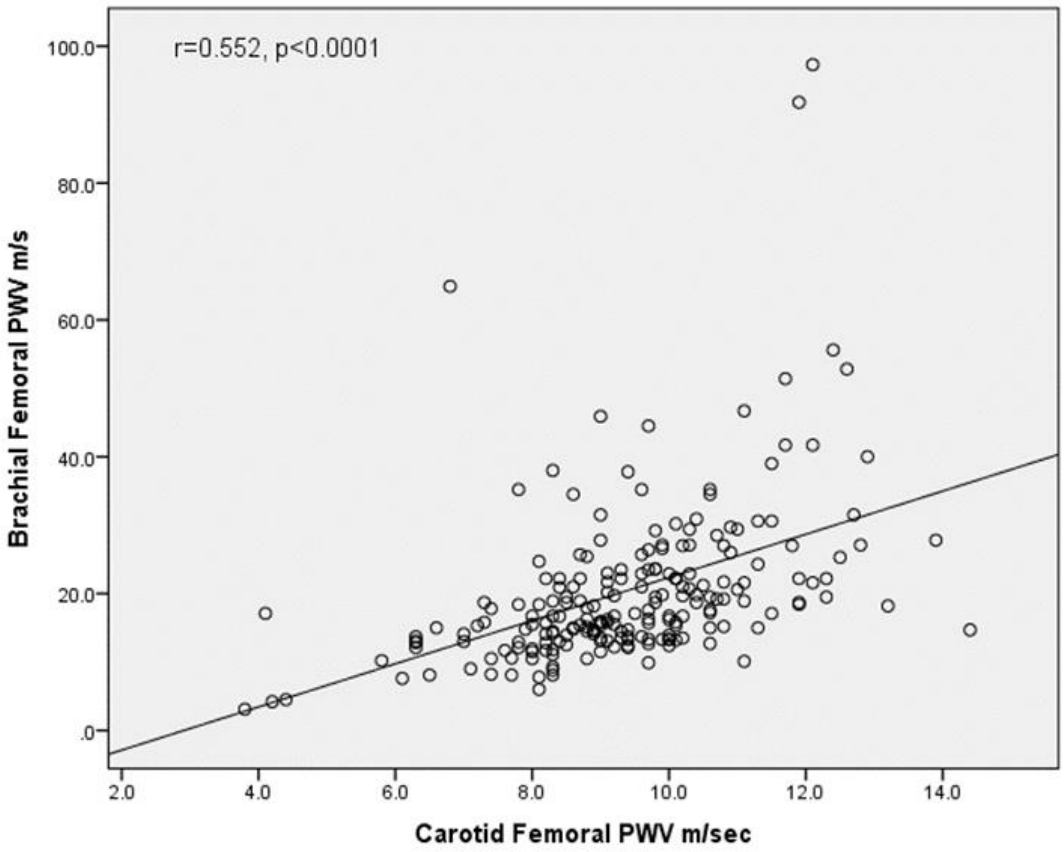


Figure 3.7: Correlation between Carotid Femoral and Brachial Femoral Pulse Wave Velocity



3.9 Frailty and Endothelial Function Assessment by EndoPAT®

Endothelial function assessment was done in 219 patients (92.4%). Recordings made in 13 patients (5.5%) were uninterpretable. Of the interpretable recordings normal (LnRHI >0.50) was noted in 126 (53.2%) patients and endothelial dysfunction (LnRHI ≤0.50) was noted in 80 (33.8%) patients. These measures are displayed according to frailty status in **Tables 3.25 and 3.26**.

3.9.1 Fried Frailty and EndoPAT® Measures

The mean LnRHI was 0.59 in frail patients, 0.59 in pre-frail patients and 0.60 in robust patients (p=0.98). The LnRHI suggested normal endothelial function in 42.5% frail patients, 56.8% in pre-frail patients and 60.9% robust patients (p=0.09). LnRHI was suggestive of endothelial dysfunction in 34.2%, 34.7% and 30.4% patients respectively. But when compared as frail and non-frail patients LnRHI was normal in 42.5% frail patients and 57.9% in non-frail patients (p=0.014). The median augmentation index was 10.5% in frail, 18.0% in pre-frail and 20.0% in robust patients (p=0.011). When compared as frail and non-frail it was 10.5% and 20.0% respectively (p=0.006).

Table 3.25: Fried Frailty and EndoPAT® Measures

	Total	Frail (F)	Pre-Frail (PF)	Robust (R)	p value F v PF v R	Non-Frail	p value F v NF
Normal Ln RHI >0.50	126 (53.2)	31 (42.5)	67 (56.8)	28 (60.9)	0.087	95 (57.9)	0.014*
Dysfunction Ln RHI ≤0.50	80 (33.8)	25 (34.2)	41 (34.7)	14 (30.4)	0.087	55 (33.5)	0.014*
Mean LnRHI (SD)	0.59 (0.25)	0.59 (0.23)	0.59 (0.25)	0.60 (0.26)	0.977	0.59 (0.25)	0.876
Heart Rate bpm	63.1 (9.8)	64.3 (9.2)	62.9 (10.7)	61.9 (8.0)	0.448	62.6 (10.0)	0.256
AI% (median)	17.0	10.5	18.0	20.0	0.011*	19.0	0.006*
AI% @ 75 bpm (median)	11.0	4.5	11.0	16.0	0.027*	12.0	0.021*

AI Augmentation Index, Ln RHI Logarithmic Reactive Hyperaemia Index

3.9.2 Rockwood Frailty and EndoPAT® Measures

The mean LnRHI was 0.57 in frail patients, 0.60 in pre-frail patients and 0.59 in robust patients (p=0.98). The LnRHI suggested normal endothelial function in 41.7% frail patients, 53.5% in pre-frail patients and 56.3% robust patients (p=0.23). LnRHI suggested endothelial dysfunction in 29.2%, 33.8% and 35.2% patients respectively. But when compared as frail and non-frail patients, LnRHI was normal in 41.7% frail patients and 54.5% in non-frail patients (p=0.06). The median augmentation index was 11.0% in frail, 17.0 % in pre-frail and 20.0% in robust patients (p=0.0329). When compared as frail and non-frail it was 11.0% and 18.0% respectively (p=0.0547).

Table 3.26: Rockwood Frailty and EndoPAT® Measures

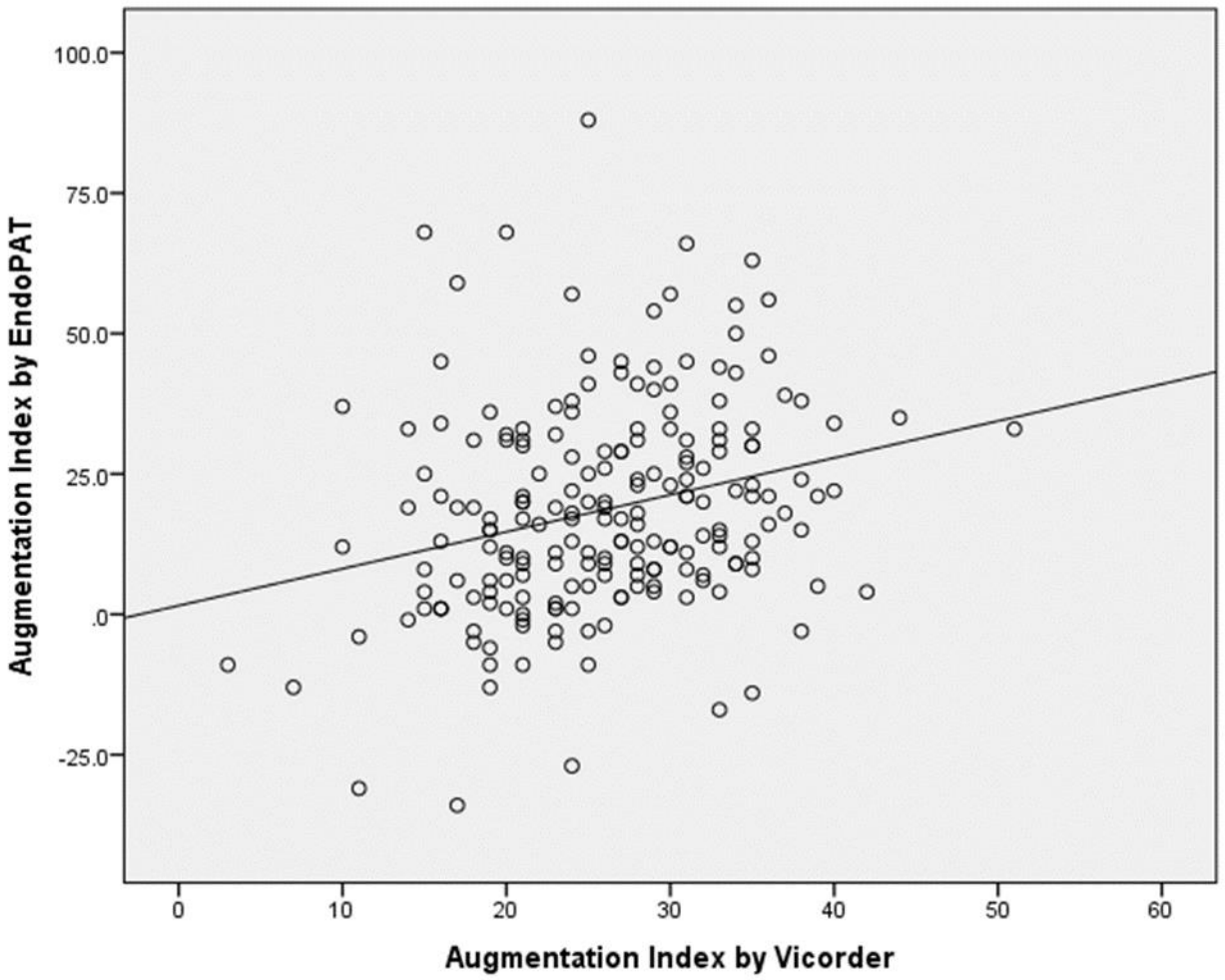
	Total	Frail (F)	Pre-Frail (PF)	Robust (R)	p value F v PF v R	Non-Frail	p value F v NF
Normal Ln RHI >0.50	126 (53.2)	10 (41.7)	76 (53.5)	40 (56.3)	0.227	116 (54.5)	0.061
Dysfunction Ln RHI ≤0.50	80 (33.8)	7 (29.2)	48 (33.8)	25 (35.2)	0.227	73 (34.3)	0.061
Mean LnRHI (SD)	0.59 (0.25)	0.57 (0.17)	0.60 (0.25)	0.59 (0.25)	0.928	0.59 (0.25)	0.701
Heart Rate bpm	63.1 (9.8)	64.4 (12.0)	64.7 (9.4)	59.7 (9.2)	0.003*	63.0 (9.6)	0.559
AI% (median)	17.0	11.0	17.0	20.0	0.029*	18.0	0.047*
AI% @ 75 bpm (median)	11.0	-2.0	10.0	12.0	0.158	11.0	0.062

AI Augmentation Index, Ln RHI Logarithmic Reactive Hyperaemia Index

3.10 Correlation between EndoPAT and Vicorder Measures

There was a significant positive correlation between augmentation indices measured by Vicorder and EndoPAT (r=0.262, p<0.0001) as in **Figure 3.8**. There was no significant correlation between carotid femoral PWV and LnRHI (r=-.003, p=0.966).

Figure 3.8: Correlation between augmentation indices by Vicorder and EndoPAT



3.11 Frailty and Carotid Intima Media Thickness

CIMT images suitable for assessment was available in 195 (82.3%) patients on the right carotid artery and 183 (77.2%) patients on the left carotid artery. The mean left posterior CIMT was 0.742 mm (SD 0.180) and right posterior CIMT was 0.743 mm (SD 0.153).

3.11.1 Fried Frailty and CIMT

There was no difference in CIMT between the three groups by Fried Frailty classification as displayed in **Table 3.27**. The mean left posterior CIMT was 0.720 mm (SD 0.188) in frail patients, 0.763 mm (SD 0.182) in pre-frail patients and 0.723 mm (SD 0.160) in robust patients (p=0.274). This was 0.752 mm (SD 0.177) in non-frail patients (p=0.259).

The mean right posterior CIMT in frail, pre-frail and robust patients was 0.772 mm (SD 0.156), 0.737 mm (SD 0.161) and 0.721 mm (SD 0.125) respectively (p=0.253). This was 0.732 mm (0.151) in non-frail patients (p=0.118).

Table 3.27: Fried Frailty and CIMT

	Number	Total	Frail (F)	Pre-Frail (PF)	Robust (R)	p value F v PF v R	Non-Frail	p value F v NF
Left posterior CIMT mm	195 (82.3)	0.742 (0.180)	0.720 (0.188)	0.763 (0.182)	0.723 (0.160)	0.274	0.752 (0.177)	0.259
Right posterior CIMT mm	183 (77.2)	0.743 (0.153)	0.772 (0.156)	0.737 (0.161)	0.721 (0.125)	0.253	0.732 (0.151)	0.118

3.11.2 Rockwood Frailty and CIMT

The mean left posterior CIMT was 0.729 mm (SD 0.170) in frail patients, 0.746 mm (SD 0.187) in pre-frail patients and 0.739 mm (SD 0.174) in robust patients (p=0.920). This was 0.744 mm (SD 0.182) in non-frail patients (p=0.740) as displayed in below **Table 3.28**.

The mean right posterior CIMT in frail, pre-frail and robust patients was 0.785 mm (SD 0.170), 0.747 mm (SD 0.144) and 0.724 mm (SD 0.165) respectively (p=0.355). This was 0.739 mm (0.151) in non-frail patients (p=0.262).

Table 3.28: Rockwood Frailty and CIMT

	Number	Total	Frail (F)	Pre-Frail (PF)	Robust (R)	p value F v PF v R	Non-Frail	p value F v NF
Left posterior CIMT mm	195 (82.3)	0.742 (0.180)	0.729 (0.170)	0.746 (0.187)	0.739 (0.174)	0.920	0.744 (0.182)	0.740
Right posterior CIMT mm	183 (77.2)	0.743 (0.153)	0.785 (0.170)	0.747 (0.144)	0.724 (0.165)	0.355	0.739 (0.151)	0.262

3.12 Frailty and Left Ventricular function

LV function was assessed by transthoracic echocardiogram (TTE). Ejection fraction was visually estimated and classified as normal (EF >55%), mild LV systolic dysfunction (EF 45-55%), moderate LV systolic dysfunction (EF 35-45%) and severe LV systolic dysfunction (EF <35%). LA size and tissue doppler measurement of E/e' was used to assess LV filling pressure a reliable measure of diastolic function.

Image quality was uninterpretable in 7.6% patients (n=18) and TTE could not be done in 8.9% patients (n=21). LV systolic function was normal in 35.9% patients (n=85), mildly impaired in 21.9% patients (n=52), moderately impaired in 16.0 % patients (n=38) and severely impaired in 9.7% patients (n=23). The mean E/e' was 10.4 (SD 4.5).

3.12.1 Fried Frailty and LV Function

According to Fried frailty classification, normal LV function was noted in 26 % frail patients, 39% of pre-frail patients and 43.5% of robust patients. Mild LV impairment was noted in 17.8%, 23.7% and 23.9% respectively. Moderate LV impairment was noted in 19.2%, 13.6% and 17.4% respectively. Severe LV dysfunction was noted in 15.1%, 8.5% and 4.3% respectively. There was no significant difference in the above findings (p=0.298). The details of LV function according to Fried frailty status are displayed in **Table 3.29**.

LA size was normal in 32.7% frail, 50.0% pre-frail and 42.1% robust patients. LA was mildly dilated in 10.9%, 8.5% and 13.2% respectively. LA was moderately dilated in 18.2%, 18.1% and 21.1% respectively. LA was severely dilated in 38.2%, 23.4% and 23.7% respectively. There was no significant difference in the above findings.

The mean E/e' in was 11.5 (SD 4.7) in frail patients, 10.4 (SD 4.5) in pre-frail patients and 9.0 (SD 2.9) in robust patients (p=0.031). The mean E/e' was 8.9 (SD 4.1) in non-frail patients (p=0.041 compared to frail patients).

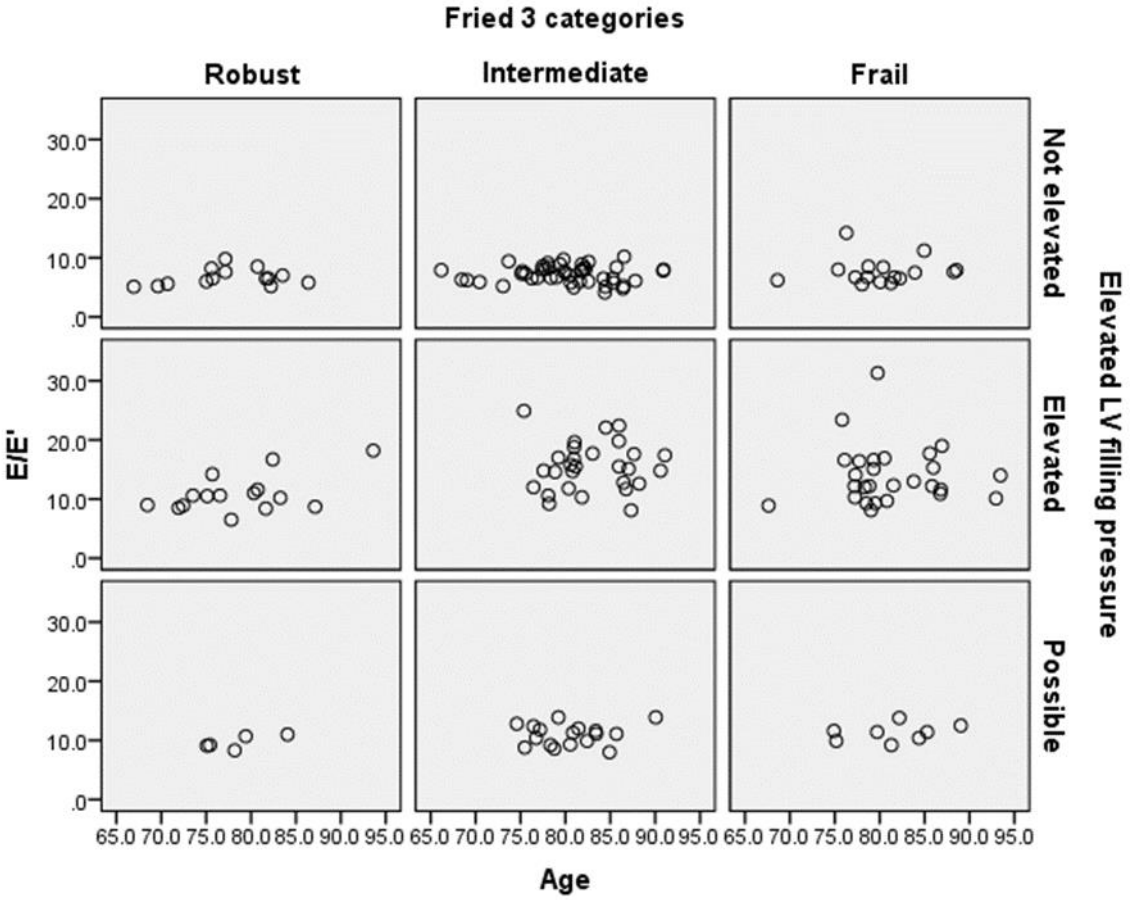
Elevated filling pressure suggestive of diastolic dysfunction was present in 52.9 % frail patients, 31.1% pre-frail patients and 44.1% robust patients. Filling pressure was not elevated in 15.7% frail, 18.9% pre-frail and 14.7% robust patients. Possible elevated filling pressure was noted in 15.7%, 18.9% and 14.7% respectively. The above were not significantly different (p=0.133). Increasing age was associated with higher E/e' and elevated filling pressures as in **Figure 3.9**.

Table 3.29: Fried Frailty and Transthoracic Echocardiogram Measures

	Total	Frail (F)	Pre-Frail (PF)	Robust (R)	p value F v PF v R	Non-Frail	p value F v NF
Normal EF >55%	85 (35.9)	19 (26.0)	46 (39.0)	20 (43.5)	0.298	66 (40.2)	0.068
Mild LVSD EF 45-55%	52 (21.9)	13 (17.8)	28 (23.7)	11 (23.9)	0.298	39 (23.8)	0.068
Moderate LVSD EF 35-45%	38 (16.0)	14 (19.2)	16 (13.6)	8 (17.4)	0.298	24 (14.6)	0.068
Severe LVSD EF <35%	23 (9.7)	11 (15.1)	10 (8.5)	2 (4.3)	0.298	12 (7.3)	0.068
LA size Normal	81 (43.3)	18 (32.7)	47 (50.0)	16 (42.1)	0.403	63 (47.7)	0.166
LA size Mildly Dilated	19 (10.2)	6 (10.9)	8 (8.5)	5 (13.2)	0.403	13 (9.8)	0.166
LA size Moderately Dilated	35 (18.7)	10 (18.2)	17 (18.1)	8 (21.1)	0.403	25 (18.9)	0.166
LA size Severely Dilated	52 (27.8)	21 (38.2)	22 (23.4)	9 (23.7)	0.403	31 (23.5)	0.166
E/e' mean (SD)	10.4 (4.5)	11.5 (4.7)	10.4 (4.5)	9.0 (2.9)	0.031*	8.9 (4.1)	0.041*
Elevated filling pressure Present	70 (40.0)	27 (52.9)	28 (31.1)	15 (44.1)	0.133	43 (34.7)	0.070
Absent	75 (42.9)	16 (31.4)	45 (50.0)	14 (41.2)	0.133	59 (47.6)	0.070
Possible	30 (17.1)	8 (15.7)	17 (18.9)	5 (14.7)	0.133	22 (17.7)	0.070

EF Ejection Fraction, LA Left Atrium, LVSD Left Ventricular Systolic Dysfunction

Figure 3.9: Correlation between Age and E/E' by Fried Frailty status and elevated Filling pressure



3.12.2 Rockwood Frailty and LV function

According to Rockwood frailty classification, normal LV function was noted in 33.3% frail patients, 35.2% of pre-frail patients and 38.0% of robust patients. Mild LV impairment was noted in 8.3%, 21.1% and 28.2% respectively. Moderate LV impairment was noted in 16.7%, 18.3% and 11.3% respectively. Severe LV dysfunction was noted in 4.2%, 12.0% and 7.0% respectively. There was no significant difference in the above findings (p=0.159). The details of LV function according to Rockwood frailty status are displayed in **Table 3.30**.

