Title: Echocardiographic assessment of cardiac function in patients with atrial fibrillation

UNIVERSITY OF BIRMINGHAM

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Abstract

Echocardiography plays an essential role in the management of patients with atrial fibrillation (AF) and the diagnosis of heart failure in these patients. Assessment of systolic and diastolic function is challenging in AF due to the irregular RR interval, resulting in variability from beat to beat. In this thesis, I have compared the reproducibility and validity of an index beat approach (similar RR intervals for the two prior beats before measurement) versus conventional averaging of three, five and ten consecutive beats in patients with permanent AF and symptoms of heart failure.

Transthoracic echocardiography was performed at baseline in 160 patients enrolled in the RAte control Therapy Evaluation in permanent AF randomised controlled trial (NCT02391337). Measurements of Simpson's biplane left ventricular ejection fraction (LVEF), global longitudinal strain (GLS) and the diastolic parameter E/e' were obtained using three index beats and 3, 5 and 10 consecutive beats. All measurements were analysed offline with the analyser blinded to clinical details and with no pre-exclusions to image quality.

The index beat method was shown to have a significantly lower within beat variability compared to consecutive beats and a single index beat measuring GLS and E/e' was more reproducible or equally reproducible to averaging 10 consecutive beats when assessing intra and inter-operator reproducibility. Using a single index beat did not impact on the validity of LVEF, GLS or E/e' when correlated with natriuretic peptides and substantially shortened the time taken for measurement of E/e' (64% quicker than assessing 10 consecutive beats).

This approach can enhance the reliability and efficiency of measurements for both systolic and diastolic left ventricular function in patients with AF.

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The research and preparation of this thesis would not have been possible without the help of several people. The research was conducted under the supervision of Dr Dipak Kotecha (Consultant cardiologist and clinician scientist) and Dr Richard Steeds (Consultant cardiologist and Honorary Senior Lecturer).

I am indebted to Dr Dipak Kotecha, for giving me the opportunity to undertake research under his guidance, and for his continued support and patience throughout my PhD. Not only has he supported me with my PhD but has provided me with opportunities for further research and has given me invaluable advice for a career as a clinical academic. I would also like to thank Dr Rick Steeds for his continued support, encouragement and invaluable wisdom throughout my PhD.

I would like to acknowledge the National Institute of Healthcare Research for supporting this research through the project grant (16/EM/0178) and the patients who enthusiastically took part and were a pleasure to work with. I would also like to thank the staff at the Wellcome Clinical Research Facility at the University Hospital Birmingham for their support and advice on running a clinical trial. I would also like to express my gratitude to Patience Domingos for her assistance throughout the trial and Dr Simrat Gill who helped with patient visits in the latter part of the trial.

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Finally, I would like to thank my parents for their consistent encouragement throughout my entire education and motivating me to reach my potential. Lastly, I would like to especially thank my Fiancé Bruce, for his overwhelming support and patience during my PhD.

Particularly during the pressures of recruitment and write-up of my thesis, he was there to encourage me to persevere and to reassure me when things did not go to plan with a large glass of chardonnay.

Statement of Contribution to Research

I screened all cardiology out-patient clinics and diagnostic referrals for potential subjects at University Hospital Birmingham between December 2016 and September 2018. The research nurse (Patience Domingos) based at City and Sandwell hospital, also assisted in the screening of potential subjects from City and Sandwell hospital and Heartland's hospital. I was responsible for recruiting and consenting all patients, for arranging and performing all study visits, reporting any serious adverse events and with the assistance of the research nurse for performing all study visit procedures as stated in the protocol with the exception of procedures and decisions related to medical management (performed by Dr Dipak Kotecha and Dr Simrat Gill).

I also maintained all the regulatory documents and was responsible for updating the site file with the ethics committee amendments and attending Data monitoring and Trial Steering committee meetings. I performed all echocardiography examinations and post-processing analysis. I analysed all data and performed statistical analyses with assistance from the statisticians Dr Samir Mehta and Dr Alice Sitch from the Birmingham Clinical Trials Unit. Blood tests throughout the study were performed by the research nurses from the Wellcome Clinical Research Facility and were analysed at University Hospital Birmingham. Specialist blood samples were processed by the Human Biomaterials Resource Centre at the University of Birmingham and analysis was carried out by Dannie Fobian (PhD student) at the Institute of Biomedical research, University of Birmingham.

The original research hypothesis, grant funding and ethics approval were obtained by Dr Dipak Kotecha, Prof Melanie Calvert, Prof Jonathon Deeks, Dr Michael Griffith, Prof Paulus Kirchhof, Prof Gregory YH Lip, Dr Samir Mehta, Gemma Slinn, Mary Stanbury, Dr Richard P Steeds and Prof Jonathon Townend.

Dr Dipak Kotecha, Dr Rick Steeds and Prof Paulus Kirchhof all provided assistance throughout the study with general advice, guidance and writing of manuscripts.