LA size was normal in 13.3% frail, 43.5% pre-frail and 50.9% robust patients (non-frail 5.9%). LA was mildly dilated in 6.7%, 9.6% and 12.3% respectively (non-frail 10%). LA was moderately dilated in 40.0%, 30.4% and 19.3% respectively (non-frail 16.9%). LA was severely dilated in 40.0%, 30.4% and 19.3% respectively (non-frail 26.7%). There was no significant difference in the above findings when compared as three groups (p=0.092) but was significant when compared as frail and non-frail groups (p=0.038).

The mean E/e' was 13.0 (SD 3.7) in frail patients, 11.0 (SD 4.6) in pre-frail patients and 8.7 (SD 3.1) in robust patients (p<0.001). The mean E/e' was 10.2 (SD 4.3) in non-frail patients (p<0.001 compared to frail patients).

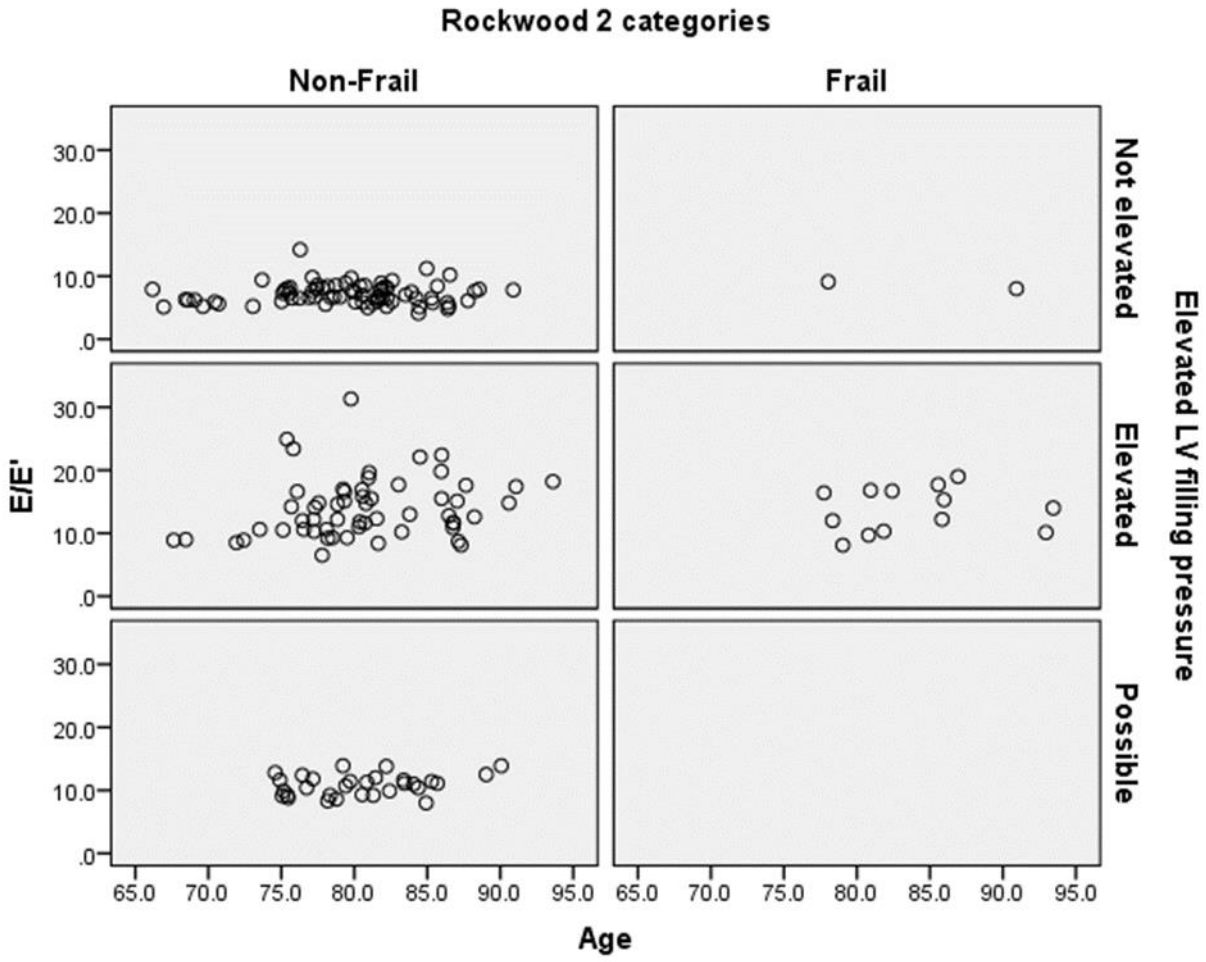
Elevated filling pressure suggestive of diastolic dysfunction was present in 86.7 % frail patients, 40.2% pre-frail patients and 26.4% robust patients. Filling pressure was not elevated in 13.3% frail, 39.3% pre-frail and 58.7% robust patients. Possible elevated filling pressure was noted in 0%, 20.6% and 15.1% respectively. The above were significantly different (p<0.001). Increasing age was associated with higher E/e' and elevated filling pressures as in **Figure 3.10**.

Table 3.30: Rockwood Frailty and Transthoracic Echocardiogram Measures

	Total	Frail (F)	Pre-Frail (PF)	Robust (R)	p value F v PF v R	Non-Frail	p value F v NF
Normal EF >55%	85 (35.9)	8 (33.3)	50 (35.2)	27 (38.0)	0.159	77 (36.2)	0.066
Mild LVSD EF 45-55%	52 (21.9)	2 (8.3)	30 (21.1)	20 (28.2)	0.159	50 (23.5)	0.066
Moderate LVSD EF 35-45%	38 (16.0)	4 (16.7)	26 (18.3)	8 (11.3)	0.159	34 (16.0)	0.066
Severe LVSD EF <35%	23 (9.7)	1 (4.2)	17 (12.0)	5 (7.0)	0.159	22 (10.3)	0.066
Uninterpretable	18 (7.6)	4 (16.7)	9 (6.3)	5 (7.0)	0.159	14 (6.6)	0.066
Not done	21 (8.9)	5 (20.8)	10 (7.0)	6 (8.5)	0.159	16 (7.5)	0.066
LA size Normal	81 (43.3)	2 (13.3)	50 (43.5)	29 (50.9)	0.092	79 (45.9)	0.038*
LA size Mildly Dilated	19 (10.2)	1 (6.7)	11 (9.6)	7 (12.3)	0.092	18 (10.5)	0.038*
LA size Moderately Dilated	35 (18.7)	6 (40.0)	19 (16.5)	10 (17.5)	0.092	29 (16.9)	0.038*
LA size Severely Dilated	52 (27.8)	6 (40.0)	35 (30.4)	11 (19.3)	0.092	46 (26.7)	0.038*
E/e' mean (SD)	10.4 (4.5)	13.0 (3.7)	11.0 (4.6)	8.7 (3.1)	<0.001*	10.2 (4.3)	0.019*
Elevated filling pressure Present	70 (40.0)	13 (86.7)	43 (40.2)	14 (26.4)	<0.001*	57 (35.6)	<0.001*
Absent	75 (42.9)	2 (13.3)	42 (39.3)	31 (58.5)	<0.001*	73 (45.6)	<0.001*
Possible	30 (17.1)	0 (0)	22 (20.6)	8 (15.1)	<0.001*	30 (18.8)	<0.001*

EF Ejection Fraction, LA Left Atrium, LVSD Left Ventricular Systolic Dysfunction

Figure 3.10: Correlation between Age and E/E' by Rockwood Frailty status and elevated Filling pressure



3.12.3 Predictors of elevated filing pressure

Ordinal logistic regression model to predict elevated filling pressure was built with gender, frailty by Fried and Rockwood criteria and history of hypertension. The regression model was statistically significant chi-square 31.1 ($p < 0.001$) and Pearson goodness of fit of 0.809. The model explained 16% of variance (Nagelkerke R^2). The model suggests frailty by rockwood criteria as the strongest predictor and female sex to be of moderate predictor of elevated filling pressure but not frailty by fried criteria or history of hypertension.

3.13 Frailty and NYHA Dyspnoea Class

Severity of dyspnoea was classified by NYHA dyspnoea classification. This data was obtained from all patients (n=237). Overall 46.0% of patients had class I dyspnoea, 38.0% class II dyspnoea, 16.0% class III dyspnoea and none reported with class IV dyspnoea.

3.13.1 Fried Frailty and Dyspnoea

Class I dyspnoea was reported in 28.8% of frail patients, 46.6% of pre-frail patients and 71.7% of robust patients ($p<0.001$). Class II dyspnoea was reported in 45.2% frail patients, 39.8% pre-frail patients and 21.7% robust patients ($p<0.001$). Class III dyspnoea was reported in 26.6%, 13.6% and 6.5% respectively ($p<0.001$). When compared as frail and non-frail groups; class I, II and III dyspnoea was reported in 53.7%, 34,8% and 11.6% respectively of non-frail patients ($p<0.001$). These findings are displayed in **Table 3.31**.

3.13.2 Rockwood Frailty and Dyspnoea

Class I dyspnoea was reported in 20.8% of frail patients, 33.1% of pre-frail patients and 80.3% of robust patients ($p<0.001$). Class II dyspnoea was reported in 33.3% frail patients, 47.9% pre-frail patients and 19.7% robust patients ($p<0.001$). Class III dyspnoea was reported in 45.8%, 19.0% and 0% respectively ($p<0.001$). When compared as frail and non-frail groups; class I, II and III dyspnoea was reported in 48.8%, 38.5% and 12.7% respectively of non-frail patients ($p<0.001$). These findings are displayed in **Table 3.32**.

Table 3.31: Fried Frailty and NYHA Dyspnoea Class

	Total	Frail (F)	Pre-Frail (PF)	Robust (R)	p value F v PF v R	Non-Frail	p value F v NF
Class I	109 (46.0)	21 (28.8)	55 (46.6)	33 (71.7)	<0.001*	88 (53.7)	<0.001*
Class II	90 (38.0)	33 (45.2)	47 (39.8)	10 (21.7)	<0.001*	57 (34.8)	<0.001*
Class III	38 (16.0)	19 (26.0)	16 (13.6)	3 (6.5)	<0.001*	19 (11.6)	<0.001*
Class IV	0 (0)	0 (0)	0 (0)	0 (0)	-	0 (0)	0 (0)

Table 3.32: Rockwood Frailty and NYHA Dyspnoea Class

	Total	Frail (F)	Pre-Frail (PF)	Robust (R)	p value F v PF v R	Non-Frail	p value F v NF
Class I	109 (46.0)	5 (20.8)	47 (33.1)	57 (80.3)	<0.001*	104 (48.8)	<0.001*
Class II	90 (38.0)	8 (33.3)	68 (47.9)	14 (19.7)	<0.001*	82 (38.5)	<0.001*
Class III	38 (16.0)	11 (45.8)	27 (19.0)	0 (0)	<0.001*	27 (12.7)	<0.001*
Class IV	0 (0)	0 (0)	0 (0)	0 (0)	-	0 (0)	-

3.14 Frailty and Severity of Angina

Severity of angina was classified by Canadian Cardiovascular Society (CCS) classification. This data was available for all the patients (n=237). Class 0 angina was reported in 27.8% of patients, class I angina was reported I 44.3% of patients, class II angina in 17.7% of patients, class III in 8.0% of patients and class IV in 2.1% of patients.

3.14.1 Fried Frailty and Severity of Angina

Class 0 angina was reported in 20.5% of frail patients, 28.0% of pre-frail patients and 39.1% of robust patients (p=0.448). Class I angina was reported in 45.2%, 44.1% and 43.5% respectively. Class II angina was reported in 21.9%, 18.6% and 8.7% respectively. Class III angina was reported by 11.0%, 6.8% and 6.5% respectively. There was no significant difference in the angina severity (p=0.448) between the three groups. In non-frail patients the reported incidence of class 0-IV angina was 31.1%, 43.9%, 15.9%, 6.7% and 2.4% respectively (p=0.343 compared to frail patients). These findings are displayed in **Table 3.33**.

Table 3.33: Fried Frailty Status and CCS Angina Category

	Total	Frail (F)	Pre-Frail (PF)	Robust (R)	p value F v PF v R	Non-Frail	p value F v NF
Class 0	66 (27.8)	15 (20.5)	33 (28.0)	18 (39.1)		51 (31.1)	
Class I	105 (44.3)	33 (45.2)	52 (44.1)	20 (43.5)	0.448	72 (43.9)	0.343
Class II	42 (17.7)	16 (21.9)	22 (18.6)	4 (8.7)		26 (15.9)	
Class III	19 (8.0)	8 (11.0)	8 (6.8)	3 (6.5)		11 (6.7)	
Class IV	5 (2.1)	1 (1.4)	3 (2.5)	1 (2.2)		4 (2.4)	

3.14.2 Rockwood Frailty and Severity of Angina

Class 0 angina was reported in 8.3% of frail patients, 27.5% of pre-frail patients and 35.2% of robust patients (p=0.448). Class I angina was reported in 44.3%, 43.7% and 45.1% respectively. Class II angina was reported in 25.0%, 19.7% and 11.3% respectively. Class III angina was reported by 12.5%, 8.5% and 5.6% respectively. There was no significant difference in the angina severity between the three groups (p=0.071). In non-frail patients the reported incidence of class 0-IV angina was 30.0%, 44.1%, 16.9%, 7.5% and 1.4% respectively (p=0.040 compared to frail patients). These findings are displayed in **Table 3.34.**

Table 3.34: Rockwood Frailty Status and CCS Angina Category

	Total	Frail (F)	Pre-Frail (PF)	Robust (R)	p value F v PF v R	Non-Frail	p value F v NF
Class 0	66 (27.8)	2 (8.3)	39 (27.5)	25 (35.2)		64 (30.0)	
Class I	105 (44.3)	11 (45.8)	62 (43.7)	32 (45.1)	0.071	94 (44.1)	0.040*
Class II	42 (17.7)	6 (25.0)	28 (19.7)	8 (11.3)		36 (16.9)	
Class III	19 (8.0)	3 (12.5)	12 (8.5)	4 (5.6)		16 (7.5)	
Class IV	5 (2.1)	2 (8.3)	1 (0.7)	2 (2.8)		3 (1.4)	

3.15 Frailty and Comorbidity

CCI weighted score of <3 was classified as lower burden and ≥3 classified as higher comorbidity burden.

CCI weigted score was available in all the patients. Lower weighted score (<3) suggestive of lesser comorbidity burden was noted in 170 patients (71.7%) and higher weighted score of (≥3) suggestive of increased comorbidity burden was documented in 67 patients (28.3%). The mean risk of mortality based on the CCI score was 13.3% (SD 5.7%) at one year.

3.15.1 Fried Frailty Status and Comorbidity Burden

As per Fried frailty criteria the prevalence of higher comorbidity burden in frail, pre-frail and robust patients was 43.8% vs. 24.6% vs. 13.0% respectively compared to lower comorobidity burden in the same group of patients (56.2% vs. 75.4% vs. 87.0%, p=0.001). When compared as frail and non-frail patients the prevalnce was 43.8% vs. 21.3% for higher comorbidity burden and 56.2% vs 78.7% for lower comorbidity burden (p<0.001). These findings are displayed in **Table 3.35**.

The mean risk of mortality at one year was 14.7% (SD 6.0) in frail patients, 13.1% (SD 5.9) in pre-frail and 11.6% (4.2) in robust patients (p=0.013). In non frail patients this risk was calculated as 12.7% (SD 5.7, p=0.013).

Table 3.35: Fried Frailty Status and Comorbidity Burden by Charlson Comorbidity Index Score

	Total	Frail (F)	Pre-Frail (PF)	Robust (R)	p value F v PF v R	Non-Frail	p value F v NF
CCI Weighted Score <3 Lower Comorbidity Burden	170 (71.7)	41 (56.2)	89 (75.4)	40 (87.0)	0.001*	129 (78.7)	<0.001*
CCI Wieghted Score ≥3 Higher Comorbidity Burden	67 (28.3)	32 (43.8)	29 (24.6)	6 (13.0)	0.001*	35 (21.3)	<0.001*
Mortality Risk % at 1 year	13.3 (5.7)	14.7 (6.0)	13.1 (5.9)	11.6 (4.2)	0.013*	12.7 (5.7)	0.013*

3.15.2 Rockwood Frailty Status and Comorbidity Burden

As per Rockwood frailty criteria the prevalence of higher comorbidity burden in frail, pre-frail and robust patients was 54.2% vs. 32.4% vs. 11.3% respectively compared to lower comorobidity burden in the same group of patients (46.8% vs. 67.6% vs. 88.7%, p<0.001). When compared as frail and non-frail patients the prevalnce was 54.2% vs. 25.4% for higher comorbidity burden and 45.8% vs. 74.6% for lower comorbidity burden (p=0.007). These findings are displayed in **Table 3.36**.

The mean risk of mortality at one year was 16.1% (SD 6.7) in frail patients, 13.8% (SD 6.1) in pre-frail and 11.3% (5.7) in robust patients (p<0.001). In non frail patients this risk was calculated as 13.0% (SD 5.5, p=0.011).

Table 3.36: Rockwood Frailty Status and Comorbidity Burden by Charlson Comorbidity Index Score

	Total	Frail (F)	Pre-Frail (PF)	Robust (R)	p value F v PF v R	Non-Frail	p value F v NF
CCI Weighted Score <3 Lower Comorbidity Burden	170 (71.7)	11 (45.8)	96 (67.6)	63 (88.7)	<0.001*	159 (74.6)	0.007*
CCI Weighted Score ≥3 Higher Comorbidity Burden	67 (28.3)	13 (54.2)	46 (32.4)	8 (11.3)	<0.001*	54 (25.4)	0.007*
Mortality Risk % at 1 year	13.3 (5.7)	16.1 (6.7)	13.8 (6.1)	11.3 (5.7)	<0.001*	13.0 (5.5)	0.011*

3.15.3 Comorbidity Burden and Cardiovascular Outcomes

Higher comorbidity burden was not associated with increased rate of procedural or in hospital complicationns. At 30-days there was no significant diifference in the erate of death, ACS, unpalnned revascularisation, major bleeding and stroke. Higher comorbidity burden was associated with increased rate of contrast nephropathy in hospital (4.5% vs. 05, p=0.022). These findings of CV outcomes inrelation to comorbidity burden are displayed in **Tables 3.37 to 3.39**.

Table 3.37: In hospital, one month and one year primary outcomes by Comorbidity burden

	Total N=237	Higher Comorbidity Burden	Lower Comorbidity Burden	p value
Procedural complication n (%)	4 (1.7)	0 (0)	4 (2.4)	0.579
In hospital n (%)	14 (5.9)	3 (4.5)	11 (6.5)	0.762
Composite MACE at 30-day n (%)	17 (7.2)	6 (9.0)	11 (6.5)	0.577

Table 3.38: In-hospital major adverse cardiovascular events by Comorbidity burden

	Total N=237	Higher Comorbidity Burden	Lower Comorbidity Burden	p value
Death n (%)	1 (0.4)	0 (0)	1 (0.6)	1.000
Acute coronary syndrome n (%)	0 (0)	0 (0)	0 (0)	-
Unplanned revascularisation n (%)	2 (0.8)	0 (0)	2 (1.2)	1.000
Major bleeding n (%)	5 (2.1)	1 (1.5)	4 (2.4)	1.000
Stroke n (%)	2 (0.8)	0 (0)	2 (1.2)	1.000
Contrast nephropathy/Renal replacement n (%)	3 (1.3)	3 (4.5)	0 (0)	0.022*

Table 3.39: 30-day major adverse cardiovascular events by Comorbidity Burden

	Total N=237	Higher Comorbidity Burden	Lower Comorbidity Burden	p value
Death n (%)	1 (0.4)	0 (0)	1 (0.6)	1.000
Acute coronary syndrome n (%)	4 (1.7)	1 (1.5)	3 (1.8)	1.000
Unplanned revascularisation n (%)	3 (1.3)	0 (0)	3 (1.8)	0.561
Major bleeding n (%)	9 (3.8)	3 (4.5)	6 (3.5)	0.715
Stroke n (%)	3 (1.3)	0 (0)	3 (1.8)	0.561
Contrast nephropathy/Renal replacement n (%)	3 (1.3)	3 (4.5)	0 (0)	0.022*

3.16 Frailty and Subclinical Cognitive Impairment

Cognitive status was assessed by Montreal Cognitive Assessment (MoCA) tool. The maximum score was 30. MoCA score <26 suggested subclinical cognitive impairment. MoCA score was assessed in 215 patients. The mean MoCA score was 25.2 (SD 2.9).