Abbreviations

2-D	Two-dimensional
3-D	Three-dimensional
AF	Atrial Fibrillation
AFEQT	Atrial Fibrillation Effect on QualiTy-of-life
ANP	Atrial natriuretic peptide
AoR	Aortic root
BCTU	Birmingham Clinical Trials Unit
BNP	Brain Naturetic Peptide
CAD	Coronary artery disease
CCT	Cardiac computed tomography
CHF	Congestive heart failure
CMR	Cardiac magnetic resonance
COPD	Chronic obstructive pulmonary disorder
CRF	Case report form
CVD	Cardiovascular disease
ECG	Electrocardiogarm
EDV	End diastolic volume
EHRA	European Heart Rhythm Association
ERNA	Equilibrium Radionuclide Angiocardiography
ESC	European society of cardiology
ESV	End systolic volume
FS	Fractional shortening
GFR	Glomerular filtration rate
GLS	Global longitudinal strain
HCM	Hypertrophic cardiomyopathy
HR	Hazard ratio
HFmrEF	Heart failure with mid-range ejection fraction
HFpEF	Heart failure with a preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
ICC	Intraclass correlation coefficient
ICD	Implantable cardioverter defibrillator
IVRT	Isovolumic relaxation time
LA	Left atrium
LV	Left ventricular
LVEDP	Left ventricular end-diastolic pressure
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy

LVM	Left ventricular mass
LVOT	Left ventricular outflow tract
MAC	Mitral annulus calcification
MAPSE	Mitral annular plane systolic excursion
MDC	Minimal detectable change
MPI	Myocardial performance index
MR	Mitral Regurgitation
MRI	Magnetic Resonance Imaging
MUGA	Multi-gated acquisition
NIHR	National Institute of Healthcare Research
NTproBNP	N-terminal B-type Natriuretic peptide
NYHA	New York Heart Association
OAC	Oral anticoagulant
PCS	Physical component score
PCWP	Pulmonary capillary wedge pressure
PET	Positron emission tomography
QoL	Quality of Life
RAAS	Renin-angiotensin-aldosterone system
RATE-AF	RAte control Therapy Evaluation in permanent Atrial Fibrillation
RWMA	Regional Wall Motion Abnormalities
SD	Standard deviation
SEM	Standard error of the mean
SPECT	Single photon positron emission tomography
SSFP	Steady-state free precession cine images
SV	Stroke volume
TAPSE	Tricuspid annular plane systolic excursion
TDI	Tissue Doppler Indices
TEE	Transoesophageal echocardiogram
TIA	Transient ischaemic attack
TR	Tricuspid Regurgitation
TTE	Transthoracic echocardiogram
Vp	Propogation velocity
VTI	Velocity time integral
VVI	Ventricular sensing-ventricular pacing- inhibitory response

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Chapter 1.

Introduction

1.1 Atrial Fibrillation, heart failure and concomitant disease

Atrial fibrillation (AF) is defined as a supraventricular tachyarrhythmia with disorganised atrial activation resulting in loss of effective atrial contraction.(1) It is characterised by a chaotic pattern of atrial activity which suppresses the sinus activity, resulting in irregular activation of the ventricle.(2) Diagnosis of AF requires an electrocardiogram (ECG), which shows irregular R to R intervals and no recognizable, distinct P waves.(3)

1.1.1 Epidemiology and Risk Factors

AF is the most common age related cardiac arrhythmia, with 1-2% of the world's population having been diagnosed with this condition.(4) The incidence of AF increases progressively as the population ages, with 10% of octogenarians suffering from AF.(5) The prevalence of AF has increased over recent years and it is likely to increase exponentially with an ageing population.(6, 7) AF not only increases the risk of mortality and morbidity, but also reduces quality of life and functional performance in these patients. Therefore, it is critical that correct management decisions can be made to improve prognosis of these patients.(8)

Multiple conditions can predispose a patient to AF. The list of causative factors is extensive including: increased age, male gender, hypertension, valvular heart disease, heart failure, coronary artery disease, congenital heart disease, obesity, pericardial fat, sleep apnoea, chronic kidney disease, alcohol consumption, smoking, diabetes, thyroid disorders, vigorous physical activity, infection, inflammation, and finally genetic factors.(4)

1.1.2 Pathophysiology

The pathophysiology of AF is complex and ultimately occurs when there are structural or electrophysiological abnormalities affecting the conduction pathways in the atria. AF is generated by rapidly firing foci usually originating from the pulmonary veins. The foci form the substrate of complex multi-circuit re-entry currents, which propagate as multiple wavelets around the atrial myocardium. Where there are areas of fibrosis, barriers are formed which slow conduction and help maintain the foci. Scarring can also damage the ion channels, resulting in increased potassium outward currents and reduced calcium inward currents. This change in membrane potential reduces the duration of the action potential and so refractory period, promoting the generation and maintenance of re-entry circuits. These changes implemented by the arrhythmia itself and structural remodelling negatively affect the heart by altering the haemodynamics, disrupting atrioventricular synchrony which results in a progressive decline in atrial and ventricular function.(4, 9)

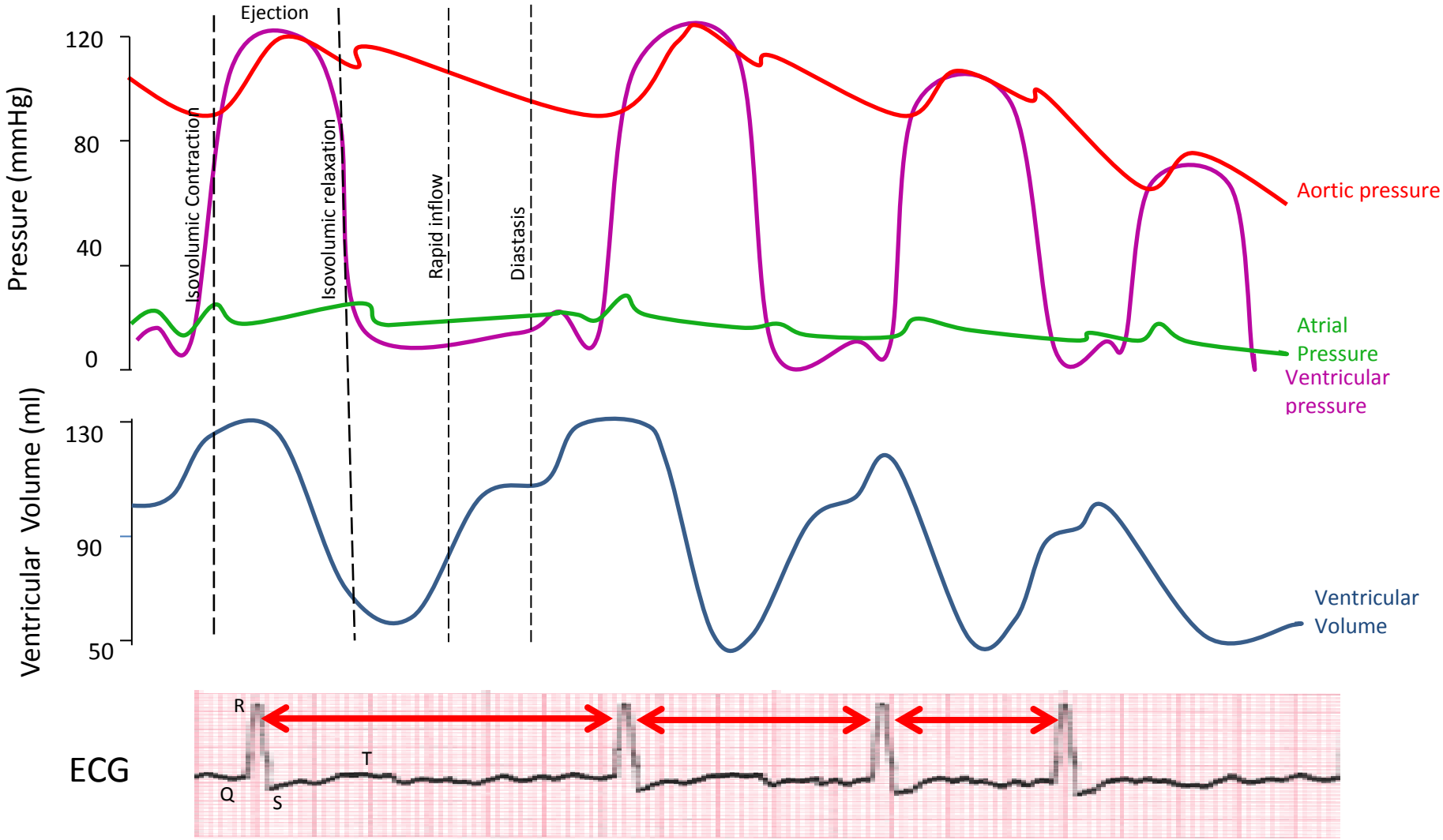
1.1.3 Effect of Atrial Fibrillation on the Cardiac Cycle

To understand the effect of atrial fibrillation on the cardiac cycle it is first important to understand the four key phases of the pressure-volume loop on the cardiac cycle. Phase I begins during diastole when the ventricle is relaxing and the valves are shut resulting in a ventricular pressure of 0 mmHg and volume ~45ml (this will vary according to body size). Meanwhile blood is returning via the systemic and pulmonary veins to the atria. The atria continue to fill, until the pressure in the atria exceeds that of the ventricles causing the mitral and tricuspid valve to open, initiating the process of ventricular filling. The ventricle will continue to fill until it reaches a volume of ~115ml (end diastolic volume) and the pressure would have risen to 5 mmHg (end diastolic pressure). At the end of atrial systole the atria

depolarise (represented as a P wave on the ECG), resulting in atrial contraction which causes a further increase in ventricular pressure. At this stage the ventricles are full and this triggers the start of Phase II, which is known as the isovolumic contraction phase. The ventricles depolarise (represented by the QRS wave on the ECG), which causes the ventricular myocardium to contract. As the ventricle contracts the ventricular pressure rises, causing the mitral and tricuspid valve to shut. The ventricle continues to contract, further increasing ventricular pressure. Phase III begins at the point in which the ventricular pressure exceeds that of the pressure in the aorta and pulmonary artery, causing the aortic and pulmonary valve to open. This is the ejection period in which the blood leaves the heart, to supply blood to the body and lungs via the aorta and pulmonary artery. The ventricular volume falls and the aortic and pulmonary valve close at which point phase IV begins. Phase IV is known as the period of isovolumic relaxation; the ventricle repolarizes (seen as the T wave on the ECG) resulting in ventricular relaxation. The pressure in the ventricle falls, meanwhile the atria continue to fill until their pressure exceeds that of the ventricles causing the mitral and tricuspid valve to open and so Phase I begins again.(10)

In AF there is no atrial contraction and so the filling of the ventricle relies entirely on passive filling from the atria (**Figure 1**). Following the Frank-Starling mechanism the greater the ventricular volume, the greater the myocardial stretch and so the greater the force of contraction, which results in a greater ejection fraction and so larger stroke volume. Therefore the length of the R to R interval significantly affects the end-diastolic volume, contractility and stroke volume. This means with short R to R intervals there is decreased filling time, causing a reduction in left ventricular (LV) systolic function due to reduced preload subsequently resulting in reduced LV contraction and so there is a reduced stroke volume.(11, 12)

Figure 1. Schematic diagram of the cardiac cycle in AF. The relationship of pressure and volume in the ventricle, aorta and atria in relation to the length of the R to R interval in AF.