3.16.1 Fried Frailty and Cognitive Status

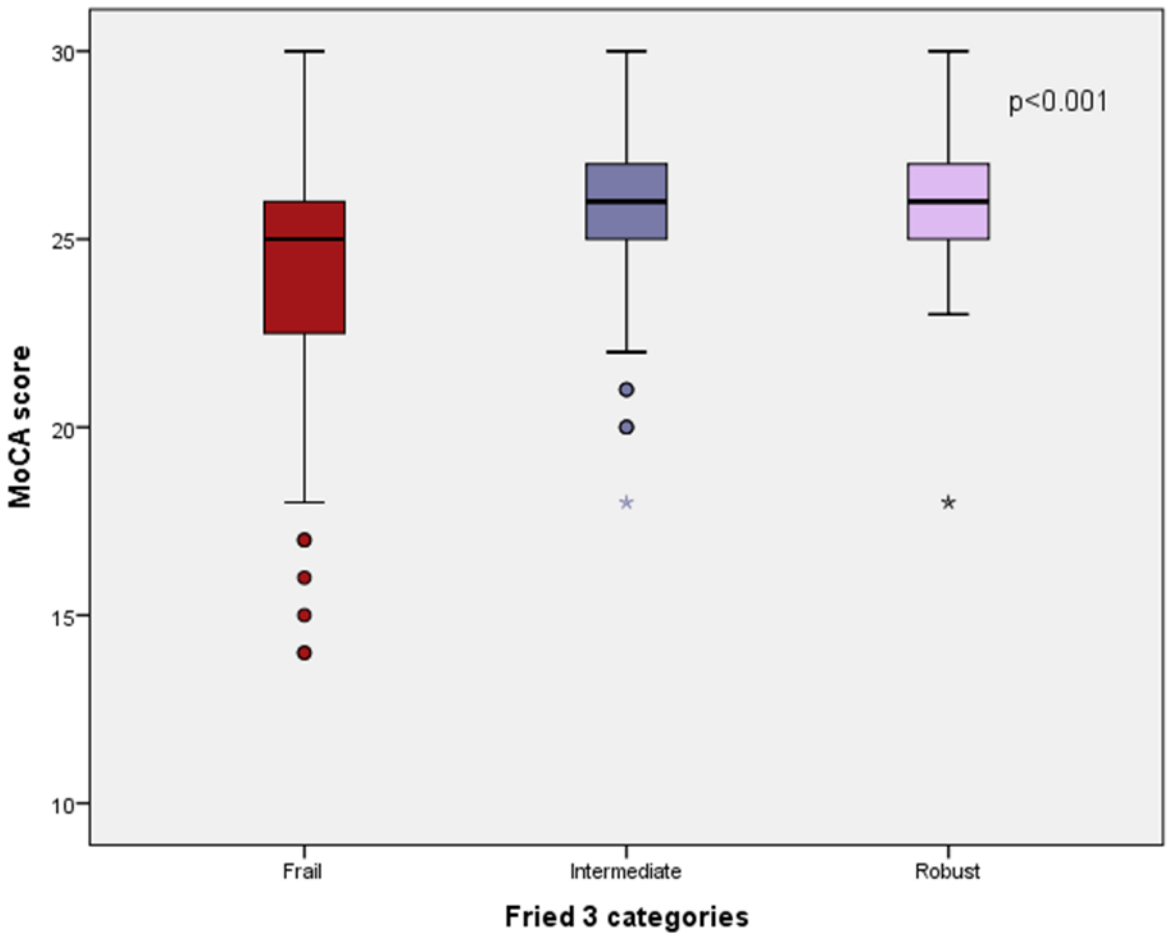
The mean MoCA score was 23.8 (SD 3.6) in frail patients, 25.8 (SD 2.4) in pre-frail patients and 25.9 (SD 2.2) in robust patients (p<0.001) as in **Figure 3.11**. In non-frail patients the mean MoCA score was 25.8 (SD 2.9, p<0.001).

MoCA score was <26 in 67.2% of frail, 39.6% of pre-frail and 42.2% of robust patients (p=0.002). This was 40.4% in non-frail patients (p<0.001). These are displayed in **Table 3.40**.

Table 3.40: Fried Frailty and Cognitive Status

N=215	Total	Frail (F)	Pre-Frail (PF)	Robust (R)	p value F v PF v R	Non-Frail	p value F v NF
MoCA score	25.2 (2.9)	23.8 (3.6)	25.8 (2.4)	25.9 (2.2)	<0.001*	25.8 (2.9)	<0.001*
MoCA score ≥26	111 (51.6)	21 (32.8)	64 (60.4)	26 (57.8)	0.002*	90 (59.6)	<0.001*
MoCA score <26	104 (48.4)	43 (67.2)	42 (39.6)	19 (42.2)	0.002*	61 (40.4)	<0.001*

Figure 3.11: Fried Frailty and MoCA score



3.16.2 Rockwood Frailty and Cognitive Status

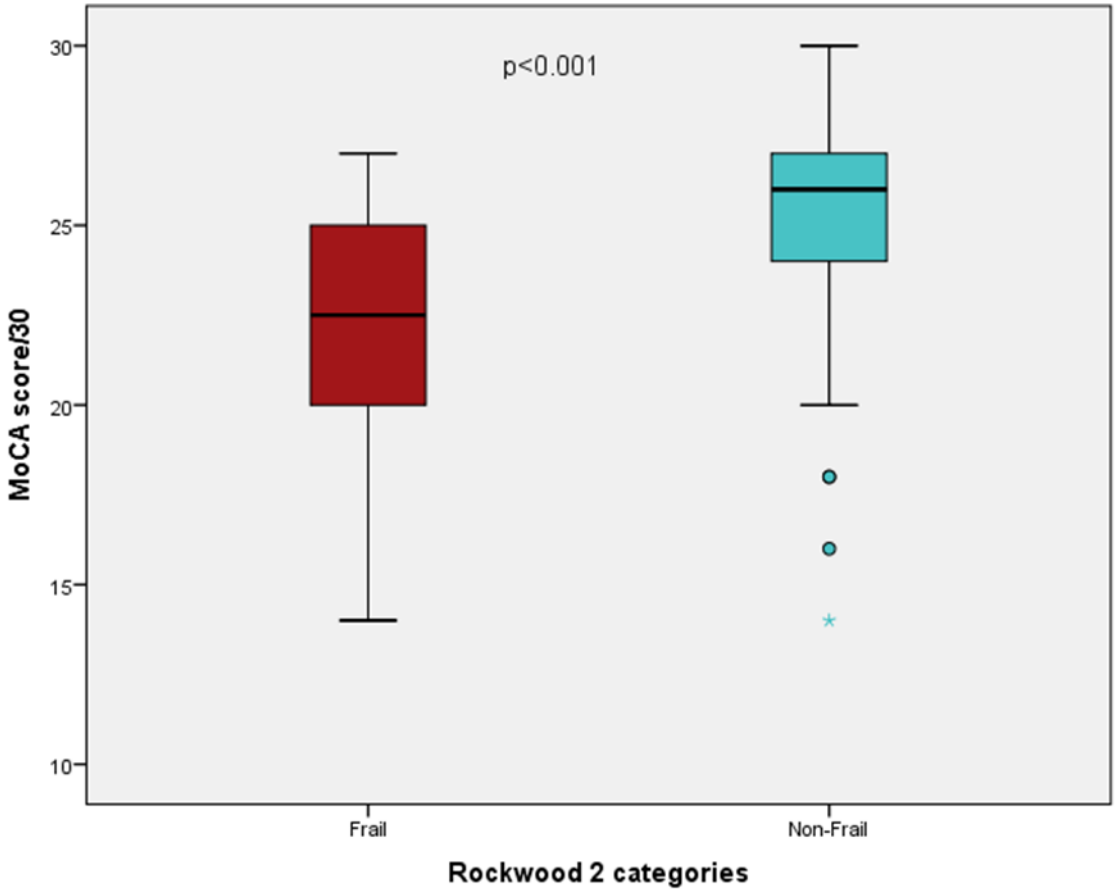
The mean MoCA score was 21.9 (SD 3.8) in frail patients, 25.3 (SD 2.4) in pre-frail patients and 26.2 (SD 2.6) in robust patients (p<0.001) as in **Figure 3.12**. In non-frail patients the mean MoCA score was 25.6 (SD 2.5, p<0.001).

MoCA score was <26 in 86.4% of frail, 50.4% of pre-frail and 31.8% of robust patients (p<0.001). This was 44.0% in non-frail patients (p<0.001). These are displayed in **Table 3.41**.

Table 3.41: Rockwood Frailty and Cognitive Status

N=215	Total	Frail (F)	Pre-Frail (PF)	Robust (R)	p value F v PF v R	Non-Frail	p value F v NF
MoCA score	25.2 (2.9)	21.9 (3.8)	25.3 (2.4)	26.2 (2.6)	<0.001	25.6 (2.5)	<0.001
MoCA score ≥26	111 (51.6)	3 (13.6)	63 (49.6)	45 (68.2)	<0.001	108 (56.0)	<0.001
MoCA score <26	104 (48.4)	19 (86.4)	64 (50.4)	21 (31.8)	<0.001	85 (44.0)	<0.001

Figure 3.12: Rockwood Frailty and MoCA score



3.17 Frailty and Health related Quality of Life Measures

3.18 EQ5D-3L

EQ5D-3L questionnaire assessment was available for all the patients (n=237). In terms of mobility 69.2% had no problems in walking about, while 30.8% patients had some problems with walking about. There were no patients confined to bed. In terms of self-care 92% of patients had no problems with self-care compared to 8% of patients some problems with washing or dressing. There was no patient who was unable to self-care. For usual activities of life 70.9% had no problems, compared to 28.3% having some problems and 0.8% patients unable to perform usual activities.

When responding to pain or discomfort 62% had no pain or discomfort, compared to 34.2% with moderate pain or discomfort and 3.8% with extreme pain or discomfort. In responding to anxiety or depression 76.8% reported not being anxious or depressed, 21.9% reported moderately anxious or depressed and 1.3% reported being extremely anxious or depressed.

The mean visual analog scale (VAS) score was 67.5 (SD 17.1). The mean EQ5D index by time trade off was 0.82 (SD 0.21) and by VAS was 0.81 (SD 0.19).

3.18.1 Fried Frailty and EQ5D-3L

In responding to problems with mobility 53.4% of frail patients had reported no problems in walking about, compared to 70.3% in pre-frail and 91.3% in robust patients ($p<0.001$) but 46.6% frail patients reported some problems with mobility compared to 29.7% in pre-frail and 8.7% in robust patients.

In responding to self-care question, 82.2% frail patients reported no problems with self-care, compared to 79.7% pre-frail and 87% robust patients ($p=0.001$). Some problems with self-care were reported by 8.0%, 17.8% and 5.1% respectively.

Usual activities were done without any problems by 46.6% of frail patients, 79.7% of pre-frail patients and 87.0% of robust patients ($p<0.001$). Usual activities were performed with some problems in 50.7%, 20.3% and 13.0% respectively while 2% of frail patients reported unable to perform usual activities.

No pain or discomfort was reported by 52.1% frail, 63.6% pre-frail and 73.9% robust patients ($p=0.191$). Moderate pain or discomfort was reported by 42.5%, 33.1% and 23.9% respectively. Extreme pain or discomfort was reported by 5.5%, 3.4% and 2.2% respectively.

There was no anxiety or depression in 71.2% frail, 78.0% pre-frail and 82.6% robust patients ($p=0.472$). Moderate anxiety or depression was reported by 26.0%, 21.25 and 17.4% respectively. Extreme anxiety or depression was reported by 2.7% frail and 0.8% pre-frail patients.

The mean VAS score was 61.1 in frail, 68.2 pre-frail and 74.8% in robust patients ($p<0.001$). The EQ5D index by time trade off was 0.74 in frail, 0.84 in pre-frail and 0.90 in robust patients ($p<0.001$). The EQ5D index by VAS was 0.73 in frail, 0.83 in pre-frail and 0.88 in robust patients. All the findings of EQ%D-3L in relation to Fried frailty status are displayed in **Table 3.42**.

Table 3.42: Fried Frailty and EQ5D-3L

EQ5D Dimension		Total	Frail (F)	Pre-Frail (PF)	Robust (R)	p value F v PF v R	Non-Frail	p value F v NF
Mobility	Level 1	164 (69.2)	39 (53.4)	83 (70.3)	42 (91.3)	<0.001*	125 (76.2)	0.001*
	Level 2	73 (30.8)	34 (46.6)	35 (29.7)	4 (8.7)	<0.001*	73 (30.8)	0.001*
	Level 3	0 (0)	0 (0)	0 (0)	0 (0)	-	0 (0)	-
Self care	Level 1	218 (92.0)	60 (82.2)	112 (94.9)	46 (100)	0.001*	158 (96.3)	<0.001*
	Level 2	19 (8.0)	13 (17.8)	6 (5.1)	0 (0)	0.001*	6 (8.0)	<0.001*
	Level 3	0 (0)	0 (0)	0 (0)	0 (0)	-	0 (0)	-
Usual activities	Level 1	168 (70.9)	34 (46.6)	94 (79.7)	40 (87.0)	<0.001*	134 (81.7)	<0.001*
	Level 2	67 (28.3)	37 (50.7)	24 (20.3)	6 (13.0)	<0.001*	30 (18.3)	<0.001*
	Level 3	2 (0.8)	2 (2.7)	0 (0)	0 (0)	<0.001*	0 (0)	<0.001*
Pain/ Discomfort	Level 1	147 (62.0)	38 (52.1)	75 (63.6)	34 (73.9)	0.191	109 (66.5)	0.100
	Level 2	81 (34.2)	31 (42.5)	39 (33.1)	11 (23.9)	0.191	50 (30.5)	0.100
	Level 3	9 (3.8)	4 (5.5)	4 (3.4)	1 (2.2)	0.191	5 (3.0)	0.100
Anxiety/ Depression	Level 1	182 (76.8)	52 (71.2)	92 (78.0)	38 (82.6)	0.472	130 (79.3)	0.219
	Level 2	52 (21.9)	19 (26.0)	25 (21.2)	8 (17.4)	0.472	33 (20.1)	0.219
	Level 3	3 (1.3)	2 (2.7)	1 (0.8)	0 (0)	0.472	1 (0.6)	0.219
EQVAS Values		67.5 (17.1)	61.1 (17.6)	68.2 (16.8)	74.8 (14.2)	<0.001*	70.0 (16.3)	0.001*
EQ5D Index by TTO		0.82 (0.21)	0.74 (0.23)	0.84 (0.20)	0.90 (0.16)	<0.001*	0.86 (0.19)	<0.001*
EQ5D Index by VAS		0.81 (0.19)	0.73 (0.19)	0.83 (0.19)	0.88 (0.15)	<0.001*	0.84 (0.18)	<0.001*

VAS Visual Analog scale, TTO Time Trade Off

3.18.2 Rockwood Frailty and EQ5D-3L

In responding to problems with mobility 29.2% of frail patients had no problems in walking about, compared to 73.7% in non-frail patients ($p<0.001$) but 30.8% frail patients reported some problems with mobility compared to 26.3% non-frail patients.

In responding to self-care question, 58.3% frail patients reported no problems with self-care, compared to 95.8% non-frail patients ($p<0.001$). Some problems with self-care was reported by 41.7% and 4.2% respectively.

Usual activities were done without any problems by 16.7% of frail patients compared to 77% of non-frail patients ($p<0.001$). Usual activities were performed with some problems in 75.0% and 23.0% respectively, while 8.3% of frail patients reported unable to perform usual activities.

No pain or discomfort was reported by 29.2% frail and 65.7% non-frail patients ($p<0.001$). Moderate pain or discomfort was reported by 54.2% and 31.9% respectively. Extreme pain or discomfort was reported by 16.7% and 2.3% respectively.

There was no anxiety or depression in 62.5% frail and 78.4% non-frail patients ($p=0.131$). Moderate anxiety or depression was reported by 33.3% and 20.7% respectively. Extreme anxiety or depression was reported by 4.2% frail and 0.9% non-frail patients.

The mean VAS score was 60.6% in frail and 68.3% non-frail patients ($p=0.037$). The EQ5D index by TTO was 0.56 in frail and 0.85 in non-frail patients ($p<0.001$). The EQ5D index by VAS was 0.57 in frail and 0.83 in non-frail patients. . All the findings of EQ%D-3L in relation to Rockwood frailty status are displayed in **Table 3.43**.

Table 3.43: Rockwood Frailty and EQ5D-3L

EQ5D Dimension		Total	Frail (F)	Pre-Frail (PF)	Robust (R)	p value F v PF v R	Non-Frail	p value F v NF
Mobility	Level 1	164 (69.2)	7 (29.2)	94 (66.2)	63 (88.7)	<0.001*	157 (73.7)	<0.001*
	Level 2	73 (30.8)	17 (70.8)	48 (33.8)	8 (11.3)	<0.001*	56 (26.3)	<0.001*
	Level 3	0 (0)	0 (0)	0 (0)	0 (0)	-	0 (0)	-
Self care	Level 1	218 (92.0)	14 (58.3)	133 (93.7)	71 (100)	<0.001*	204 (95.8)	<0.001*
	Level 2	19 (8.0)	10 (41.7)	9 (6.3)	0 (0)	<0.001*	9 (4.2)	<0.001*
	Level 3	0 (0)	0 (0)	0 (0)	0 (0)	-	0 (0)	-
Usual activities	Level 1	168 (70.9)	4 (16.7)	99 (69.7)	65 (91.5)	<0.001*	164 (77.0)	<0.001*
	Level 2	67 (28.3)	18 (75.0)	43 (30.3)	6 (8.5)	<0.001*	49 (23.0)	<0.001*
	Level 3	2 (0.8)	2 (8.3)	0 (0)	0 (0)	<0.001*	0 (0)	<0.001*
Pain/ Discomfort	Level 1	147 (62.0)	7 (29.2)	85 (59.9)	55 (77.5)	<0.001*	140 (65.7)	<0.001*
	Level 2	81 (34.2)	13 (54.2)	52 (36.6)	16 (22.5)	<0.001*	68 (31.9)	<0.001*
	Level 3	9 (3.8)	4 (16.7)	5 (3.5)	0 (0)	<0.001*	5 (2.3)	<0.001*
Anxiety/ Depression	Level 1	182 (76.8)	15 (62.5)	107 (75.4)	60 (84.5)	0.157	167 (78.4)	0.131
	Level 2	52 (21.9)	8 (33.3)	33 (23.2)	11 (15.5)	0.157	44 (20.7)	0.131
	Level 3	3 (1.3)	1 (4.2)	2 (1.4)	0 (0)	0.157	2 (0.9)	0.131
EQVAS Values		67.5 (17.1)	60.6 (18.9)	64.9 (17.1)	75.0 (13.8)	<0.001*	68.3 (16.8)	0.037*
EQ5D Index by TTO		0.82 (0.21)	0.56 (0.26)	0.81 (0.21)	0.92 (0.11)	<0.001*	0.85 (0.19)	<0.001*
EQ5D Index by VAS		0.81 (0.19)	0.57 (0.16)	0.80 (0.19)	0.90 (0.12)	<0.001*	0.83 (0.17)	<0.001*

VAS Visual Analog scale, TTO Time Trade Off

3.19 Short Form -36 Health Survey

Short from 36 health survey questionnaire was completed by all 237 patients at the time of recruitment during the hospital stay. The responses when entered in the calculator provides with scale score and norm based score for each of the following eight domains: Physical functioning (PF), Role-Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role-Emotional (RE) and Mental Health (MH). Overall a summary score for physical and mental components were calculated.

3.19.1 Fried Frailty and SF-36

These findings as detailed below are displayed in **Table 3.44**.

3.19.2 Scale Score

The median scale score for PF was 30 in frail, 55 in pre-frail and 80 in robust patients (p<0.001). This score was 70 in non-frail patients. The median SS RP was 0 in frail, 25 in pre-frail and 62.5 in robust patients (p<0.001). The median SS BP was 41, 62 and 73 respectively (p=0.001). The median GH was 45, 62 and 73 respectively (p<0.001). The median SS VT was 45, 62 and 72 respectively (p<0.001). The median SS SF was 50, 62.5 and 81.2 respectively (p<0.001). The median SS RE was 100, 100 and 100 respectively (p=0.191). The median SS MH was 76, 84 and 86 respectively (p=0.022).

3.19.3 Norm Based Score

The calculated median NB PF score was 27.8 in frail, 38.3 in pre-frail and 48.8 in robust patients (p<0.001). The NB RP scores were 28, 35 and 45.6 respectively (p<0.001). The NB BP scores were 37.5, 46.5 and 51.2 respectively (p=0.001). The NB GH scores were 38.2, 46.2 and 50.9 respectively (p<0.001). The NB VT scores were 44.3, 49.1 and 51.4 respectively (p<0.001). The NB SF scores were 35.4, 40.9 and 49 respectively (p<0.001). The NB RE scores were 55.3, 55.3 and 55.3 respectively (p=0.191). The NB MH scores were 50.4, 55 and 56.1 respectively (p=0.022).

3.19.4 Summary Score

The median PCS was 27.7 in frail patients, 37.1 in pre-frail patients and 46.5 in robust patients (p<0.001). The median MCS score was 52.4 in frail, 54.4 in pre-frail and 54.4 in robust patients (p=0.580).

Table 3.44: Fried Frailty and SF36

	Total	Frail (F)	Pre-Frail (PF)	Robust (R)	p value F v PF v R	Non-Frail	p value F v NF
SS PF	50.0	30.0	55.0	80.0	<0.001*	70.0	<0.001*
SS RP	0.0	0.0	25.0	62.5	<0.001*	37.5	<0.001*
SS BP	62.0	41.0	62.0	73.0	0.001	62.0	0.001*
SS GH	57.0	45.0	62.0	72.0	<0.001*	62.0	<0.001*
SS VT	50.0	45.0	62.0	72.0	<0.001*	55.0	<0.001*
SS SF	62.5	50.0	62.5	81.2	<0.001*	75.0	<0.001*
SS RE	100.0	100.0	100.0	100.0	0.191	100.0	0.081
SS MH	84.0	76.0	84.0	86.0	0.022*	84.0	0.011*
NB PF	36.2	27.8	38.3	48.8	<0.001*	44.6	<0.001*
NB RP	28.0	28.0	35.0	45.6	<0.001*	38.5	<0.001*
NB BP	46.5	37.5	46.5	51.2	0.001*	46.5	0.001*
NB GH	43.9	38.2	46.2	50.9	<0.001*	46.2	<0.001*
NB VT	46.7	44.3	49.1	51.4	<0.001*	49.1	<0.001*
NB SF	40.9	35.4	40.9	49.0	<0.001*	46.3	<0.001*
NB RE	55.3	55.3	55.3	55.3	0.191	55.3	0.081
NB MH	55.0	50.4	55.0	56.1	0.022*	55.0	0.011*
PCS	34.7	27.7	37.1	46.5	<0.001*	39.5	<0.001*
MCS	54.0	52.4	54.4	54.4	0.580	54.4	0.301

SS Scale Score, NB Norm Based, PF Physical Functioning, RP Role-Physical, BP Bodily Pain , GH General Health VT Vitality , SF Social Functioning, RE Role-Emotional, MH Mental Health, PCS Physical Component Summary, MCS Mental Component Summary

3.20 Rockwood Frailty and SF-36

These findings as detailed below are displayed in **Table 3.45**.

3.20.1 Scale Score

The median scale score for PF was 22.5 in frail and 55 in non-frail patients (p<0.001). The median SS RP was 0 in frail and 0 in non-frail patients (p=0.004). The median SS BP was 41 and 62 respectively (p=0.001). The median GH was 32.5 and 62 respectively (p<0.001). The median SS VT was 32.5 and 55 respectively (p<0.001). The median SS SF was 31.2 and 62.5 respectively (p<0.001). The median SS RE was 66.7 and 100 respectively (p=0.501). The median SS MH was 74 and 84 respectively (p=<0.001).