1.1.4 Management of Atrial Fibrillation

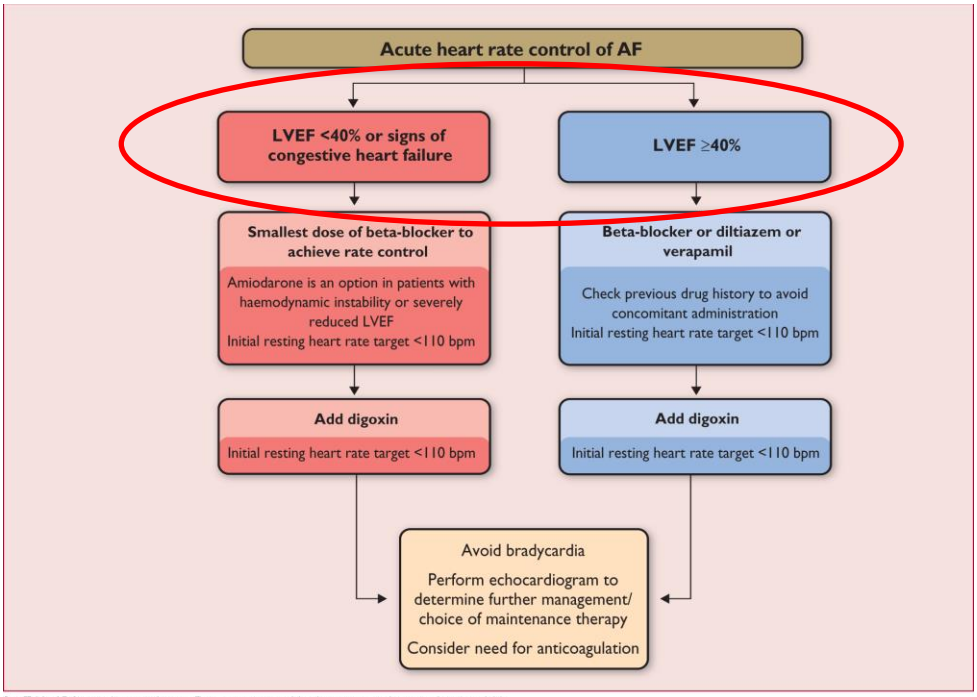
Atrial Fibrillation significantly increases mortality, hospitalisation and risk of cardiovascular events as well as reducing quality of life. The management of AF is strongly guided by the degree of ventricular function, which is most commonly assessed using echocardiography.(13) The risk of stroke is increased 5-fold in patients with AF and in those who do suffer strokes caused by AF, the consequences are more severe with increased risk of morbidity, mortality and poor functional outcome. The main cause of stroke is from thrombi originating from the left atrial appendage embolizing to the brain. The pathophysiology of AF forms perfect conditions for Virchow's triad for thrombus formation: dilated atria and loss of atrial contraction results in blood stasis, endothelial injury from the erratic fibrillating atrium and an increase in hemoconcentration from raised atrial natriuretic peptide (ANP) levels.(14)

Stroke risk in AF patients is calculated using the CHA_2DS_2-VAS_c score, which is determined according to age, gender and whether the patient has congestive heart failure, diabetes, hypertension, vascular disease or a history of a cerebrovascular event. The European Society of Cardiology (ESC) guidelines 2016 recommend the use of oral anticoagulants (OAC) in men with a score of 1 or more and in women with a score of 2 or more.(3) LV function assessment using echocardiography is an important determinant for the heart failure criterion, which is defined by the ESC guidelines 2016 as "Signs/symptoms of heart failure or objective evidence of reduced left-ventricular ejection fraction".(3)

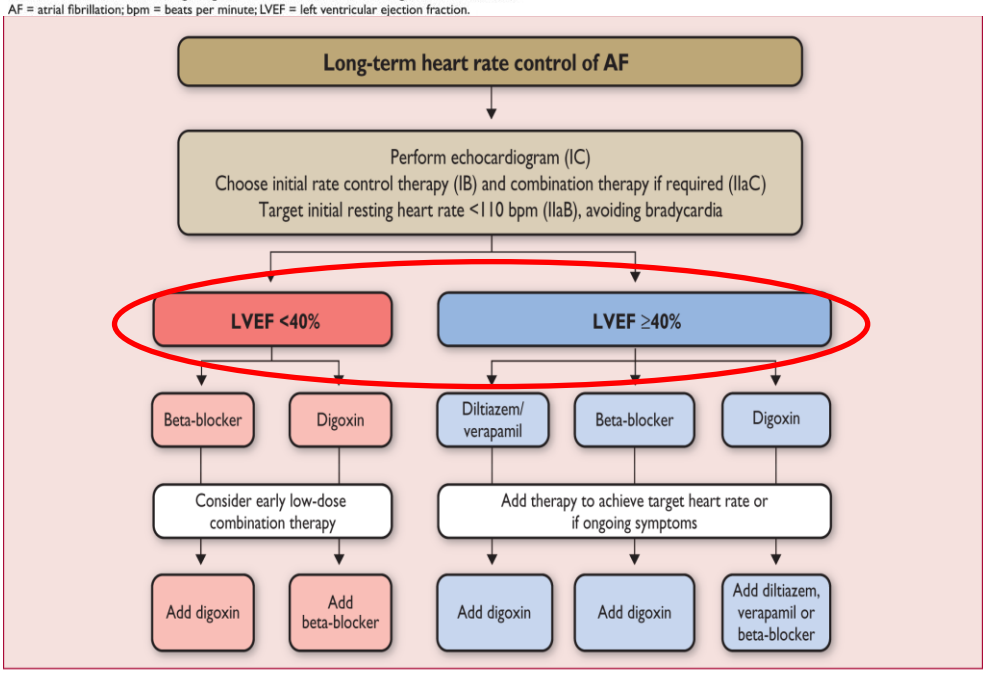
Rate control is recommended to improve symptoms and maintain haemodynamic stability. The choice of therapy will significantly depend on left ventricular ejection fraction. For acute rate control the heart rate should be aimed to get below 110 bpm. The choice of medication will depend on whether the LVEF (Left Ventricular Ejection Fraction) measured is ≥40% or <40%. For long-term rate control the aim is to achieve a heart rate <80 bpm at rest and <110