3.20.2 Norm Based Score

The calculated median NB PF score was 24.6 in frail and 38.3 in non-frail patients (p<0.001). The NB RP scores were 28 and 28 respectively (p=0.004). The NB BP scores were 37.5 and 46.5 respectively (p=0.001). The NB GH scores were 30.0 and 46.2 (p<0.001). The NB VT scores were 38.4 and 49.1 respectively (p<0.001). The NB SF scores were 27.3 and 40.9 respectively (p<0.001). The NB RE scores were 44.8 and 55.3 respectively (p<0.001). The NB MH scores were 49.3 and 55 respectively (p=0.016).

3.20.3 Summary Score

The median PCS was 23.5 in frail patients and 36.6 in non-frail-patients (p<0.001). The median MCS score was 46.0 in frail and 54.6 in non-frail patients (p=0.016).

Table 3.45: Rockwood Frailty and SF36

	Total	Frail (F)	Pre-Frail (PF)	Robust (R)	p value F v PF v R	Non-Frail	p value F v NF
SS PF	50.0	22.5	40.0	85.0	<0.001*	55.0	<0.001*
SS RP	0.0	0.0	0.0	100.0	<0.001*	0.0	0.004*
SS BP	62.0	41.0	61.0	74.0	<0.001*	62.0	0.001*
SS GH	57.0	32.5	55.0	72.0	<0.001*	62.0	<0.001*
SS VT	50.0	32.5	50.0	87.5	<0.001*	55.0	<0.001*
SS SF	62.5	31.2	50.0	87.5	<0.001*	62.5	<0.001*
SS RE	100.0	66.7	100.0	100.0	0.146	100.0	0.501
SS MH	84.0	74.0	82.0	88.0	<0.001*	84.0	<0.001*
NB PF	36.2	24.6	32.0	50.9	<0.001*	38.3	<0.001*
NB RP	28.0	28.0	28.0	56.2	<0.001*	28.0	0.004*
NB BP	46.5	37.5	46.0	51.6	<0.001*	46.5	0.001*
NB GH	43.9	30.0	42.9	50.9	<0.001*	46.2	<0.001*
NB VT	46.7	38.4	46.7	53.8	<0.001*	49.1	<0.001*
NB SF	40.9	27.3	35.4	51.7	<0.001*	40.9	<0.001*
NB RE	55.3	44.8	55.3	55.3	0.146	55.3	0.503
NB MH	55.0	49.3	53.8	57.3	<0.001*	55.0	<0.001*
PCS	34.7	23.5	32.6	48.6	<0.001*	36.6	<0.001*
MCS	54.0	46.0	54.0	55.6	0.033*	54.6	0.016*

SS Scale Score, NB Norm Based, PF Physical Functioning, RP Role-Physical, BP Bodily Pain , GH General Health VT Vitality , SF Social Functioning, RE Role-Emotional, MH Mental Health, PCS Physical Component Summary, MCS Mental Component Summary

CHAPTER 4: DISCUSSION AND CONCLUSION

In the following section the key findings, which are grouped in the table below are discussed.

Table 4.1: Table of Key Findings

Measures	Key Findings
Frailty Status	Frailty was very common among older patients managed by invasive strategy A third of patients were frail by Fried criteria and only a tenth of patients were frail by Rockwood criteria
Revascularisation	There was lesser rate of radial access in frail patients Very high proportion of patients (85%) were revascularised by coronary intervention There was no difference between frailty groups in the revascularisation strategy
Cardiovascular Outcomes	There was no significant difference in the rate of procedural complications and, in hospital and one month MACE by Fried and Rockwood criteria
Arterial Stiffness	Increasing age was associated with increased PWV Arterial stiffness measures by Vicorder did not vary according to frailty status
Endothelial function	Normal endothelial function was noted more in non-frail patients by Fried frailty criteria Augmentation index by EndoPAT was lower in frail patients by both frailty status tools
Carotid Intima Media Thickness	No difference in carotid intima media thickness
LV function	LV systolic function did not vary according to frailty status E/e', a measure of diastolic dysfunction was higher in frail patients by both frailty status Diastolic dysfunction was more prevalent in frail patients by Rockwood criteria only

Comorbidity	Increased comorbidity burden as per CCI score was present in almost a third of patients Increased comorbidity burden was significantly associated with frailty Similar to frailty, there was no significant difference in in-hospital or one moth MACE based on increased comorbidity
Quality of life	More frail patients reported some problems with mobility, self-care and daily activities by EQ5D-3L EQ5D index was lower in frail patients Physical component summary score was lower in frail patients by SF-36
Cognitive status	Sub clinical cognitive impairment was more prevalent in frail patients

4.1 Frailty Status Variation

4.1.1 Prevalence of Frailty and Frailty Status Variation

Frailty status varied significantly between the two assessment tools used. Patients were three times more likely to be frail by Fried criteria compared to Rockwood criteria. 30.8% were frail by Fried Frailty criteria and 10.1% patients were frail by Rockwood criteria.

Fried criteria uses objective assessment with grip strength and walking speed in addition to three responses from patient - weight loss in the last year, poor physical endurance and low physical activity. The most common variable in the frail patients was weakness by handgrip strength which was measured in 91.8%. As the invasive treatment strategy involved coronary angiogram, and the default access was right radial approach (86.9% radial procedures) I assessed the frailty status before patient had been to the catheterisation laboratory so that grip strength measure was not affected by the procedure. Only 26% of patients classified as frail were similarly classified as frail by the Rockwood criteria, whereas 73.9% of patients classified as robust by fried criteria were categorised as robust by Rockwood criteria. When classified as frail and non-frail groups 97% of non-frail patients by Fried criteria were classified non-frail by Rockwood criteria. ($p<0.0001$). There was a high degree of correlation between the Fried frailty score and Rockwood frailty scale (Kendall's tau-b $R =0.591$, $p<0.0001$), but this does not translate into categorising patients into different frailty groups.

Though there are different frailty assessment tools used and validated in community population, Fried and Rockwood assessment tools are the ones that had been used in patients with coronary artery disease. There is no consensus on the use of a standardised frailty assessment tool. Hence two commonly used tools were used in the same group of patients to understand more about the frailty status variation. As frailty status is a syndrome encompassing physical, functional and cognitive components it can vary depending on the assessment tools used. It also depends on the subjective or objective nature of the assessment tool. Several frailty assessment tools have been tested and validated in community population but the prevalence of frailty was different by different criteria in hospitalised older patients.(van Iersel and Rikkert, 2006) Only 7 out of 27 frailty instruments (26%) have been tested for reliability and validity.(Bouillon *et al.*, 2013) The Fried frailty assessment tool has been the most

extensively tested for validity and the most commonly used tool in frailty research.(Bouillon *et al.*, 2013) Having been used commonly in studies allows for easier comparisons of outcomes from different studies. It has to be acknowledged that there is no gold standard frailty assessment tool yet available. A consensus need to be reached on the various criteria and components to be included in a frailty assessment tool.

More patients were classified frail by Fried criteria and this is possibly related to responses from hospitalised patients being affected by their hospital stay in relation to energy levels and physical activity. Also it might have taken longer for patients to do the timed up to go test as they were hospitalised with restricted mobility compared to being at home and also possible effects of initiation of multiple cardiac medications.

Only a tenth of patients were classified as frail by Rockwood criteria and this is possibly due to the referral bias from local hospitals, that invasive treatment strategy is harmful to frail patients. Another factor to be considered in the variation is both frailty assessment tools were implemented by me, the primary researcher. I had assessed the frailty status by Rockwood criteria before using the Fried criteria. Both patient and the PCI operator in the catheterisation laboratory were blinded to the frailty status. This was to ensure that the routine treatment was not influenced by the frailty status.

Different frailty scores classify different subsets of population as frail with agreement highest for accumulation of deficits model, but more accurate classification with multidimensional model**.(**Aguayo *et al.*, 2017)

In view of the variation in frailty status by different tools, a consensus on the frailty assessment tool to be used in hospitalised patients with ischemic heart disease need to be agreed upon. This will help in standardised frailty classification which can be compared between studies for outcomes.

4.1.2 Frailty in relation to age and gender

In this study, increased age and female gender were independently associated with frailty. The mean age of patients was 80.3 (SD 4.9) years and 62.4% were males. In the study by Ekerstad et al, 48.5% of 307 hospitalised NSTEMI patients were classified frail by Rockwood criteria.(Ekerstad *et al.*, 2011) The patients in this study were ≥ 75 years old and the mean age of the study population was 84 years and 49% of patients

were females. In the study by Singh et al, (Singh *et al.*, 2011) 629 patients ≥ 65 years old were recruited and frailty status was assessed by Fried frailty criteria. Frailty status was not available in 13.3% of patients. Mean age of patients was 74.3 (6.4) years and 31% were females. Of the 545 patients with frailty status available 18.6% were frail, 47.4% were pre-frail and 20.6% were not frail. In the study by Murali-Krishnan et al,(Murali-Krishnan *et al.*, 2015) 745 patients were recruited and frailty was assessed by Rockwood frailty criteria. The mean age of patients were 62.2 (SD 12.0) years. In this study 11% of patients were frail and 30% of patients were female. In the study by Graham et al, of the 183 patients ≥ 65 years old, 30% of patients had high Edmonton Frailty Score (≥7). The mean age was 75.4 years and 33% were females.

Frailty was common among patients with NSTEMI who were managed by invasive strategy. The mean age was 80 years and more than half of the patients (54.4%) were ≥ 80 years old and only 7.5% patients were 65-74 years old. Increased age was associated with frailty by both Fried (80.8 vs. 80.8 vs. 78.3 years of F vs. PF vs. R, p=0.007) and Rockwood criteria (83.1 vs. 80.0 years for F vs. NF, p =0.004). Only the study by Ekerstad et al had such a high proportion of octogenarians. In my study 37.6% were females. Though the proportion of female patients were higher in the frail group this was not statistically significant by Fried criteria (F vs. PF vs. R of 47.9% vs. 34.7% vs. 28.35, p=0.065). But there was strong association between female gender and frailty by Rockwood criteria (F vs. NF of 62.5% vs. 34.7%, p=0.013). In the study by Ekerstad et al, frailty was associated with increased mean age (F vs. NF of 85 years and 83 years, p=0.0003) and female gender was not significantly associated with frailty (54.4% vs. 43.7% respectively, p=0.068). Increased age was associated with frailty in the study by Singh et al (F vs. PF vs. R of 77.4 vs. 74.6 vs. 72.6 years, p<0.001) and females were more likely to be frail (54% vs. 31% vs. 18% respectively, p<0.001). In the study by Murali-Krishnan et al, increased age (71.2 vs. 61.1 years for F vs. NF, p<0.001) and female gender (51.9% vs. 71.2% respectively, p<0.001) was associated with frailty. In the study by Graham et al, increased age was associated with frailty (77.2 vs. 73.9 years (p=0.031) but not female gender (38.2 vs. 22.2, p=0.088).

Similar to the other studies of frailty in coronary artery disease, older age is associated with frailty syndrome. As frailty is a result of declining physiological reserve and impaired resistance to stressors, older age predisposes to the development of frailty. Also older age is associated with increased comorbidity burden which plays a key role

in the development of frailty. In my study frailty assessment was done in patients with NSTEACS admitted to hospital, with NSTEACS being the recent significant stressor event To reduce the impact of invasive procedure on the frailty status, frailty assessment was done prior to invasive procedure. Compared to other studies my study had an increasing proportion of octogenarians and female patients, reflecting the current real world clinical practice.

4.1.3 Baseline characteristics of patients

CV risk factors profile like hypertension, diabetes, smoking history and hyperlipidaemia were not different between the frailty groups by Fried criteria. Similarly there was no significant difference for the above variables between frail and non-frail groups by Rockwood criteria.

Known cardiovascular disease like previous MI, known angina, previous PCI, and previous cerebrovascular disease was more prevalent in frail patients both by Fried and Rockwood frailty criteria. Known renal impairment and PVD was not significantly different between the frailty groups both by Fried and Rockwood assessment tools. Prevalence of osteoarthritis was more common in frail patients by both frailty criteria.

In the study by Singh et al, the prevalence of hypertension, diabetes, PVD, renal impairment, CCF, COPD and arthritis was significantly higher in frail patients compared to pre-frail and robust groups respectively.(Singh *et al.*, 2011) In the study by Ekerstad et al, there was significantly higher proportion of patients with COPD, severe renal impairment, dementia and anaemia in the frail group compared to non-frail group. In the study by Murali-Krishnan et al, hypertension, diabetes, hyperlipidaemia, PVD, cerebrovascular disease, chronic renal impairment and CCF was more common in frail than in non-frail patients.(Murali-Krishnan *et al.*, 2015)

Frailty was not associated with conventional risk factors for IHD like hypertension, diabetes, and hyperlipidaemia but were more associated with renal impairment, previous IHD, CCF, cerebrovascular disease, arthritis and COPD. Rather than the risk factors for CVD; established CVD, lung disease and joint disease were associated with frailty by contributing to the physical and functional limitations resulting from these comorbidities.

4.1.4 Underlying Presentation and Diagnosis

The initial diagnosis was NSTEMI in majority of patients (83%) and less than a fifth of patients had been diagnosed with unstable angina (17%). The inclusion criteria was narrowed down to NSTEACS alone, so that emergency presentations with STEMI would not be a confounding factor in the analysis of clinical outcomes. There was no significant difference in the underlying diagnosis of either NSTEMI or UA, both by Fried and Rockwood frailty groups. In the study by Ekerstad et al, though all the patients in

the study had NSTEMI, more than a third (34.6%) of the patients had Type 2 MI. According to the third universal definition of myocardial infarction, (Thygesen *et al.*, 2012) type 2 MI is defined as myocardial injury with necrosis due to imbalance between myocardial oxygen supply and/or demand other than that caused by CAD (like anaemia, arrhythmia, and coronary vasospasm). In the study by Singh et al, though all the patients were ≥ 65 years old and underwent PCI. There was no significant difference in the diagnosis of NSTEMI (17%), STEMI (14%) and no MI within 24 hours (69%) between the frailty groups. In the study by Murali-Krishnan et al, about 40% of patients had presented with STEMI and no difference between frail and non-frail patients. Haemodynamic instability was noted in 11% of patients with significant difference between the two groups (21% vs. 9.8%, p=0.002).

Frailty assessment tools were developed and validated in community populations. The same tools were being applied in hospitalised patients with coronary artery disease. As per the patient cohort in the studies above, even with acute coronary syndrome, the clinical state can vary from type 2 MI secondary to underlying cause like pneumonia or anaemia secondary to gastro intestinal bleeding or emergency STEMI presentation with cardiogenic shock. The nature of clinical presentation would have impacted the frailty assessment irrespective of the tool used. Also the initial presentation would have resulted in more adverse clinical outcomes. Hence to get a clearer picture, in my study patients with type 2 MI, STEMI and cardiogenic shock were excluded from recruitment.

4.1.5 Invasive Management of NSTEACS

All patients were managed by invasive strategy. Majority of patients were revascularised by PCI (85%) and there was no difference in either SVPCI or MVPCI. Similarly there was no difference in the vessel intervened between the groups of patients either by Fried or Rockwood frailty assessments. There was no significant difference in my study between the groups of patients managed by CABG (4%) or medical management (11%) by either Fried or Rockwood frailty assessments. The lesser proportion of patients referred for CABG reflects the older age group in whom CABG has more adverse outcomes peri-operatively. This also explains more revascularisation by PCI in which the risks are lesser compared to CABG. Medical management was decided in small proportion of the patients in whom even PCI was considered to be higher risk.

Patients were referred from secondary care hospitals to the tertiary care hospital for invasive management. There was no difference in length of time from local hospital admission to invasive management (mean days) by coronary angiogram at the tertiary hospital between the groups by Fried criteria (5.7 vs. 5.4 vs. 5.6 days, p=0.895). Similarly there was no difference when compared as frail and non-frail by Rockwood criteria (6.2 vs. 5.5 days, p=0.244). All the patients in my study had invasive coronary angiogram as part of the management plan. The frailty status assessment was done on the day prior to the invasive procedure, so hospital stay for five days could have had an impact on the frailty assessments. Further management including revascularisation by PCI or CABG and medications only was at the discretion of the interventional cardiologist and or the heart team.

In the study by Ekerstad et al, less than a third (31.2%) of the patients underwent coronary angiography. Frail patients were less likely to have coronary angiography (15.4% vs. 46.2%, p<0.0001) compared to non-frail patients. This difference was significant for revascularisation too (6.7% vs. 30.4%, P<0.0001). In this study more than third of patients had type 2 MI. So both the initial presentation and subsequent management was not comparable to contemporary clinical practice. In the study by Singh et al, 545 patients had percutaneous coronary intervention for either stable angina or ACS. Of these 35% were elective, 47% were urgent and 18% were emergency PCI procedures. There was no significant difference between frail, pre-frail and non-frail patients for elective urgent and emergency PCI procedures. In the study

by Murali-Krishnan et al, all the patients had PCI for stable angina or ACS without any difference in emergency PCI between frail and non-frail patients. But in both these studies, the nature of underlying presentations could have had an impact on clinical outcomes.

Coronary angiography and or PCI was done by radial access in 87% of patients and by femoral access in 13% of patients in the study presented in this thesis. As per Fried frailty status, frail patients were less likely to have the procedure by radial access and hence more likely to have procedure done by femoral access. But when compared by Rockwood frailty status there was no significant difference in the use of either radial or femoral access. The reason for lesser use of radial access could be due to increased proportion of frail patients having had previous PCI (28% vs 15%) resulting in radial artery occlusion leading onto femoral access. Previous CABG was the major predictor of femoral access followed by previous PCI and PVD by regression analysis. In patients with previous CABG femoral access makes it easier to engage and view the grafts better. The data on which access route was used for previous PCI was not available. Frailty assessment was done prior to the invasive procedure so arterial access did not have an impact on the frailty status.

There was a high proportion (86.0%) of patients revascularised by PCI. There was no significant difference in either SVPCI (73%) or MVPCI (27%) between the frailty groups of both Fried and Rockwood criteria. This compares to the intervention strategy in the study by Singh et al., there was no significant difference in SVPCI (83%) and MVPCI (17%).

Compared to other studies a very high proportion of patients underwent PCI and all patients had coronary angiogram. Contemporary invasive treatment strategy was used in all patients which helped to assess the impact of invasive strategy on adverse CV outcomes in a single cohort of patients with NSTEACS, unlike other studies which had a combination of clinical presentations.

4.2 Frailty Status and Major Adverse Cardiovascular Outcomes

There was no significant difference in the rate of procedural complications, in-hospital and 30-day major adverse cardiovascular outcomes based on Fried and Rockwood frailty statuses in my study.

Overall the rate of procedural complications was low at 1.7%, and more importantly there was no difference either by Fried frailty status (1.4% vs. 1.7% vs. 2.2%, p=0.946) or by Rockwood status (0% vs. 1.9%, p=1.000). This is similar to the findings in the study by Singh et al. This is the only comparable study in which data for procedural complications was available. There was no difference in procedural complications between F vs. PF vs. R groups for the incidence of pseudo-aneurysm, femoral bleeding, blood loss requiring transfusion and retroperitoneal bleed.

Of the 237 patients recruited only single patient died to peri-procedural stroke. This compares with outcomes in younger patients for procedure related mortality. Even the death of one patient was not significantly different based on frailty status. But it is important to note that this patient was classified as frail by Fried criteria and non-frail by Rockwood criteria, emphasising the importance of frailty status variation noted and discussed earlier.

Composite major adverse- CV outcomes (including death, acute coronary syndrome, unplanned revascularisation, major bleeding, stroke and contrast nephropathy or renal replacement therapy) was no different either by Fried groups (11.0% vs. 5.9% vs. 4.3%, p=0.30) and Rockwood groups (8.3% vs. 7.0%, p=0.685). But in the study by Ekerstad et al, in-hospital mortality was significantly higher in the frail patients compared to non-frail patients (10.1% vs. 1.9%, p=0.003). The rate of in-hospital major bleeding, stroke or need for dialysis was not significantly different between the groups (9.4% vs. 3.8%, p=0.06). The increased rate of mortality with no significant difference in other major adverse outcomes could be explained by the patient cohort included in the study. The inclusion of type 2 MI secondary to conditions like pneumonia, major GI bleeding potentially contributed to increased death.

In my study, at 30 days, there was no additional death of patients other than the one discussed above. Composite MACE outcomes at 30 days were not different either by Fried (11.0% vs. 5.9% vs. 4.3%, p=0.30) or Rockwood classification (8.3% vs. 7.7% vs. 5.6%, p=0.831). In the study by Ekerstad et al, frailty was associated with increased

30-day mortality (15.4% vs. 3.2%, p<0.0001). Re-infarction at 30 days (7.5% vs. 5.2%, p=0.470) and composite of major bleeding, stroke/TIA or need for dialysis (3.2% vs. 1.5%, p=0.456) were not significantly different F vs. NF groups. In the study by Singh et al, the composite of death, MI, PCI or CABG was 9% vs. 10% vs. 8% (p=0.83) between F vs. PF vs. R groups of patients. In the study by Murali-Krishnan et al, the 30-day mortality rate was 4.9% vs. 1.1% with frail patients five times more likely to die compared to non-frail patients (HR 4.8, 95% CI 1.4 to 16.3, p=0.013).

In my study there was no difference in procedural complications, in-hospital and 30 day MACE rate. This possibly is explained by the contemporary management strategy adopted in all the patients in my study. Also it has to be noted that patients in my study are a highly selected cohort of patients due to possible referral bias from the district hospitals. I do not have the data of all patients who were admitted with NSTEACS and proportion of patients referred for invasive management. The results in my study are similar to the study by Singh et al, in which there was no difference in the composite outcomes of death, MI, PCI or CABG. In the study by Ekerstad et al, mortality was higher in frail patients at 30 days. The patient groups comprised almost a third of patients with type 2 MI due to other acute medical presentations and known patients with dementia, which are likely to contribute to adverse CV outcomes. Contemporary management strategy was not employed as less than a third of patients underwent invasive treatment and frail patients were less likely to undergo coronary angiography or revascularisation. In the study by Murali-Krishnan et al, mortality was increased in frail patients at 30 days and the patient group consisted of nearly 40% with STEMI presentation and haemodynamic instability was more common in frail patients. This is the likely explanation for the increased mortality in that study. Overall the increased incidence of adverse outcomes noted in other comparable studies were likely related to the inclusion of different patient cohorts like type 2 MI, STEMI and cardiogenic shock. In my study the narrowed inclusion criteria for diagnosis with NSTEACS did not show any major differences in adverse outcomes amongst the frailty groups by both assessment tools. On the basis that patients at increased risk stand to benefit more from contemporary treatment possibly frail patients would benefit from invasive strategy as non-frail patients.

4.2.1 Time from Presentation to invasive treatment and total Length of Stay

There was no significant difference in the time from initial presentation to the local hospital to invasive treatment at the tertiary hospital either by Fried (5.7 vs. 5.4 vs. 5.6 days, p=0.895 for F vs. PF vs. R groups) or Rockwood criteria (6.2 vs. 5.5 days, p=0.244 for F vs. NF groups). These times are influenced by the decision by the local team to refer the patient for invasive strategy and the availability of beds at the tertiary centre. There was no significant difference in the length of stay in hospital between the patient groups either by Fried (7 vs. 6 vs. 6 days, p=0.55) or Rockwood frailty (7 vs. 6 days, p=0.09) classification. In the study by Ekerstad et al, frail patients stayed longer in hospital compared to non-frail patients (13.4 vs. 7.5 days, p<0.0001) but it has to be noted that large proportion of patients had type 2 MI and patients with dementia were included in the study.(Ekerstad *et al.*, 2011) In the study by Murali-Krishnan et al, frail patients stayed longer in hospital compared to non-frail patients (14.1 vs. 3.5 days, p<0.01). In this study almost 40% of patients had PCI for STEMI.(Murali-Krishnan *et al.*, 2015)

The reason frail patients did not have a delay in invasive treatment and did not stay longer in hospital was because of the patient cohort being highly selected for NSTEACS diagnosis. These patients were haemodynamically stable at the time of recruitment. Patients with Type 2 MI and established cognitive impairment were excluded from the study, conditions which could have led to prolonged stay. The procedural and in-hospital complications were very low which prevented prolonged hospital stay.

4.3 Frailty and Cardiovascular Status

4.3.1 Arterial stiffness

Arterial stiffness measures were not significantly different between the groups of patients classified by either Fried or Rockwood classification. In my study frailty was not associated with arterial stiffness measures of carotid femoral PWV, aortic pulse pressure and augmentation index assessed non-invasively by Vicorder. These findings are similar in that conventional risk factors for CVD like hypertension, diabetes and hyperlipidaemia were not associated with frailty. Not many studies have explored the relation between frailty and arterial stiffness. Sarcopenia, a risk factor for frailty was associated with increased brachial ankle PWV in elderly men but not in women in the community.(Ochi *et al.*, 2010) In another study of older patients, frailty by Fried classification was not associated with increased aortic stiffness measured by non-invasive assessment of aortic PWV.(L.M. Kannegieter, 2016) Frailty and arterial stiffness measures in the community population can be independent predictors of cardiovascular outcomes. So I sought to explore any possible relation between frailty and arterial stiffness in patients with established coronary artery disease.

In my study there was a significant positive correlation between age and pulse wave velocity and pulse pressure. Aging is an independent risk factor for atherosclerosis and aging arteries are predisposed to vascular smooth muscle hypertrophy leading to increased arterial stiffness. Increased stiffness results in pressure waveform reaching the ascending aorta in systole rather than diastole as happens in elastic arteries, augmenting systolic pressure and decreasing diastolic pressure. These pathophysiological mechanisms explains the correlation noted between age and arterial stiffness markers of PWV and pulse pressure. Though increased age was associated with frailty and increased PWV, arterial stiffness was not associated with frailty. This suggests possibly increased age with resultant comorbidities rather than the risk factor for the comorbidities like arterial stiffness leads to frailty. In older age due to increased pulse pressure and PWV, angina may be precipitated even in the absence of significant CAD due to decreased coronary perfusion in diastole.

4.3.2 Endothelial Dysfunction

There was no significant association between frailty and endothelial dysfunction by both Fried and Rockwood classification. A third of the patients had endothelial dysfunction as per the mean LnRHI but this was similar between the three groups (F vs. PF vs. R) by Fried classification and between the two groups by Rockwood classification (F vs. NF). Endothelial dysfunction is a precursor for coronary artery disease but my study patients had established coronary artery disease presenting with NSTEACS. As patients had presented with NSTEMI most of my patients were on ACE inhibitor and atorvastatin, which possibly could have an effect on endothelial function measures. In the Toledo Study for Healthy Aging, endothelial dysfunction assessed by measurement of biomarker, asymmetric dimethyl arginine (ADMA) levels was associated with frailty assessed by Fried frailty assessment tool.(Alonso-Bouzon *et al.*, 2014)

Augmentation index, a measure of arterial stiffness measured by EndoPAT was significantly different between the groups of patients classified by both Fried and Rockwood classification. AI by EndoPAT has not been validated as a marker of arterial stiffness unlike AI by Vicorder. Also AI can vary according to the central or peripheral artery used for its measurement. AI by Vicorder utilises a major peripheral artery which has been correlated with central aortic AI. AI by EndoPAT utilises the microvasculature in the in the pulp of the finger, which may not be reliable for measuring AI but very helpful in assessing endothelial dysfunction. There was significant positive correlation between AI measured by EndoPAT and Vicorder ($r=0.262$, $p<0.0001$). But it has to be noted AI measured by Vicorder was similar between the groups of patients. The correlation between EndoPAT AI and cfPWV was weak and not significant ($r=0.111$, $p=0.129$). In a small study of hypertensive patients arterial stiffness measured by flow mediated dilatation had poor correlation with AI measured by EndoPAT ($r=0.18$, p=not significant).(Takase and Higashimura, 2013)

4.3.3 Carotid Intima Media Thickness

There was no difference in the CIMT measurements on both the sides between all groups of patients by Fried and Rockwood classification. In community population higher common carotid artery CIMT was associated with slower gait speed which is a marker of underlying frailty.(Elbaz *et al.*, 2005) In another study of community population increase in CIMT thickness was associated with increased probability of being frail.(Avila-Funes *et al.*, 2014) Though CIMT measurement can improve CV risk prediction a metanalysis suggested that this improvement is not of much clinical importance.(Den Ruijter *et al.*, 2012)

There was no significant difference according to frailty on measures of arterial stiffness, endothelial dysfunction and CIMT. These measures have been shown to be predictors of CVD in addition to conventional risk factors like hypertension, diabetes, hyperlipidaemia and smoking. Hence it can be postulated that frailty is associated with disability and the diseases causing it rather than the risk factors causing these disease presentations.

From my study there was no association between CV disease burden like arterial stiffness, endothelial dysfunction and CIMT to frailty status. But these were predictors of CV outcomes in the community population. It can be interpreted that the frailty models used in my study were based on phenotype and accumulation of deficits. In these models functional limitation that is symptoms related to underlying comorbidities has a role in development of frailty rather than the risk factors or predictors of diseases per se.

4.3.4 Left Ventricular Function

There was no difference in the prevalence of systolic dysfunction assessed by transthoracic echocardiogram in relation to frailty by both Fried and Rockwood classification. Just more than a third of the patients had normal systolic function and one tenth of the patients had severe systolic dysfunction. 40% of the patients had diastolic dysfunction. Diastolic dysfunction as assessed by elevated filling pressure was significantly more common in frail patients by Rockwood criteria but not by Fried criteria. Frailty by Rockwood criteria and female gender were predictors of elevated filling pressure by regression analysis. Elevated filling pressure is dependent on the measurement E/e' and LA size. E/e' is an important predictor of diastolic dysfunction and this value was increased in frail patients by both the frailty classifications. Limited studies have examined the association of echocardiographic findings and frailty. In a study of octogenarians in the community, frailty by Fried frailty assessment was associated with impaired LV systolic dysfunction assessed by ejection fraction but not with diastolic dysfunction measured by E/E'.(Leibowitz *et al.*, 2016) In another study of older patients (>65 years old) frailty was assessed in patients who underwent transthoracic echocardiography for clinical reasons. In this study frailty was associated with increased left atrial volume, decreased stroke volume and higher pulmonary artery pressure.(Gharacholou *et al.*, 2015) My study findings adds to the limited existing data on LV function and frailty, but it has to be noted that patients with known severe LVSD and presentation with pulmonary edema were excluded. This might be a reason for no relation between frailty and systolic dysfunction. Also even the patients with LV systolic function are likely to develop symptoms only after hospital discharge. LV dysfunction noted is the effect of NSTEACS presentation which would improve with successful revascularisation. Increased age is a predictor of diastolic dysfunction which is in turn associated with frailty. This explains the relation between frailty and diastolic dysfunction. Diastolic dysfunction cause symptoms of dyspnoea which in turn can lead to frailty due to functional limitation. Again the effect of LV dysfunction either systolic or diastolic resulting in clinical symptoms are likely to be associated with frailty. This can be noted in the increased association of previous history of CCF with frailty as seen in the baseline demographics of the patient cohort.

4.4 Comorbidity

Higher comorbidity burden as calculated by Charlson Comorbidity Index (CCI) was present in almost a third of patients. As expected higher comorbidity burden was associated with frailty by both Fried and Rockwood classification. This is because increased age and comorbidity leads to decreased response to stressors which results in frailty. There was no significant association between higher comorbidity burden and major adverse cardiovascular events at 30 days except for the higher incidence of contrast nephropathy. Comorbidity has significant overlap with frailty and disability.(Fried *et al.*, 2004) It is important to recognise this, as each of these can have an impact on the specific disease management. Comorbidity burden can be a predictor of prognosis in patients undergoing PCI.(Singh *et al.*, 2011) But it has to be noted that benefits of appropriate early revascularisation of patents with higher comorbidity burden was significantly higher in NSTEACS patients compared with lower comorbidity burden.(Palau *et al.*, 2012) Evidence for management of patients with comorbidity burden is lacking due to exclusion of patients from research trials.(Sachdev *et al.*, 2004) The process by which higher comorbidity burden affects outcomes is complex and multifactorial. Patients who are older with multiple comorbidities are least likely to be treated by invasive strategy. Not offering invasive strategy when needed could result in adverse outcomes. Higher comorbidity burden may result in patients not receiving appropriate treatment due to interaction of a disease specific treatment having adverse effect on the other comorbid condition. Higher comorbidity burden may be deemed to increase the risk of a proposed invasive procedure. But these need to be weighed against the potential benefits of contemporary management like percutaneous coronary intervention. In my study higher comorbidity burden was not associated with increased CV outcomes in the short term, likely due to the contemporary invasive treatment utilised on these patients. Though comorbidity and frailty are related they are defined by different mechanisms, but did not have any impact on major CV outcomes. This is likely due to contemporary management with invasive strategy in a high volume tertiary centre and also possibly due to selection bias from the referral hospitals. My study has shown that invasive coronary procedures can be done safely with good outcomes in the short term. How these translate into long term better outcomes need to be explored.

4.5 Health Related Quality of Life

4.5.1 Symptom burden of Dyspnoea and Angina

Frail patients were more likely to have worsening dyspnoea symptom as per NYHA classification. This difference was present in frail patients classified by both Fried and Rockwood criteria. Dyspnoea possibly contributes to the frailty status due to functional limitation and disability. Though only a small proportion of patients (7.6%) had history of CCF at the time of recruitment more patients described NYHA class II and III dyspnoea (54%). Higher prevalence of CCF and worsening dyspnoea were noted in frail patients by both frailty criteria. LV systolic dysfunction is not significantly different between the patient groups but E/E' which is a marker of diastolic dysfunction was higher in frail patients. Diastolic dysfunction possibly contributes to the worsening severity of dyspnoea noted in frail patients in my study. Increasing severity of dyspnoea is significantly associated with self-reported low physical activity, lesser physical endurance, slow walking speed but not with history of weight loss and grip strength which are measures of the Fried frailty classification. No association of frailty with NYHA dyspnoea has been reported. But a systematic review of heart failure in older patients assessed for frailty by various tools concluded an association between frailty and mortality and morbidity.(Jha *et al.*, 2015) The findings from my study sheds light on the association between severity of dyspnoea with frailty by Fried and Rockwood classification and three of the five criteria of Fried frailty assessment. Symptom burden of dyspnoea possibly contributes to the Frailty syndrome which can have many pathophysiological etiology. The association of dyspnoea to frailty in my study renders to the accumulation of deficits theory of frailty syndrome due to physical and functional limitation. Severity of angina classified by CCS classification was not associated with frailty by Fried criteria but was slightly more prevalent in frail patients classified by Rockwood criteria. In older patients symptoms of angina are not typical with chest pain but could present with angina equivalent like dyspnoea which possibly explains more prevalent symptom of dyspnoea. Association between severity of angina and frailty has not been documented before.

4.5.2 EQ5D-3L

In my study more frail patients reported some problems with mobility, self-care and usual daily activities by both Fried and Rockwood frailty classification. In addition to the above three dimensions, more patients in the frail group reported some pain and discomfort by Rockwood criteria but not by Fried criteria. Anxiety and depression was not significantly different between the groups by both criteria. It has to be noted that no patients reported they were confined to bed or unable to self-care. Only a very small proportion of patients reported unable to perform usual activities (0.8%), in extreme pain or discomfort (3.8%) and extreme anxiety or depression (1.3%). These findings possibly explains the difference in frailty status by the two frailty criteria in my study. Majority of the patient cohort did not have any difficulty with activities in daily living and thus Rockwood criteria classified only a tenth of patients as frail Rockwood criteria classified patients based on activities of daily living and need for help with self-care, whereas Fried criteria classified patients on subjective and objective criteria which does not reflect on their daily activities and managing self-care. It is very interesting to note that anxiety and depression were not significantly related to frailty status. It can be inferred that frailty is associated with effects on physical limitation rather than any psychological effects.

As per the visual analogue score marked by patients from worst imaginable health state (scale 0) to best imaginable health state (scale 100), frail patients had scored lesser both by Fried and Rockwood criteria. Even frail patients felt that their health state was moderate and not worse. So frailty not necessarily means worse health state from the patient's perspective.

EQ5D index by visual analogue scale technique and by time trade off (TTO) technique were low in frail patients by both Fried and Rockwood Frailty groups. EQ5D index by TTO and VAS were lower respectively by Rockwood frailty group (0.56 and 0.57) compared to fried frailty status (0.74 and 0.73). EQ5D indices are lower in Rockwood frailty group for the same reasons discussed above.

4.5.3 SF-36

Based on responses to the SF-36 questionnaire, frail patients scored significantly lower scale and norm based scores for Physical functioning (PF), Role-Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF) and Mental Health (MH) by both Fried and Rockwood frailty classification. The scores for Role-Emotional (RE) were not significantly different by both frailty classification.

For the summary score, physical component was significantly lower in frail patients by Fried classification but not the mental component score. But by Rockwood classification both physical and mental components were significantly lower in frail patients. This is possibly because rock wood classification of frailty with more physical limitation had an impact on the mental health.

In a metanalysis, frailty assessed by Fried criteria was associated with poorer physical and mental components of quality of life assessed by SF-36 in community dwelling older population.(Kojima *et al.*, 2016) HRQoL measured by EQ5D and SF 36 showed improvement at 4 months and one year in NSTAECS patients managed by invasive strategy.(Kim *et al.*, 2005) The biggest gain was noted in the physical component. In another study, irrespective of management strategy all aspects of health status measured by SF-36 improved in ACS patients treated with clopidogrel.(Chudek *et al.*, 2014) Poor QoL was independent predictor of long term mortality in patients undergoing PCI and addition of frailty, comorbidity and QoL by SF-36 increased the discriminatory ability of Mayo Clinic risk score.(Singh *et al.*, 2011) In older patients undergoing PCI improves HRQoL improved by its impact on physical functioning.(Graham *et al.*, 2006; Li *et al.*, 2012; Johnman *et al.*, 2013; Panasewicz *et al.*, 2013)

Health related quality of life (HRQoL) measures were associated with frailty in my study patients. They were mainly associated with the physical components of the measures. Thus physical functioning and independent activities of daily living have an impact on the frailty status due to accumulation of deficits impacting functional status. The patient cohort did not have severe limitations in the physical functions which may explain the favourable CV outcomes in hospital and at 1 month. It is not known what the outcomes will be if all patients with NSTEACS were included in the study. The recruitment to the study was limited to the patients referred to tertiary hospital. Patients whose functional ability was very poor may not have been referred to the tertiary hospital.

It will be interesting to know the difference in QoL measures at one year and to compare with the CV outcomes at one year. By studying these at one year improvement or deterioration in QoL measures could be attributed to the invasive treatment strategy. Overall functional status assessment measured by QoL measures need to be routinely done in older patients to measure difference in absolute CV outcomes and QoL difference made by various treatment strategies. Even patients would prefer an improvement in functional ability from invasive treatment strategy in addition to better CV outcomes. QoL measures should be considered in the frailty status assessment.

4.6 Subclinical Cognitive Impairment

Almost half of 215 patients scored <26 on the Montreal cognitive Assessment indicative of subclinical cognitive impairment. The study excluded patients with known dementia. Frailty by both Fried and Rockwood classification was associated with increased proportion of patients with MoCA score <26. The mean MoCA score was lower in frail patients by both classifications. It can be inferred that frailty was associated with subclinical cognitive impairment. Frailty syndrome in addition to the physical components includes cognitive decline too. Subclinical cognitive impairment can have an impact on the delay in presentation, informed decision making and compliance with medications. All of these can eventually have an impact on outcomes.

Cardiovascular disease is an independent predictor of dementia. Dementia is an independent predictor of 30 day and one year mortality in hospitalised patients with acute myocardial infarction.(Sloan *et al.*, 2004) The two most common etiology of dementia are Alzheimer's and vascular dementia. Subclinical cognitive impairment predisposes to dementia.(Petersen *et al.*, 1999) Silent cerebral infarctions are associated with diagnostic coronary angiography and this increases the risk of developing dementia.(Vermeer *et al.*, 2003; Kim *et al.*, 2011) But it has been shown in another study that IHD patients managed by PCI compared to medical management had lower risk of dementia with a mean follow up period of five years.(Mutch *et al.*, 2011) The impact of contemporary management of coronary artery disease on subclinical cognitive impairment to development of dementia and cardiovascular outcomes is not known. Frailty as assessed by Fried criteria was strongly associated with cognitive impairment and dementia.(Kulmala *et al.*, 2014) In the study by Ekerstad et al, dementia was more prevalent in frail patients than non-frail patients (27.5% vs. 5.7%, p<0.0001).(Ekerstad *et al.*, 2011) Though frailty was an independent predictor of mortality at 30 days and one year, the impact of dementia on mortality was not analysed. But most of the frailty assessment tools do not have cognitive impairment as a scoring variable. Both the frailty assessment tool used by us did not include cognitive assessment and patients with known dementia were excluded from my study. It is also not known how many of patients with known dementia were deemed not suitable for invasive treatment by referring local acute medical physicians and cardiologists. In my study frailty was significantly associated with lower MoCA score and subclinical

cognitive impairment. It is important to consider cognitive impairment as part of the frailty syndrome and to include cognitive assessment in the assessment of frailty.

4.7 Strengths and Limitations

The main strength of the study was the recruitment of older patients undergoing contemporary invasive treatment in a tertiary centre for NSTEACS, excluding STEMI as the outcomes vary depending on the presentation. The study used both Fried and Rockwood frailty scores, which are tools validated in community population for a specific group of IHD patients presenting with NSTECAS, seeking to understand the frailty classification with two different tools on the same group of patients. Holistic assessment of patients undertaken in exploring frailty in relation to comorbidity, cardiovascular status, cognitive status and quality of life in addition to CV outcomes.

Inclusion of patients was limited to the patients referred to the tertiary cardiac centre by the secondary care team and hence the patient group were highly selected. Patients deemed not suitable for invasive treatment for varied reasons by the referral team were not known as they would have potentially altered the outcomes. Moreover even from 346 patients managed invasively for NSTEACS, only 237 patients were included in the study as 60 patients declined to take part and 49 patients were unable to consent for various reasons. Though this is common in clinical research inclusion of those patients could have altered the outcome in my study. It would have been ideal to include every consecutive patient but this was not feasible. Also patients with known dementia was an exclusion criteria, as frailty status and outcomes in these patients were not known. The analysis was done on 237 patients who were recruited by me and the power was not enough to show definitive difference between the patient groups. So the results and conclusions were more of a pilot study analysis and were not powered enough to make conclusions but provided insight into the relatively newer concept of frailty in patients managed by PCI especially in the ever increasing proportion of older patients with NSTEACS. In case of cardiovascular status assessment, because of the acute presentation and limited time of stay at the cardiac centre, medications that may have an impact on the measurements like endothelial function and arterial stiffness could not be stopped. Transthoracic echocardiogram findings were not available for a proportion of patients due to poor image quality and unavailability of echocardiogram during the limited stay.

4.8 Conclusion

Older patients usually underrepresented in clinical trials can be recruited in a research study. Frailty was prevalent in older patients with NSTEACS managed by invasive strategy but the frailty status varied depending on the assessment tool used. Three times more patients were classified frail by Fried frailty assessed by a combination of subjective and objective assessment compared to Rockwood frailty using subjective assessment alone. Most of the clinical presentation was with NSTEMI (82.7%) and there was no significant difference between the frailty groups for either NSTEMI or UA by both frailty assessment tools. All the patients underwent invasive coronary angiogram. Almost 85% of patients were managed by PCI with no difference in the frailty groups for management by PCI, CABG or medical management. There was no significant difference between the patient groups in length of hospital stay according to the management strategy. Procedural complications were very small in number and there was no difference between the patient groups. There was no significant difference in the rate of in-hospital and 30-day major adverse cardiovascular events (MACE) of death, ACS, unplanned revascularisation, major bleeding, stroke and contrast nephropathy or renal replacement therapy between the patient groups by both Fried and Rockwood assessment tools. Measures of vascular status like arterial stiffness, endothelial dysfunction and CIMT were not significantly different in frail patients by both the frailty assessment tools. Though LV systolic dysfunction was similar among patient groups, but E/e', a measure of diastolic dysfunction was significantly higher in frail patients. Severity of angina was worse in frail patients by Rockwood classification only, but severity of dyspnoea was significantly worse in frail patients by both frailty assessment tools. Comorbidity burden by Charlson comorbidity Index was higher in frail patients by both frailty classification, but the higher comorbidity burden was not associated with increased rate of in hospital and 30-day MACE. Patients with known dementia were excluded from the study but sub clinical cognitive impairment assessed by MoCA was more prevalent in frail patients by both frailty assessment tools. HRQoL measures by EQ5D and SF-36, were significantly lower in frail patients by both frailty assessment tools for physical components, but measures for mental component by SF-36 was lower in frail patients by Rockwood classification only.