bpm during moderate exercise. Similarly to acute rate control the choice of medication is determined according to whether the patient has an LVEF ≥40% or <40% (see **Figure 2**).

Figure 2. The ESC guidelines on acute rate control according to LVEF (top) and long term rate control (bottom) (reproduced and adapted with permission from Kirchhof P. et al, 2016) (3)



See Table 15 for medication dosage. Digitoxin is a suitable alternative to digoxin, where available.
AF = atrial fibrillation; bpm = beats per minute; LVEF = left ventricular ejection fraction.

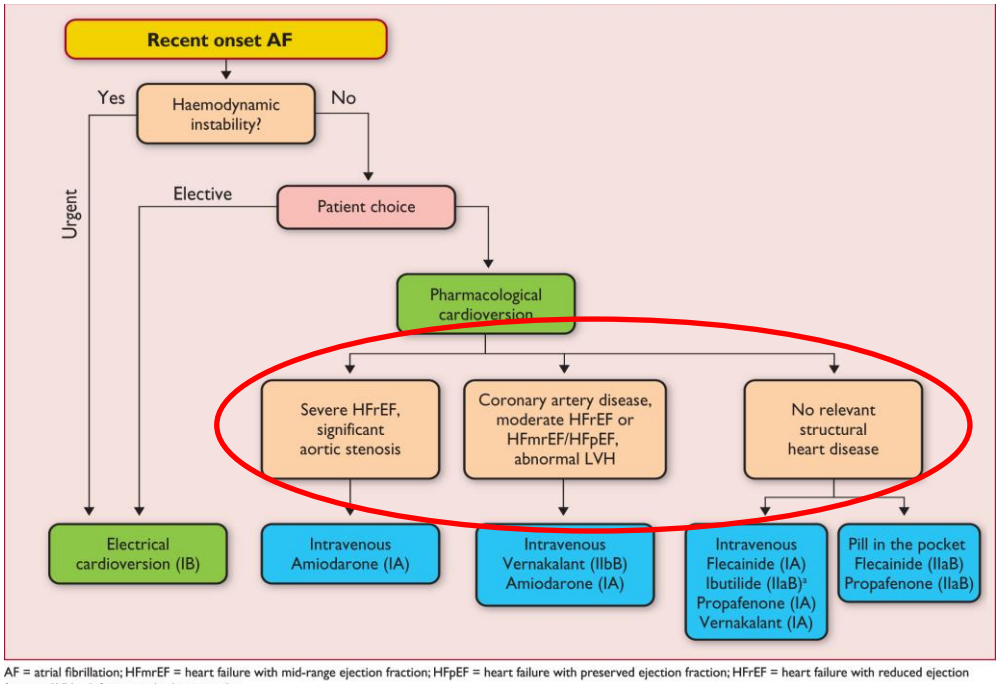


See Table 15 for medication dosage. Digitoxin is a suitable alternative to digoxin, where available.
AF = atrial fibrillation; bpm = beats per minute; LVEF = left ventricular ejection fraction.

If rate-control medication fails to control heart rate and symptoms the alternative is rhythm control or to ablate the atrio-ventricular node and implant a permanent ventricular sensing-ventricular pacing- inhibitory response (VVI) pacemaker. In the case of patients with reduced LVEF a biventricular pacemaker or implantable cardioverter defibrillator (ICD) may also be implanted depending on the patient's clinical background.(3)

Rhythm therapy is indicated in patients who despite being adequately rate controlled; still suffer from symptoms related to the AF. The choice of therapy depends on how long the patient has been in AF. In AF of recent onset urgent electrical cardioversion is recommended in those who are haemodynamically unstable, otherwise the choice between pharmacological cardioversion and electrical cardioversion is guided by the patient's choice. The choice of which pharmacological treatment to use is largely guided by the presence and severity of structural heart disease, which is often assessed by echocardiography; this particularly involves the challenge of classifying heart failure according to ejection fraction (see **Figure 3**).

Figure 3. ESC guidelines recommendations on rhythm control therapy (reproduced and adapted with permission from Kirchhof P.et al, 2016)(3)



AF = atrial fibrillation; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVH = left ventricular hypertrophy.
[a]Ibutilide should not be used in patients with long QT interval.