4.9 Future Directions

The development of a dedicated frailty assessment tool for older patients undergoing cardiovascular procedures would more accurately risk stratify patients and identify optimal management strategies.

Frailty should not preclude the older patient provision of standard contemporary treatments as, in addition to improving CV outcomes, these treatments may significantly improve quality of life.

Frailty assessments in older patients should include cognitive status and quality of life measures in addition to the physical component measures.

Long term CV and quality of life outcomes should be studied in older patients with frailty and comorbidity in larger studies to demonstrate the impact of contemporary treatment on those outcomes.

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Appendix

Fried Frailty Index derived from Cardiovascular Health Study

Criterion	Frailty Status
Shrinking	Frailty cut point: Baseline: Self-reported unintentional weight loss ≥10lb in previous year Follow-up: Unintentional weight loss ≥5% of previous year's body weight *OR* BMI <18.5kg/m^2
Physical endurance/energy	*Geriatric Depression Scale:* *Do you feel full of energy?* *During the last 4 weeks how often you rested in bed during day?* Response options: Every day, every week, once, not at all. Frailty cut point: No to 1 and every day or every week to 2.
Low physical activity	*Frequency of mildly energetic, moderately energetic and very energetic physical activity.* Response options: ≥3 times per week, 1-2 times per week, 1-3 times per month, hardly ever/never Frailty cut point: Hardly ever/never for very energetic physical activity AND for moderately energetic physical activity.
Weakness	Hand grip strength in Kg: GRIP-D hand held dynamometer, dominant hand, average of 3 measures. Frailty cut point: Grip strength: lowest 20% (by gender, body mass index) *Men* / *Women* BMI ≤24 ≤29 / BMI ≤23 ≤17 BMI 24.1–26 ≤30 / BMI 23.1–26 ≤17.3 BMI 26.1–28 ≤30 / BMI 26.1–29 ≤18 BMI >28 ≤32 / BMI >29 ≤21
Slow walking speed	Walking time in seconds (usual pace) over 15 feet Frailty cut point: Slowest 20%, stratified by gender and median standing height. *Men* / *Women* Height ≤173 cm ≥7 seconds / Height ≤159 cm ≥7 seconds Height >173 cm ≥6 seconds / Height >159 cm ≥6 seconds *OR* Time to complete "timed up and go test" (TUG) Frailty cut point: TUG time ≥19 seconds

Frail: ≥3 criteria present; **Intermediate or Pre-Frail:**1 or 2 criteria present; **Robust :** 0 criteria present

Adapted from Fried et al, Cardiovascular Health Study Collaborative Research G. Frailty in older adults: Evidence for a phenotype. The Journals of Gerontology. Series A, Biological sciences and medical sciences. 2001;56:M146-156.

Rockwood Frailty Index derived from Canadian Study of Health and Aging

1	Very fit – robust, active, energetic, well-motivated and fit; these people commonly exercise regularly and are in the most fit group for their age
2	Well – without active disease, but less fit than people in category 1.
3	Well, with treated co-morbid disease – disease symptoms are well controlled compared with those in category 4
4	Apparently vulnerable – although not frankly dependent, these people commonly complain of being “slowed up” or have disease symptoms.
5	Mildly frail – with limited dependence on others for instrumental activities of daily living
6	Moderately frail – help is needed with both instrumental and non-instrumental activities of daily living
7	Severely frail – completely dependent on others for the activities of daily living, or terminally ill.

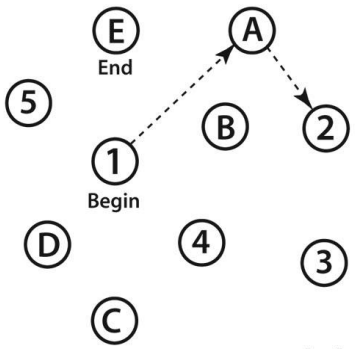
Adapted from Rockwood et al, A global clinical measure of fitness and frailty in elderly people. Canadian Medical Association Journal 2005;173:489-495

Montreal Cognitive Assessment

MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education : **Date of birth :**
Sex : **DATE :**

VISUOSPATIAL / EXECUTIVE — POINTS



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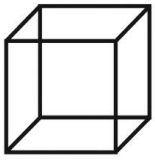


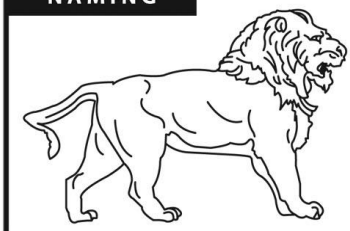
[ ] [ ]

Draw CLOCK (Ten past eleven)
(3 points)

[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING



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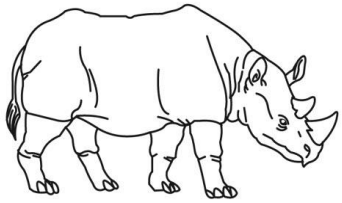

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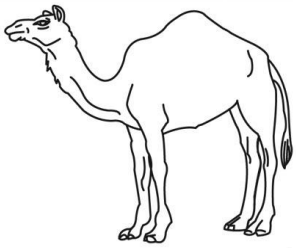

[ ]

__/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)

__/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

__/2

DELAYED RECALL

	Has to recall words **WITH NO CUE**	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

© Z.Nasreddine MD **www.mocatest.org** Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

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Short Form-36® Standard Health Survey

1- In general, would you say your health is:

□ 1. Excellent □ 2. Very good □ 3. Good □ 4. Fair □ 5. Poor

2- Compared to ONE YEAR AGO, how would you rate your health in general NOW?

□ 1. MUCH BETTER than one year ago.

□ 2. Somewhat BETTER now than one year ago.

□ 3. About the SAME as one year ago.

□ 4. Somewhat WORSE now than one year ago.

□ 5. MUCH WORSE now than one year ago.

3- The following items are about activities you might do during a typical day. **Does your health now limit you** in these activities? If so, how much?

Activities	**1. Yes, Limited A Lot**	**2. Yes, Limited A Little**	**3. No, Not Limited At All**
a) **Vigorous activities,** such as running, lifting heavy objects, participating in strenuous sports?	□	□	□
b) **Moderate activities,** such as moving a table, pushing a vacuum cleaner, bowling, or playing golf?	□	□	□
c) Lifting or carrying groceries?	□	□	□
d) Climbing **several flights** of stairs?	□	□	□
e) Climbing **one** flight of stairs?	□	□	□
f) Bending, kneeing or stooping?	□	□	□
g) Walking **more than a mile**?	□	□	□
h) Walking **several** blocks?	□	□	□
i) Walking **one** block?	□	□	□
j) Bathing or dressing yourself?	□	□	□

4- During the **past 4 weeks**, have you had any of the following problems with your work or other regular activities *as a result of your physical health*?

	Yes	No
a) Cut down on the **amount of time** you spent on work or other activities?	□ 1. yes	□ 2. No
b) **Accomplished less** than you would like?	□ 1. yes	□ 2. No
c) Were limited in the **kind** of work or other activities?	□ 1. yes	□ 2. No
d) Had **difficulty** performing the work or other activities (for example it took extra effort)?	□ 1. yes	□ 2. No

5. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	Yes	No
a) Cut down on the **amount of time** you spent on work or other activities?	□ 1. yes	□ 2. No
b) **Accomplished less** than you would like?	□ 1. yes	□ 2. No
c) Didn't do work or other activities as **carefully** as usual?	□ 1. yes	□ 2. No

6. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

□ 1. Not at all □ 2. Slightly □ 3. Moderately □ 4. Quite a bit □ 5. Extremely

7. How much **bodily pain** have you had during the **past 4 weeks**?

□ 1. None □ 2. Very mild □ 3. Mild □ 4. Moderate □ 5. Severe □ 6. Very severe

8. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

□ 1. Not at all □ 2. A little bit □ 3. Moderately □ 4. Quite a bit □ 5. Extremely

9. These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the **past 4 week** …

	1. All of the time	2. Most of the time	3. A good bit of the time	4. Some of the time	5. A little of the time	6. None of the time
a) Did you feel full of pep?	□	□	□	□	□	□
b) Have you been a very nervous person?	□	□	□	□	□	□
c) Have you felt so down in the dumps that nothing could cheer you up?	□	□	□	□	□	□
d) Have you felt calm and peaceful?	□	□	□	□	□	□
e) Did you have a lot of energy?	□	□	□	□	□	□
f) Have you felt downhearted and blue?	□	□	□	□	□	□
g) Do you feel worn out?	□	□	□	□	□	□
h) Have you been a happy person?	□	□	□	□	□	□
i) Did you feel tired?	□	□	□	□	□	□

10. During the **past 4 weeks**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

□ 1. All of the time

□ 2. Most of the time.

□ 3. Some of the time

□ 4. A little of the time.

□ 5. None of the time.

11. How TRUE or FALSE is **each** of the following statements for you?

	1. Definitely true	2. Mostly true	3. Don't know	4. Mostly false	5. Definitely false
a) I seem to get sick a little easier than other people?	□	□	□	□	□
b) I am as healthy as anybody I know?	□	□	□	□	□
c) I expect my health to get worse?	□	□	□	□	□
d) My health is excellent?	□	□	□	□	□

EuroQol-5D-3L Health Questionnaire

Please tick which statements best describe your own health state today.

1A. Mobility

I have no problems in walking about □

I have some problems in walking about □

I am confined to bed □

1B. Self-Care

I have no problems with self-care □

I have some problems washing or dressing myself □

I am unable to wash or dress myself □

1C. Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities □

I have some problems with performing my usual activities □

I am unable to perform my usual activities □

1D. Pain/Discomfort

I have no pain or discomfort □

I have moderate pain or discomfort □

I have extreme pain or discomfort □

1E. Anxiety/Depression

I am not anxious or depressed □

I am moderately anxious or depressed □

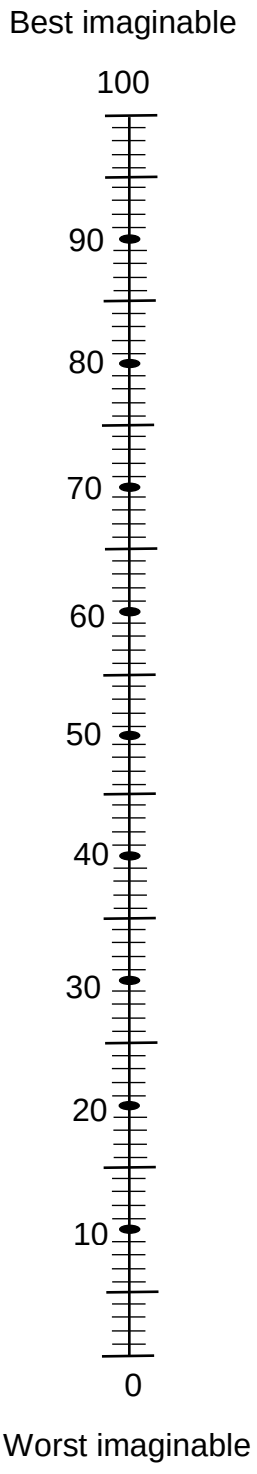
I am extremely anxious or depressed □

EQ5D Visual Score

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Definitions of outcome measures

Outcome	Definition
Death	Death from any cause Classified as cardiovascular or non-cardiovascular
Myocardial Infarction*	Defined as below
Type 1	Spontaneous myocardial infarction related to ischaemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection
Type 2	Myocardial infarction secondary to ischaemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anaemia, arrhythmias, hypertension, or hypotension
Type 3	Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischaemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood
Type 4a	Myocardial infarction associated with PCI
Type 4b	Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy
Type 5	Myocardial infarction associated with CABG
Revascularisation	PCI to lesions not identified previously. CABG for new symptoms or complications of PCI Target lesion or target vessel revascularisation
Target Lesion Revascularisation	Re-interventions inside the implanted stent or within 5 mm proximally or distally
Target Vessel Revascularisation	Re-interventions in the same vessel by PCI or by CABG
Stroke	Stroke is defined as the presence of a new focal neurologic deficit thought to be vascular in origin, with signs or symptoms lasting more than 24 hours. It is strongly recommended (but not required) that an imaging procedure such as CT scan or MRI be performed. Stroke will be further classified as ischaemic, haemorrhagic or type uncertain.
Heart Failure	Heart failure will be defined as a hospital admission with any of the following symptoms and signs: worsening breathlessness, fatigue, fluid overload, pulmonary oedema, elevated venous pressure and elevated Brain Natriuretic Peptide. Confirmation of heart failure according to local expert judgement and evidence of impaired left ventricular function will be required for the event to be classified as heart failure.
Rehospitalisation	Repeat hospitalisation for any reason during follow up period
Adverse Event	Any untoward medical occurrence
Serious Adverse Event	Any untoward medical occurrence that: Results in death and is life-threatening. The term "life-threatening" in the definition of "serious adverse event" refers to an event that 1. Requires hospitalisation or prolongation of existing inpatient's hospitalisation; 2. Results in persistent or significant disability or incapacity.

PCI-Percutaneous Coronary Intervention, CABG-Coronary Artery Bypass Graft, CT-Computerised Tomography, MRI-Magnetic Resonance Imaging

Outcome definition as per British Cardiovascular Intervention Society

** Adapted from Thygesan et al, Universal definition of myocardial infarction, European Heart Journal (2007) 28, 2525–2538*

Bleeding Academic Research Consortium (BARC) definition for bleeding

Type 0	No bleeding
Type 1	Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional. May include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional.
Type 2	Any overt, actionable sign of haemorrhage (e.g. more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for Type 3, 4 or 5 but does meet at least one of the following criteria: (1) requiring non-surgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation.
Type 3a	Overt bleeding plus haemoglobin drop of 3 to <5g/dl* (provided haemoglobin drop is due to bleed) Any transfusion with overt bleeding
Type 3b	Overt bleeding plus haemoglobin drop ≥5g/dl* (provided haemoglobin drop is due to bleed) Cardiac tamponade Bleeding requiring surgical intervention for control (excluding dental/ nasal/ skin/ haemorrhoid) Bleeding requiring intravenous vasoactive agents
Type 3c	Intracranial haemorrhage (does not include micro-bleeds or haemorrhagic transformation, does include intraspinal) Subcategories confirmed by autopsy or imaging or lumbar puncture Intraocular bleed compromising vision
Type 4:	CABG-related bleeding Perioperative intracranial bleeding within 48 hours Reoperation following closure of sternotomy for the purpose of controlling bleeding Transfusion of ≥5 units of whole blood or packed red blood cells within a 48-hour period† Chest tube output ≥ 2 litres within a 24-hour period If a CABG-related bleed is not adjudicated as at least a Type 3 severity event, it will be classified as 'not a bleeding event'.
Type 5a	Probable fatal bleeding; no autopsy or imaging confirmation, but clinically suspicious
Type 5b	Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

**Corrected for transfusion (1 U packed red blood cells or 1 U whole blood1 g/dL haemoglobin).*

†Cell saver products are not counted.

Adapted from Mehran et al, Standardized bleeding definitions for cardiovascular clinical trials: A consensus report from the bleeding academic research consortium Circulation. 2011;123:2736-2747

Standard Operating Procedures

Hand-grip Strength Test for Fried Frailty Assessment

Title: SOP for assessment of Handgrip Strength

Author: M Veerasamy

Responsibilities:

Research investigators trained in the method of handgrip strength assessment are responsible for proper assessment

Clear explanation of the procedure to the patients

Ensuring that the equipment used for the assessment is in optimal working condition

Equipment:

Electronic Hand Dynamometer and 2 x AAA batteries

Aim

The purpose of this test is to measure the maximum isometric strength of the hand and forearm muscles.

Procedure

Press ‘On/Set’ button on the front of the dynamometer

Then press ‘Start’ and it is ready to be used

The patient holds the dynamometer in the dominant hand to be tested, with the arm at right angles and the elbow by the side of the body.

The handle of the dynamometer is adjusted if required - the base should rest on first metacarpal (heel of palm), while the handle should rest on middle of four fingers.

When ready the subject squeezes the dynamometer with maximum isometric effort, which is maintained for about 5 seconds.

The subject should be strongly encouraged to give a maximum effort.

The strength is displayed on the LCD screen in kilogram

Record the finding in the study database

Pulse Wave Velocity and Pulse Wave Analysis

Title: SOP for recording of PWA, PWV and ABI

Author: M Veerasamy

Responsibilities:

Research investigators trained in the method are responsible for accurate measurement and recording of PWA, PWV and ABI using Vicorder from patients

Clear explanation of the procedure to the patients

Ensuring that all equipments used for the procedure are in optimal working condition

Equipments:

Vicorder console

3 pressure cuffs - Brachial, Thigh and Ankle

1 pressure cuff - Neck

2 colour coded (Blue and Red) pneumatic hoses

1 measuring tape

Toshiba Satellite Pro Laptop with Vicorder software installed

Carry bag for above

User manual

General Precautions:

Make sure all the connections are secure

When using cuffs the patients should be informed about the mild constriction when they are inflated

Cuffs should automatically deflate from the controls 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 calibration every six months as per instruction manual of its pressure channels to maintain its accuracy

There are no other special pre-warnings or contra-indications

Instructions for using the Vicorder

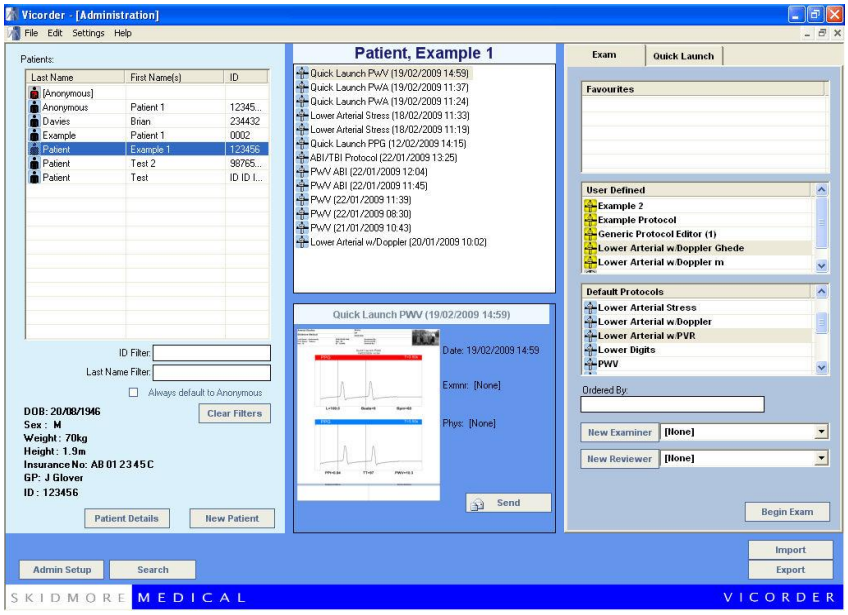
The investigators must read the accompanying instruction manual and familiarise themselves with the equipments. Step-by-step instructions for day-to-day use will be kept with each device.

Connecting the Vicorder:

1. Connect the USB Cable to the Laptop

2. Connect the 2 colour coded pneumatic hoses to Press1 and Press2 on the Vicorder front panel.

3. The Vicorder software may be activated by double clicking on the Vicorder icon in the Control Panel or by launching it from the Start menu which will open the administration page.



Navigation and setting

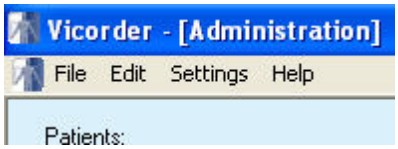
Navigate and set within the screens:

Screen buttons - To move left / right use the Laptop left / right arrow keys or the Vicorder left / right quadrant keys or the Laptop Function keys or the mouse pointer and left click.

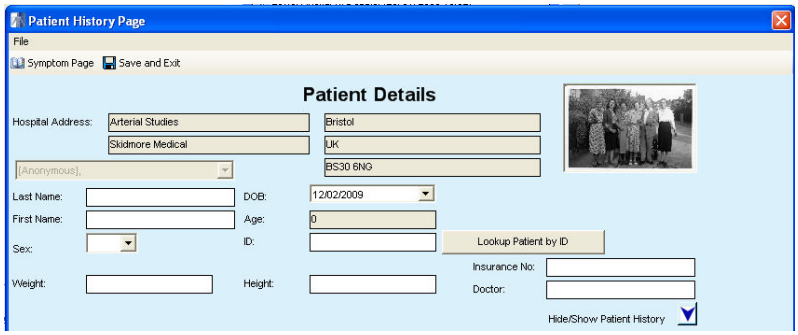
Settings - To change up / down use the Laptop up / down arrow keys or the Vicorder up / down quadrant keys or the left / right mouse keys.

New Patient entry screen

Click ‘File’ on the Vicorder administration page and click ‘New Patient’.



Enter Study ID, DOB, Sex, Height, Weight. No patient identifiable details are entered for confidentiality reasons.



Click ‘Save and Exit’

Patient Position

Patient to be comfortable and lying in supine position at with head and shoulders at about 30 degree angle – this will prevent venous signals affecting arterial signals

A pillow or a neck wedge can be used for this purpose

Positioning the pressure cuffs

Neck cuff is placed around the patient’s neck with pressure pad over right carotid area,

Arm cuff above the cubital fossa

Thigh cuff around the upper part of the thigh

Ankle cuff just above the ankle joints

Recording the measurements

Connect the blue pneumatic hose to the thigh cuff and the red pneumatic hose to the brachial cuff.

From the Quick Launch menu in the administration page click ‘OSC BP’.