Catheter ablation is recommended as a second-line therapy to restore and maintain sinus rhythm in patients with symptomatic persistent, paroxysmal and long-standing persistent AF, in which pharmacological rhythm control, has either been ineffective or to which the patient has become intolerant.(3)

1.2 Atrial Fibrillation and Heart Failure

AF and heart failure are two of the most common cardiac diseases in the population. Both conditions have increased in prevalence causing increased morbidity, including hospitalisation and mortality.(15) AF and heart failure often co-exist together and can be responsible for causing each other, with 30-50% of patients having both AF and heart failure.(16)

Heart failure is defined as a condition in which the heart is unable to pump a sufficient amount of blood to provide adequate blood flow to the body's organs such as the lungs, brain and kidneys. Heart failure may present as: Heart failure with a preserved ejection fraction (HFpEF) which is defined as having an LVEF ≥50% and heart failure with reduced ejection fraction (HFrEF), which is defined as having an LVEF ≤40%. Heart failure with an ejection fraction that falls between these two categories is known as Heart Failure with a mid-range ejection fraction (HFmrEF).(17)

In HFrEF as the name suggests the ejection fraction is reduced (<40%). It is most commonly caused by coronary artery disease but there are many other causes such as viral infection, alcohol or drug abuse, chemotherapy and idiopathic dilated cardiomyopathy. As a result of damage to the myocardium, contractility is impaired.(18, 19)

HFpEF manifests itself as a normal ejection fraction but the pathophysiology of heart failure remains under debate as it may be caused by impaired diastolic dysfunction and/or reduced longitudinal function. Diastolic dysfunction presents as prolonged isovolumic LV relaxation,

slow LV filling and stiffening of the left ventricle. Stiffening follows excessive collagen deposition in the extracellular matrix, which occurs due to external stressors such as high blood pressure. As a result of the stiffness there is slow LV filling, which causes the stroke volume to reduce due to a lower preload, resulting in a lower cardiac output. This may be worsened with faster heart rates as the ventricle has less time to fill with blood, causing a blunted increase in preload volume on exertion. As the name suggests the ejection fraction remains normal, however longitudinal function may be impaired, suggesting some dysfunction in myocardial contractility. However it has been found on exertion that there is no increase in LVEF due to a failure to increase end-diastolic volume and no change in end-systolic volume, meaning that stroke volume cannot increase. (20)

Both AF and heart failure share similar risk factors which cause myocardial, extracellular, electrophysiological and neurohormonal changes, resulting in a similar pathophysiology that results in a cycle of negative events on the heart, with one perpetuating the other causing an incremental decline in left ventricular (LV) function (**Figure 4**). As a result of low cardiac output either due to reduced contractile function (HFrEF) or ventricular stiffening (HFpEF) in heart failure, the renin-angiotensin-aldosterone system (RAAS) is activated to increase blood flow back to the heart, in an attempt to compensate failing contractility. This however has a negative effect on the heart, causing raised filling pressures and increased afterload. This results in increased left atrial pressure, causing the atria to dilate and areas of fibrosis may form. These areas of scar act as foci which initiate and maintain AF. Fibrosis leads to re-entry circuits, as a result of abnormal distribution of gap junctions and delayed after depolarizations, caused by reduced current through the L-type Ca^{2+} channels and K^{+} outward current but increased activity of Na^{+}/ Ca^{2+} current. The increase in catecholamines and angiotensin II causes interstitial fibrosis, which contribute to impaired intracellular calcium handling due to down-regulation of the ryanodine receptor channel and Ca^{2+}-ATPase pump

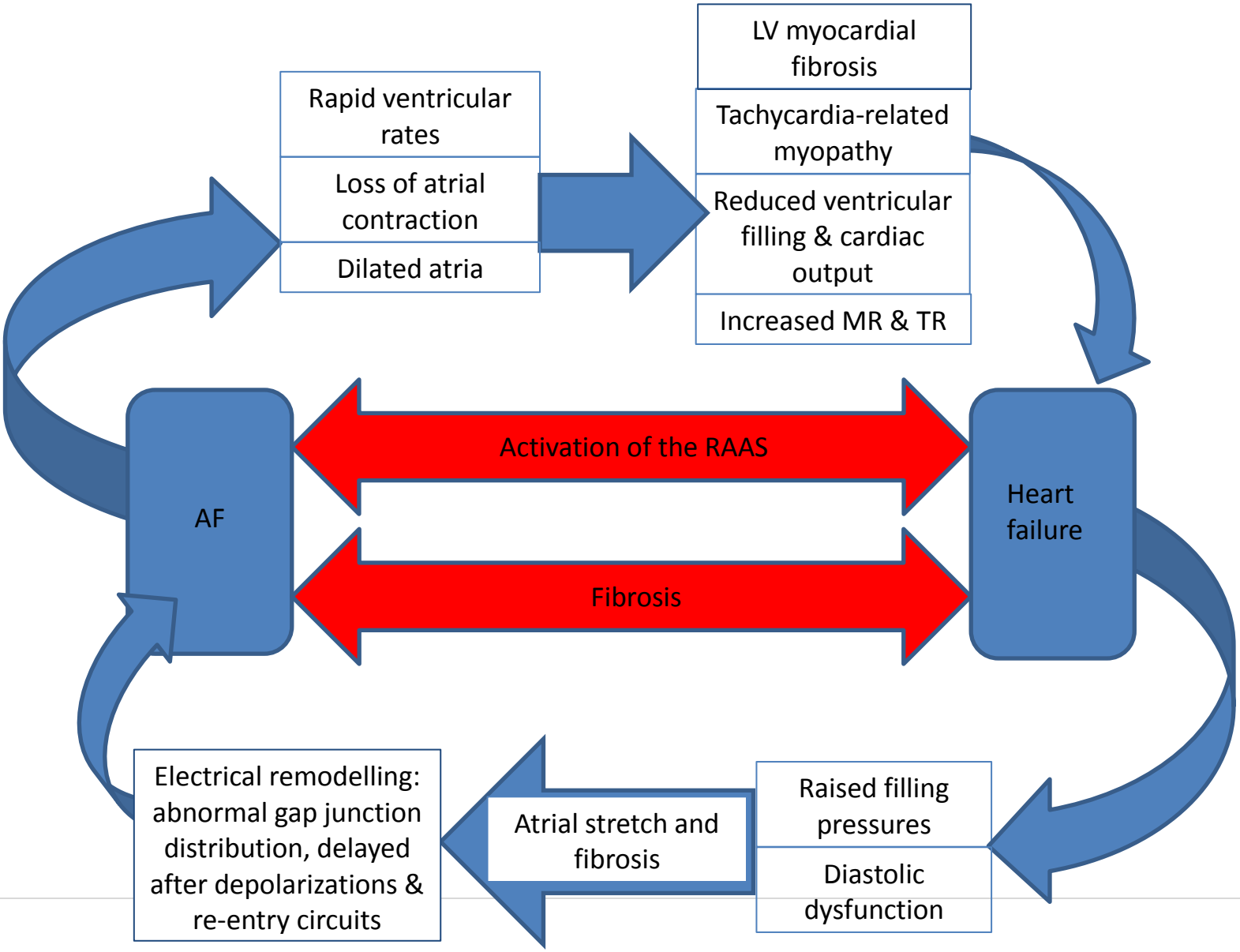
found on the sarcoplasmic reticulum. Also as a result of increased atrial pressure, ionic currents are activated by stretch that cause dispersion of refractoriness and changes in conduction properties further encouraging AF. The induction of AF causes a loss of atrial systole, which reduces LV filling and so reduces cardiac output, which then further activates the RAAS perpetuating the cycle. This is worsened during faster ventricular rates because there is even less diastolic filling.

Fast ventricular rates can also lead to tachycardia-induced cardiomyopathy. The mechanism of this condition is unclear, but may be due a combination of reduced blood flow to the coronaries causing myocardial ischaemia, myocardial energy depletion and abnormalities in calcium regulation. Thus the cycle continues as the maintenance of AF worsens the severity of the heart failure and the risk of AF onset increases with worsening heart failure.(6, 15, 21, 22)

The presence of AF strongly increases the risk of the development of heart failure: Hazard ratio (HR) of 2.3 for HFrEF and 2.5 for HFpEF. HFpEF and AF share more pathophysiological mechanisms; hence they are more likely to co-exist.(22)

Echocardiography is the primary imaging tool for assessment of heart failure and its aetiology; therefore it is important that clinicians can rely on measurements made to stratify an appropriate treatment plan. Patients with AF who develop heart failure have a poor prognosis; the SOLVD trial concluded that patients in with a LVEF <35% AF is an independent predictor of all-cause mortality, progressive ventricular failure and death or hospitalisation for heart failure. Therefore it is essential that the onset of heart failure is detected early.(15, 23)

Figure 4. The pathophysiology of AF and heart failure. Abbreviations: RAAS, Renin-Angiotensin-Aldosterone-System; TR, Tricuspid Regurgitation; MR, Mitral Regurgitation (adapted from Anter et al, 2009)(15)



1.3 Role of Echocardiography in atrial fibrillation

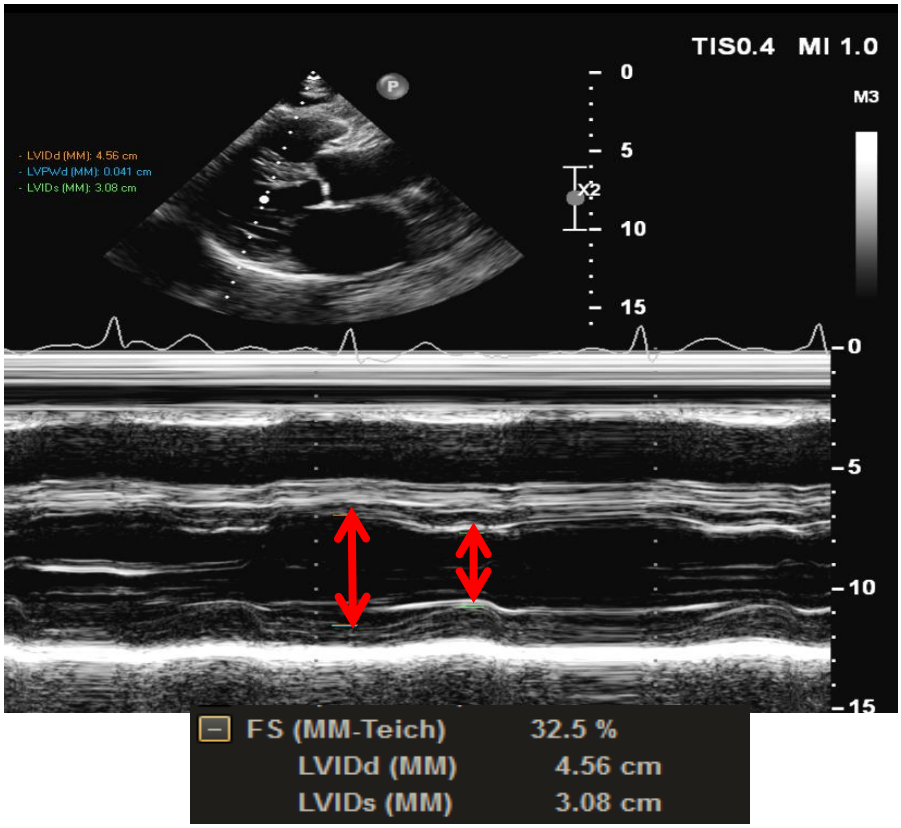
The ESC 2016 guidelines have made a class 1 recommendation for all AF patients in need of treatment to undergo a transthoracic echocardiogram (TTE).(24) The assessment of LV function is crucial to guide the management of patients in AF in deciding anticoagulation therapy, whether it is safe to proceed with cardioversion, ablation and the choice of medication (both rate and rhythm control). Therefore accurate assessment of systolic and diastolic parameters is essential, so that clinicians can make appropriate management choices for the patient. It also plays an important role in establishing any structural cause for the onset of atrial fibrillation, for example; valve disease, previous myocardial infarction, hypertensive heart disease or restrictive cardiomyopathy.(24, 25)