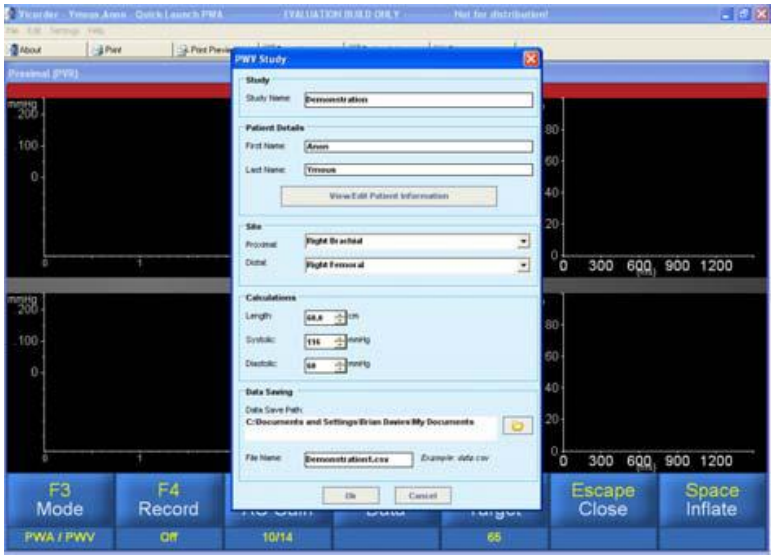
Click ‘Inflate’ and click ‘Save’ to store the systolic and diastolic blood pressure.

Press ‘Escape’ to go to the administration page.

Pulse Wave Analysis (PWA)

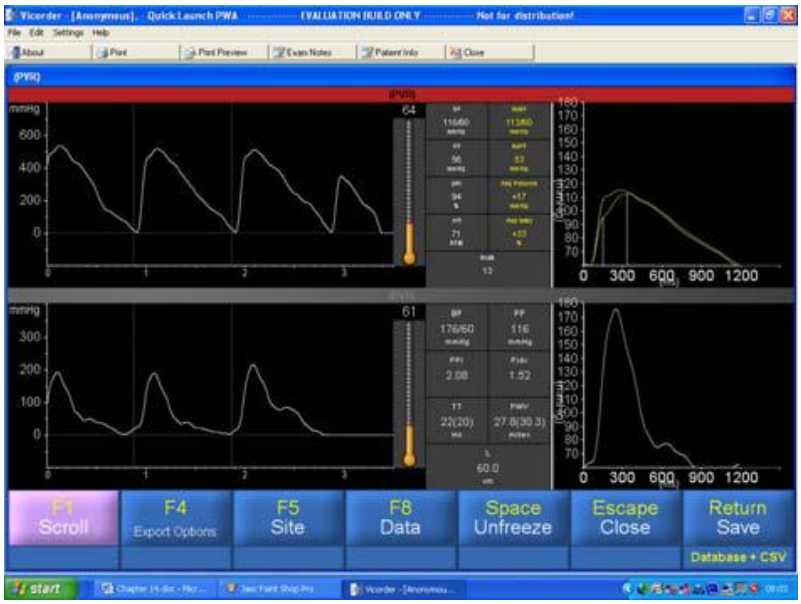
From the Quick launch menu click on ‘PWA’.

On the pop up PWV/PWA study screen enter length measured in cm between the top of the brachial and thigh cuffs. Also enter systolic, MAP and diastolic pressures. Click ‘OK’.



Then click ‘Multi-Chan’ which will show two traces on the screen one for the brachial and the other for the thigh cuff.

Click ‘Inflate’ and after acquiring steady pulses of data click ‘freeze’. Scrolling left or right allows selection of the trace.

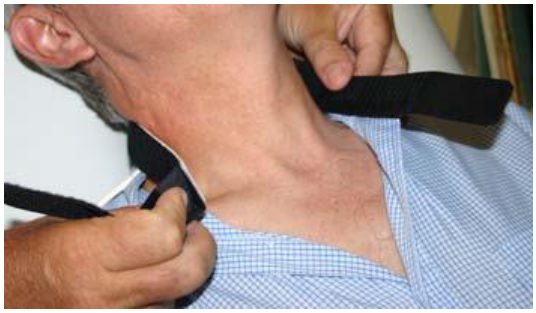


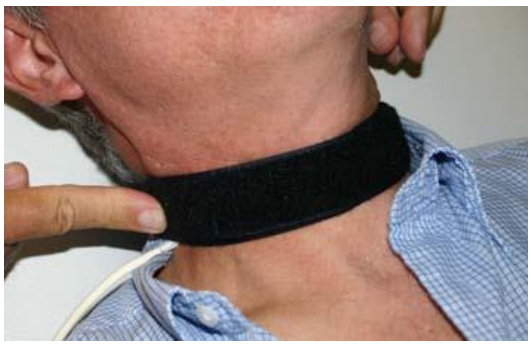
Calculated readings are stored by clicking ‘Save’.

Press ‘Escape’ to go to administration page.

Pulse Wave Velocity (PWV)

1. The neck pad is placed around the patient’s neck with the pressure pad over the right Carotid area and secured with the Velcro fixing, do not over-tighten and connect the red pneumatic hose to the neck cuff.





Measure the distance from the suprasternal notch to the top of the thigh cuff. From the Quick Launch menu select PWV and on the pop up window enter the measured length in cm. Also enter systolic, MAP and Diastolic pressures. Click ‘OK’.

In PWV mode the display is always Dual channel. After acquiring several steady pulses of data pressing the space bar will freeze the display, the Pulse Wave Velocity in metres per second and the Transit Time in milliseconds will then be displayed. Then click ‘Save’

Ankle Brachial Pressure Index (ABI)

Connect the red pneumatic hose to brachial cuff and the blue pneumatic hose to ankle cuff.

From the quick launch menu select ‘ABI’. Press ‘Inflate’. After acquiring several steady pulses of data pressing the space bar will freeze the display and calculated ABI is shown. Click ‘Save’ to store.

At the end of the procedure

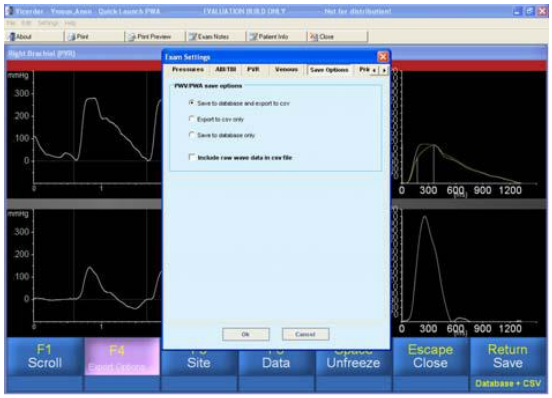
After completing the study press ‘File’ and select ‘Exit Vicorder’

Remove the cuffs and pack all equipment.

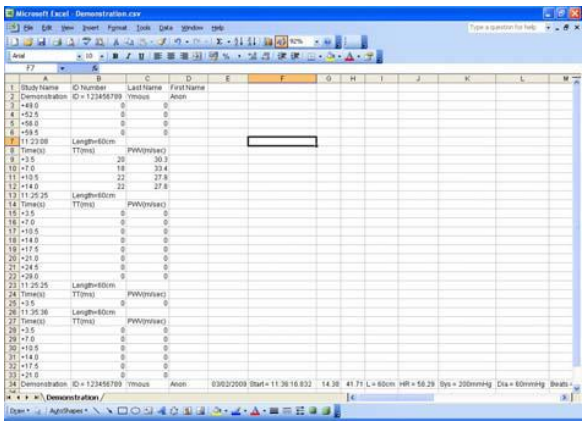
Thank the patient

Exporting data into spreadsheet

All the saved measurements are uploaded by default into the Vicorder excel spreadsheet in addition to being stored in the Vicorder patient list



Spreadsheet to be backed up periodically.



Peripheral Arterial Tonometry

Author: M Veerasamy

Responsibilities:

Research investigators trained in the method are responsible for

accurate measurement and recording of Endothelial Function using EndoPAT 2000
Clear explanation of the procedure to the patients

Ensuring that all equipments used for the procedure are in optimal working condition

Equipments:

One Endo-PAT2000 device

Two pneumo-electric tubing

Power adapter

Power cable

Foam finger anchors

Toshiba Satellite Pro Laptop with EndoPAT software installed

Carry Bag

A set of two PAT probes

Blood pressure cuff (capable of sustaining high pressures for 5 minutes)

Adhesive tape

Pair of arm supports

Equipments needed for EndoPAT were stored in a locked cupboard in a room in ward 27.

Connecting the Endo-PAT2000 to the Computer

Place the Endo-PAT2000 and computer in close proximity to the examination bed or chair. The device should be placed at a distance from the bed or chair that is shorter than the pneumo-electric tubing (less than 1.8 meters/ 6 feet).

Plug in the adapter to your USB port

Connect the MOXA Adapter to the COM TO COM cable and tightly screw the bolts.

Connect the COM TO COM cable to the ENDO device and tightly screw the bolts.

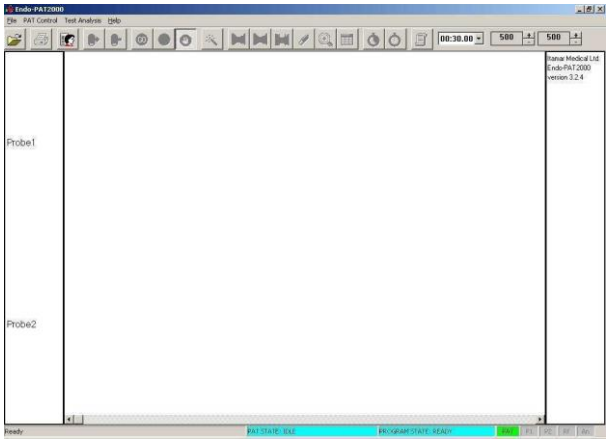
Connect both pneumo-electric tubing to the Endo-PAT2000 front panel pneumoelectric connectors and secure by hand tightening the screws

Make sure the power switch is off. Connect the power supply first to the Endo-PAT2000 and then to an electrical outlet. Turn the power switch on.

The power indicator light will glow orange, indicating that the power is turned on.

Main Screen

From the Windows desktop double click EndoPAT icon. The following screen will appear



Prepare the Patient for an Endo-PAT Study

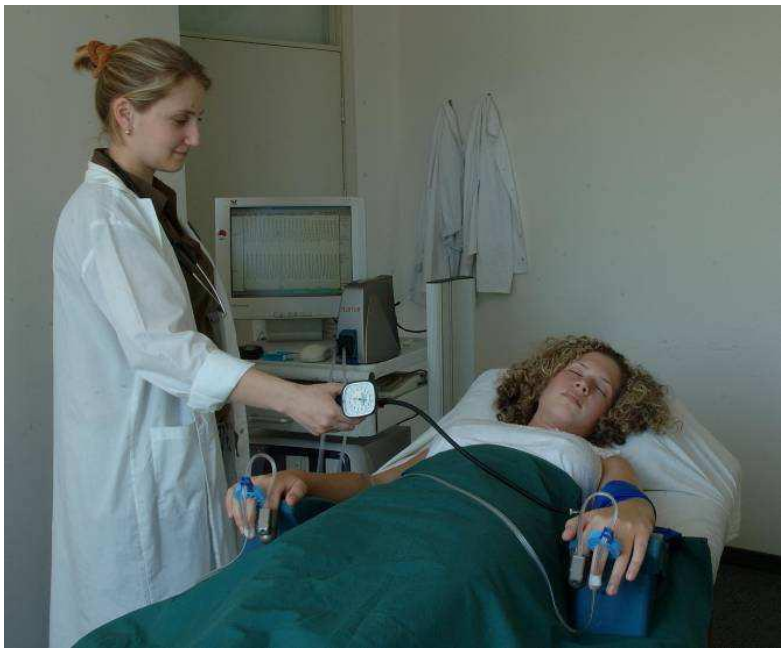
Prior to the study, ensure the patient has fasted for at least 4 hours, and has refrained for at least 8 hours from caffeine, tobacco, vitamins or medications that might affect vascular tone. The patient may wish to use the restroom prior to the study.

The Endo-PAT study should be conducted in a quiet, dimly lit, temperature-controlled exam room to reduce fluctuations in vascular tone. Thermoneutral room temperature must be maintained at all times: 21ºC-24ºC

Cell phones or paging devices should be silenced, and restrictive clothing that could interfere with blood flow to the arms should be removed. The patient should also remove watches, rings, or other jewellery on the hands or fingers.

Inspect the patient's fingers for any deformities or injuries that could affect the study. Do not place the probes on a finger that is cut or injured. Fingernails should not extend more than 5mm or 1/5 of an inch beyond the tip of the finger tissue. Trim or file fingernails if necessary to avoid damaging the internal membranes of the PAT probes and displacing the finger from the sensing region of the probe.5. The index finger is recommended for the study; however, if this finger is unsuitable, a different digit (except the thumb) may be used, as long as the same finger is used on both hands.

The patient should be supine and comfortable for 15 minutes so as to attain a cardiovascular steady-state. Place the two arm supporters along each of the patient's sides.



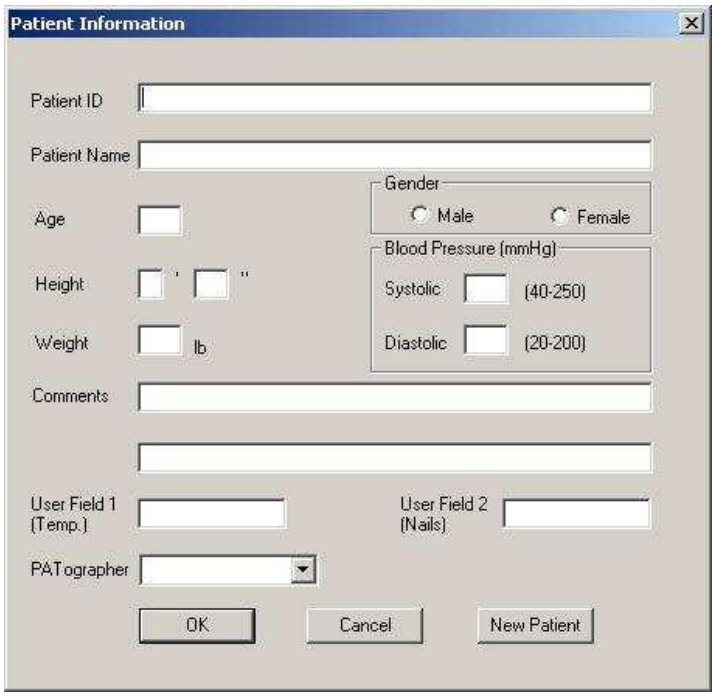
Measure the blood pressure using the control arm (the arm that is not occluded during the Endo-PAT study.

Place a blood pressure cuff on the arm to be occluded during the Endo-PAT study. Apply the cuff snugly, but without excess pressure. Do not inflate the cuff at this time.

Prepare the Endo-PAT System for Study

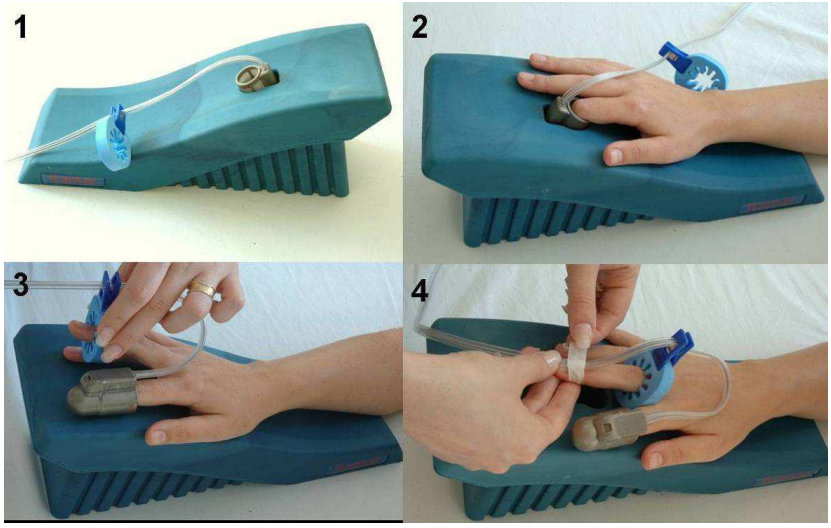
Launch the Endo-PAT 2000 software and click the "Patient Information" icon on the tool bar to create a new patient file.

Complete the Patient Information dialog box, including patient ID, name (optional), age, gender, height, weight, systolic and diastolic blood pressures. Optional fields allow for free text comments. Select your name from the pre-defined list in the Patographer name field.



Select two new PAT probes and connect to the pneumo-electrical tubing. To connect the probes, insert the connector tab into the probe slit and gently press the connector onto the probe until it clicks into place.

Probe and Finger Positions



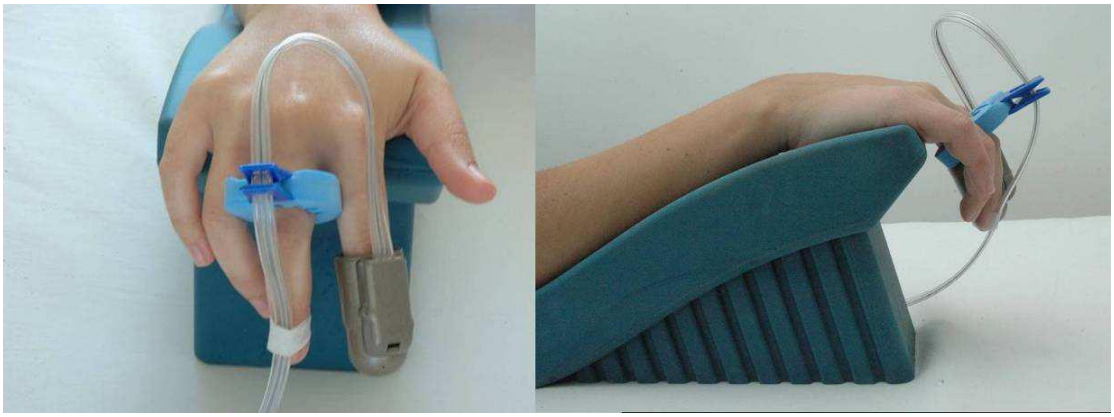
Place the connected probes into the sockets of the arm-supports and press the "Deflate" button on the top of the Endo-PAT 2000 device.

Place the patient’s index fingers completely into the probes, confirm with the patient that he or she can feel the very end of the probes, and press the "Inflate" button on the top of the Endo-PAT 2000 device.

Place a foam anchor ring at the base of the adjacent middle finger. Ensure that the foam ring and the PAT sensor do not touch. Otherwise the ring may mechanically interfere with the sensor.

Create an approximately 7-10cm loop with the pneumo-electrical tubing. The loop should extend from the PAT sensor and return to the foam ring on the adjacent finger while the rest of the tubing that connects to the EndoPAT device is pointing out tubing to the tip of the finger.

Hands setup

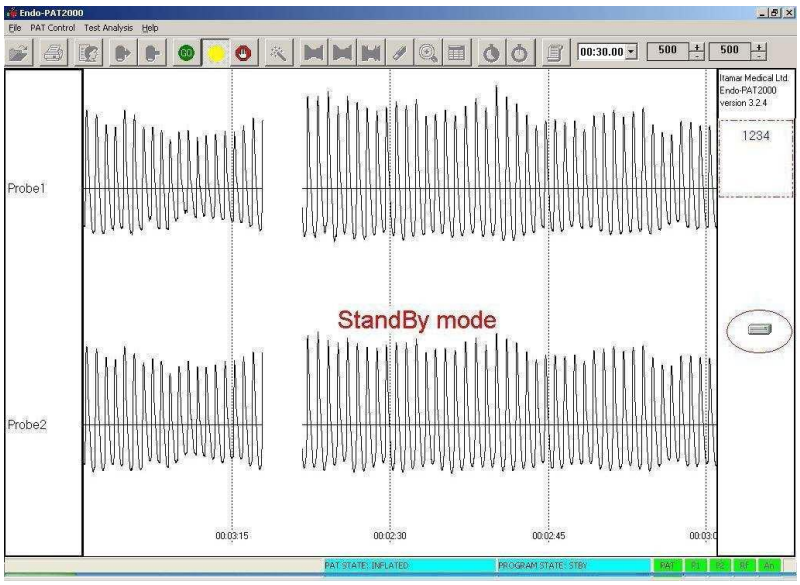


Position the patient's arms so the forearms are supported on the arm supports and the fingers dangle freely off the edge of the support. Make sure the probes are not in contact with any object, including the arm support, foam ring, tubing, the mattress or another finger.

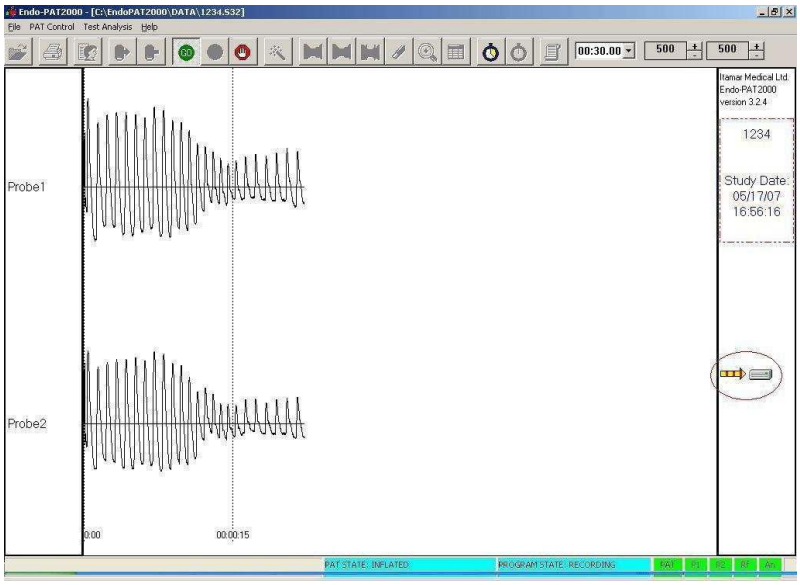
Ask the patient to refrain from moving the fingers, as this will create mechanical artefact. It is important for the patient to be relaxed throughout the study. Explain to the patient that during the test you will inflate the arm cuff, and during that time they may feel some discomfort, numbness, or tingling.

Performing the Study

Click the "Standby" icon  on the Endo-PAT's computer interface. Adjust the time base to 1 minute and adjust the signal gain on the screen to maximize signal clarity. Inspect the tracings of the PAT signals from the two probes to confirm that they are free of artifactual signals. If artifactual signals are present, verify that the probes are not touching anything and that the patient is not moving the fingers.



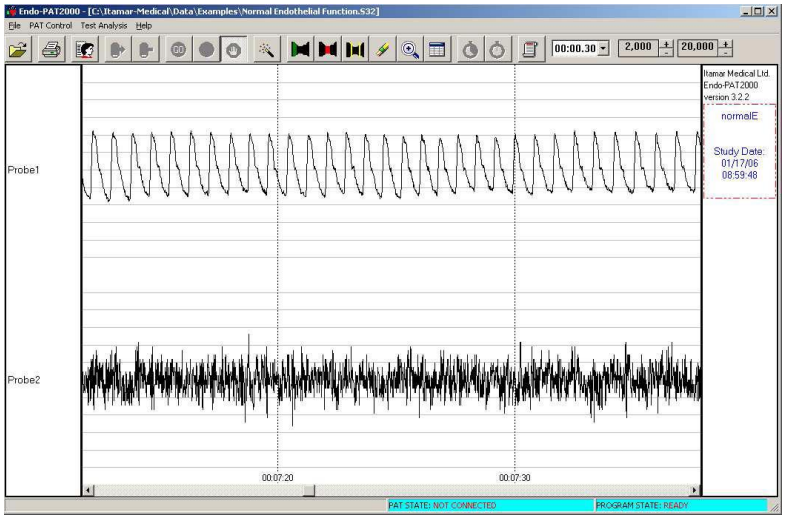
To begin the study, click the "Go" icon  on the computer interface. Start the stopwatch, by clicking the "Start/Stop Timer" icon. This will initiate a five minute count down for the baseline recording period. After five minutes, stop the stopwatch by clicking the "Start/Stop Timer" icon.



Tell the patient that you are going to inflate the cuff for the occlusion phase and that he or she should stay relaxed and not move the fingers.

Rapidly inflate the blood pressure cuff to a supra-systolic pressure of 60mmHg above the patient's systolic pressure or 200mmHg, whichever is higher and start the stopwatch again. Complete cessation of blood flow to the hand is verified by the

absence of a PAT signal from the occluded arm. To confirm occlusion increase the gain on the screen of the channel of the occluded side to 20,000 while keeping the gain of the contra-lateral side constant. Decrease the time base of both channels to 30 seconds. Verify that you do not observe any signals at a periodicity that matches the signal from the control arm as this indicates an incomplete occlusion. If this is the case then further inflate the cuff until no signals are seen. The cuff may be inflated to a maximum of 300mmHg.



This will initiate a five minute count down for the arterial occlusion recording period. Toward the end of the occlusion period tell the patient you are going to release the cuff and that they should continue to refrain from moving their fingers. After exactly five minutes, deflate the cuff abruptly as quickly as possible and stop the stopwatch by clicking the "Start/Stop Timer" icon  .

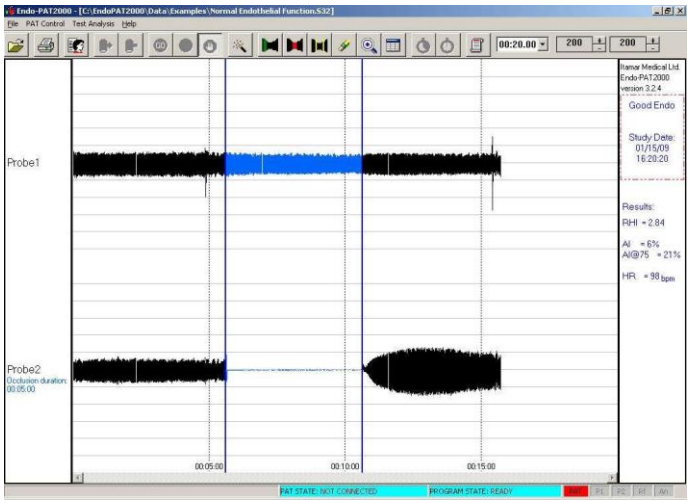
Click the "Start/Stop Timer" icon  again to initiate a five-minute post occlusion recording period. Stop the timer after five minutes and click the

"Test Stop" icon  to complete the study. The probes will automatically deflate.

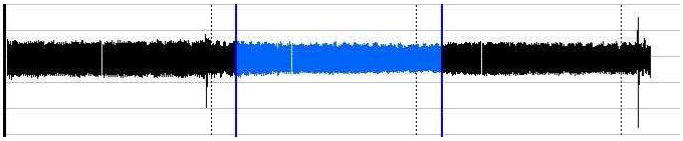
Remove the probes, tape, and foam rings from the patient's fingers and disconnect the PAT probes from the pneumo-electrical tubing. Discard the used probes.

Review and Analysis

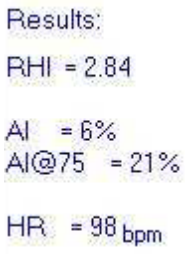
Click the Icon  , or select Automatic Analysis from the Test Analysis menu. In the Endo-PAT2000 main screen, the test result's value appears in the right column



The occlusion period will be highlighted in blue



The test result will be displayed, including the Reactive Hyperaemia Index (RHI) and Heart Rate (HR), in the right-hand column of the screen as below.

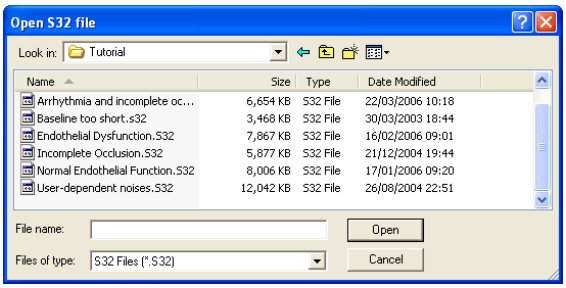


To review the results of the study, click the icon  . The table lists relevant study parameters and results, for all analyses performed to date, with the last line in the table containing data from the most recent analysis performed.

To review the study report select the “View report” option in the Test Analysis pull down menu or click the icon  . The report will be exported to a picture viewer (it will take a few seconds). This report can be printed or exported to other formats (i.e. PDF).

Study Data Retrieval

From the toolbar click the icon  or select Open File from the menu bar. The following dialog box appears:



Select the desired file from the list (note that the file name is the same ID number used when entering the patient’s information) and click Open.

Carotid Intima Media Thickness

Title: SOP for CIMT measurement

Author: M Veerasamy

Responsibilities:

Trained research investigators are responsible for performing CIMT measurement by using Vivid-I

Clear explanation of the procedure to the patients

Ensuring that all equipments used for the procedure are in optimal working condition

Equipment:

Vivid-I (GE)

12L-RS phased array probe

Power adapter unit and cord

3 ECG leads – red, green and black

Hospital bed or couch with recliner facility for patient positioning

Skintact Ultrasonic Gel

Carry bag

Connections

Connect the AC power adaptor output plug into the appropriate socket on the rear of the Vivid I

Ensure that the wall outlet is of appropriate type

Secure the power plug in the wall outlet

Connect the probe to the appropriate socket and make sure it is locked

Connect the ECG cable

Instructions for Using Vivid-I

The investigator must read the accompanying manual and familiarise themselves with the equipment.

Beginning an exam consists of three steps:

• Creating a new patient record

• Selecting Probe and Application

• Start scanning

Entering a new Patient

Press ‘On/Off’ key on top right of the control panel to turn the machine on.

Press ‘Patient’ key which will bring the patient list screen.

Press ‘Create New Patient’

Enter Patient’s details – Study ID and DoB

Press ‘Create Patient’ to store details

Selecting the vascular probe

Press ‘Application’ on the control panel

A list of the connected probes will pop up

Make sure 12L-RS probe is selected.

Patient positioning

Patient to be lying down in supine position comfortably with pillow below the head

The head is rotated by 45 degree to the left or right according to the side of examination

Both neck regions need to be fully exposed

Inform the patient about slight discomfort when the probe is placed on the neck

Acquiring Images

The side of examination to be marked on the image by using ‘Txt’ key on the control panel

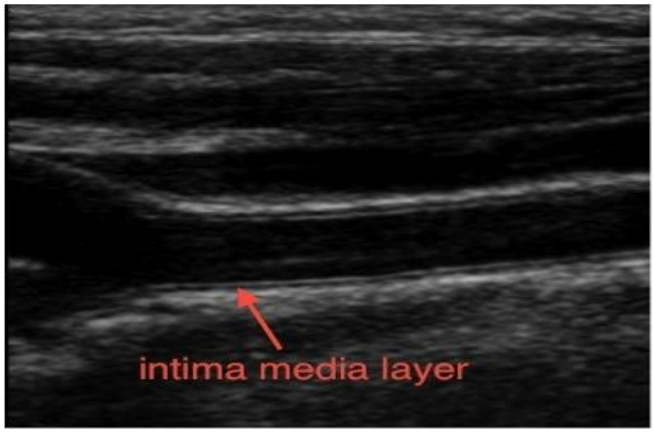
Use gel on the probe and start acquiring images

A longitudinal image of carotid artery to be obtained as per CIMT imaging protocol

Optimise the image by using depth and focus settings

Press ‘Freeze’

Scroll to end-diastolic frame when the intima layer is clearly visible



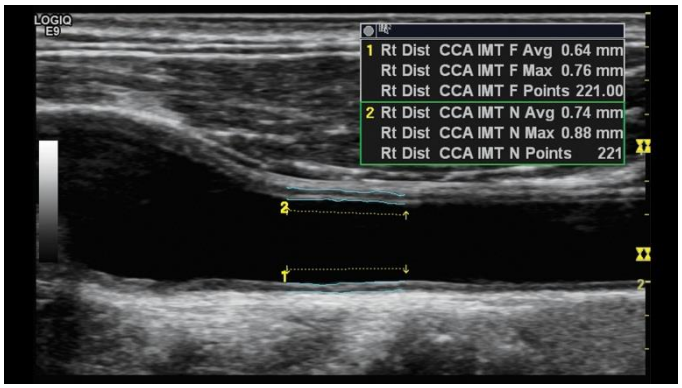
Press ‘Measure’, select ‘Vascular’ and select ‘IMT’

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 endpoint of the search region. Make sure the intima and media are within 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 on top of the screen



Images are stored by pressing ‘Store’

Complete the exam by clicking ‘End Exam’

Provide tissue for the patient to wipe off the gel

Disconnect the probe, clean and pack the equipment in the carry bag

Copy the images into CD-R

Measurements to be entered on to the database

Title: SOP for Transthoracic Echocardiogram

Author: M Veerasamy

Responsibilities:

Trained research investigators are responsible for performing transthoracic echocardiogram by using Vivid-I

Clear explanation of the procedure to the patients

Ensuring that all equipment used for the procedure are in optimal working condition

Equipment:

Vivid-I (GE)

3S-RS phased array probe

Power adapter unit and cord

3 ECG leads – red, green and black

Hospital bed or couch with recliner facility for patient positioning

Skintact Ultrasonic Gel

Connections

Connect the AC power adaptor output plug into the appropriate socket on the rear of the Vivid I

Ensure that the wall outlet is of appropriate type

Secure the power plug in the wall outlet

Connect the probe to the appropriate socket and make sure it is locked

Connect the ECG cable

Instructions for Using Vivid-I

The investigator must read the accompanying manual and familiarise themselves with the equipment.

Patient positioning

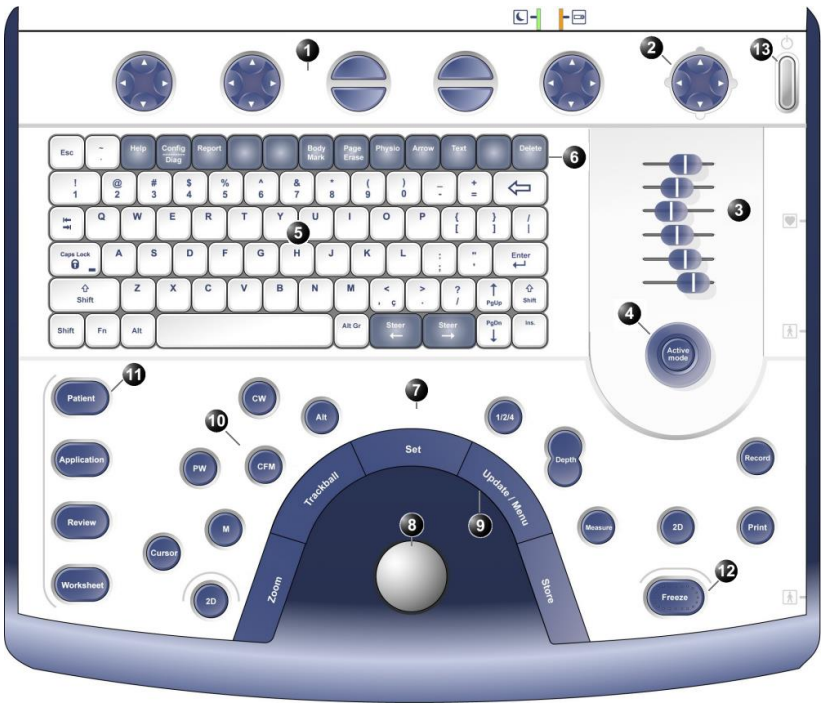
Patient to be lying down on the bed or couch in left lateral decubitus position with head end reclined at around 45 degrees.

Make sure the patient is comfortable, if not perform the scan in a comfortable position for the patient and make a record of the position

Patient has to undress down to umbilicus level

Place three ECG stickers and connect them with respective leads (Red to right shoulder, Yellow to left shoulder and Black to right flank)

Control Panel



1. Assignable keys (soft-menu elements; part of the Extended keyboard)
2. Soft menu rocker
3. TGC sliders
4. GAIN rotary
5. Alphanumeric keyboard
8. Trackball
9. Trackball buttons
10. Mode selection keys
11. Navigation keys
12. Freeze keys
13. On/Off button

6. Alphanumeric function keys: (*Help, Config…)*

7. Extended keyboard

Starting an examination

Beginning an exam consists of three steps:

Creating a new patient record

Selecting Probe and Application

Start scanning

Entering a new Patient

Press ‘On/Off’ key on top right of the control panel to turn on the machine

Press ‘Patient’ key which will bring the patient list screen

Press ‘Create New Patient’

Enter Patient’s details – Study ID and Date of Birth

Press ‘Create Patient’ to store details

Selecting the cardiac probe

Press ‘Application’ on the control panel. A list of the connected probes will pop up.

Make sure 3S-RS probe is selected.

Acquiring Images

Make sure a good ECG tracing is available in the bottom of the screen. If not press ‘Physio’ and adjust gain.

Place ultrasonic gel on the probe and start acquiring images

Images are to be acquired as per the minimum dataset for a standard Transthoracic Echocardiogram from the British Society of Echocardiography education committee.

Images in this SOP are for illustration purposes only

To store a cineloop

While in scanning mode, press the ‘Store’ button to store the last heart-cycle loop

Cineloops may be stored directly or after preview, depending on how the system is configured

While in cine-loop preview mode press ‘Store’ to store the selected loop.

To store a single image

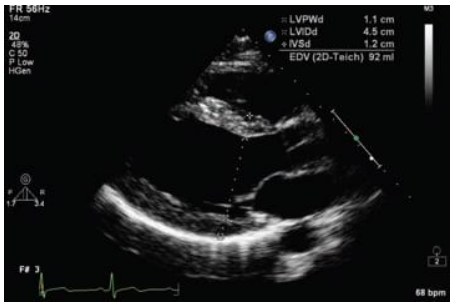
Press ‘Freeze’

Press ‘Store’ to store the image digitally

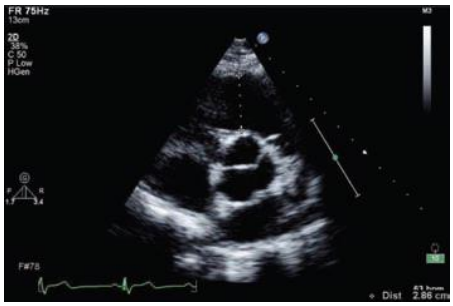
The thumbnail of the image is displayed on the clipboard

Views:

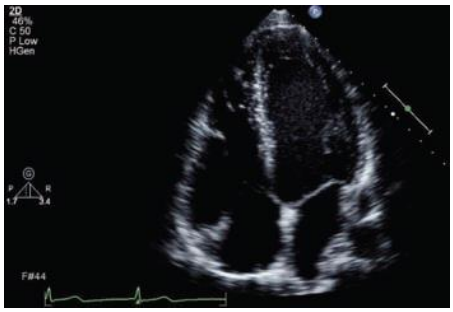
PLAX parasternal long axis



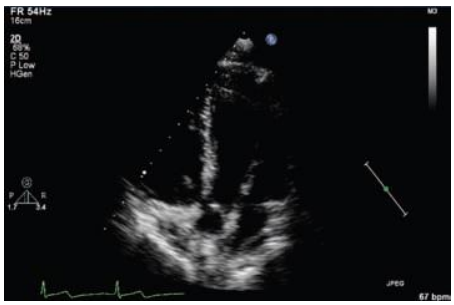
PSAX parasternal short axis



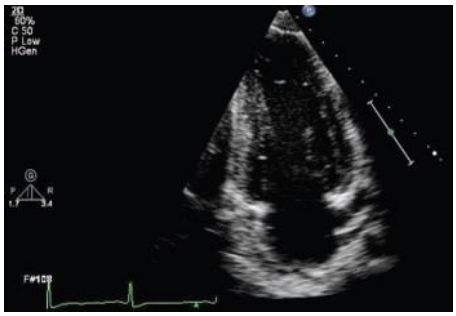
A4C apical four chamber



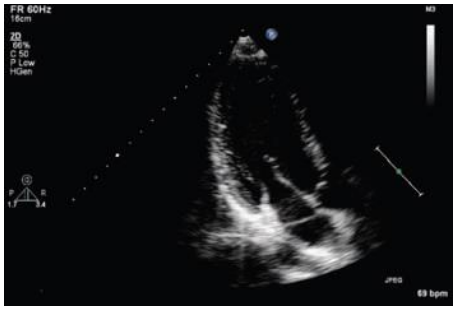
A5C apical five chamber



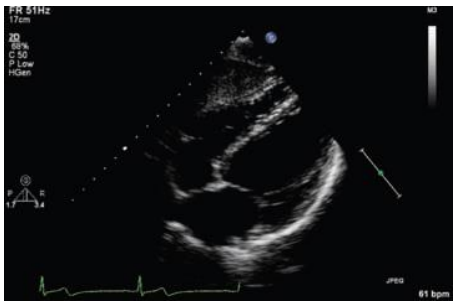
A2C apical two chamber



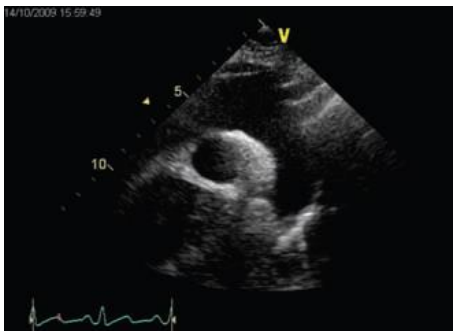
ALAX apical long axis or apical three chamber



SC sub costal

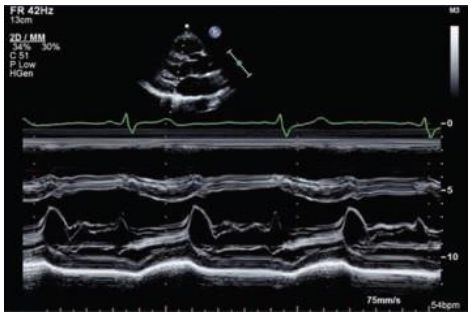


SSN suprasternal

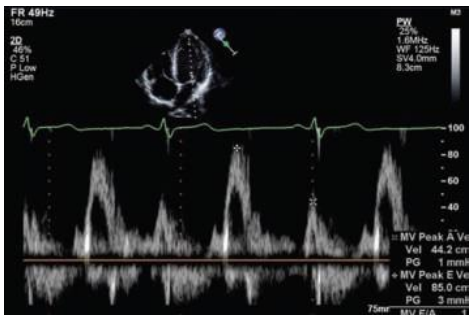


Modality:

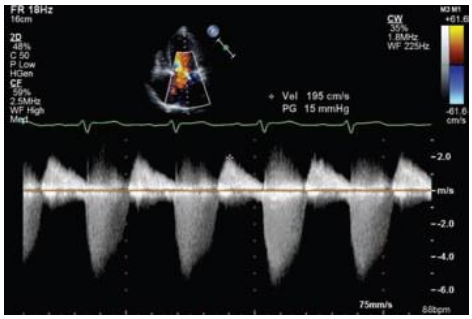
M mode Doppler



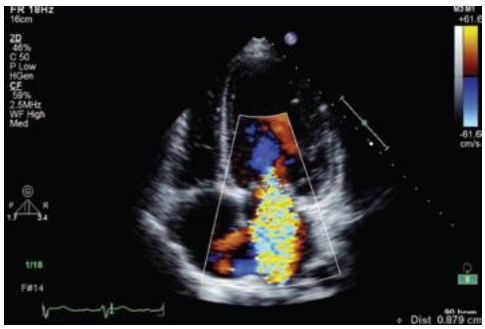
PW pulse wave Doppler



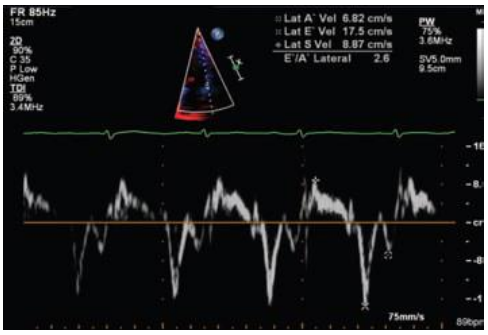
CW continuous wave Doppler



CFM colour Doppler



TDI tissue Doppler imaging



At the end of the Examination

Press ‘End Exam’

Provide tissues for the patient to wipe off the gel

Clean the probe and ECG leads

Disconnect the probe and ECG leads

Store them in the carry bag

Images will be analysed offline and report generated as per BSE protocol

Archiving and exporting data in to database

Insert removable media in the drive (CD-R)

Press ‘PATIENT’ on the control panel and then select ‘Patient List’

Select the source archive in dataflow field: Local Archive-Int.HD

Press ‘Export’, and then select ‘CD/DVD Archive’ as destination

Press OK, a window will appear: Current media is not formatted. Do you want to format it? Select Yes.

Select the examination from ‘Patient List’ that you want to export

Press ‘Copy’ and then OK to resume export. And finally press ‘Done’ in the Export patient window to complete the process

Press Alt+E to eject the CD

The CD will be filed as part of the study documents.