1.3.1 Parameters typically used in AF patients to assess systolic function

There are several different parameters used to assess systolic function, all of which have their own advantages and disadvantages, see **Table 1**.

Fractional shortening (FS) (**Figure 5**). This method assesses LV systolic function by measuring the change in LV diameter (from the parasternal long axis view) during systole and diastole. This method is flawed because it only measures in one plane and in only two walls. Therefore, it does not represent global ventricular function, but only basal antero-septal and inferolateral contractility. It is also significantly affected by preload and afterload, so will vary according to the haemodynamics of the heart, therefore in atrial fibrillation the FS will be variable from beat to beat.(26)

Figure 5. Fractional Shortening. Red arrows depict measurements of the left ventricular internal diameter in diastole and systole, which are used to calculate fractional shortening.

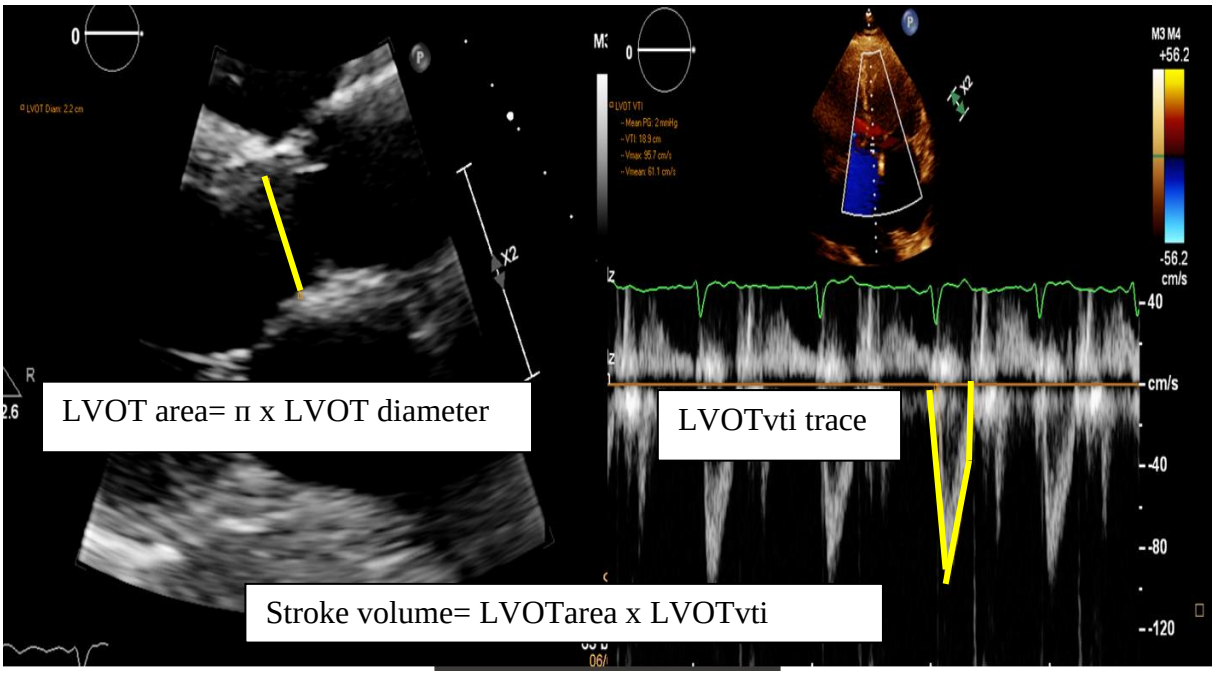


Stroke Volume (SV) (**Figure 6**). This method measures the volume of blood leaving the heart in systole; in patients with reduced LV function the stroke volume is low. SV is derived from the Left ventricular outflow tract velocity time integral (LVOT VTI) trace and the cross-sectional area of the LVOT using the equation:

SV= LVOT area x LVOT VTI

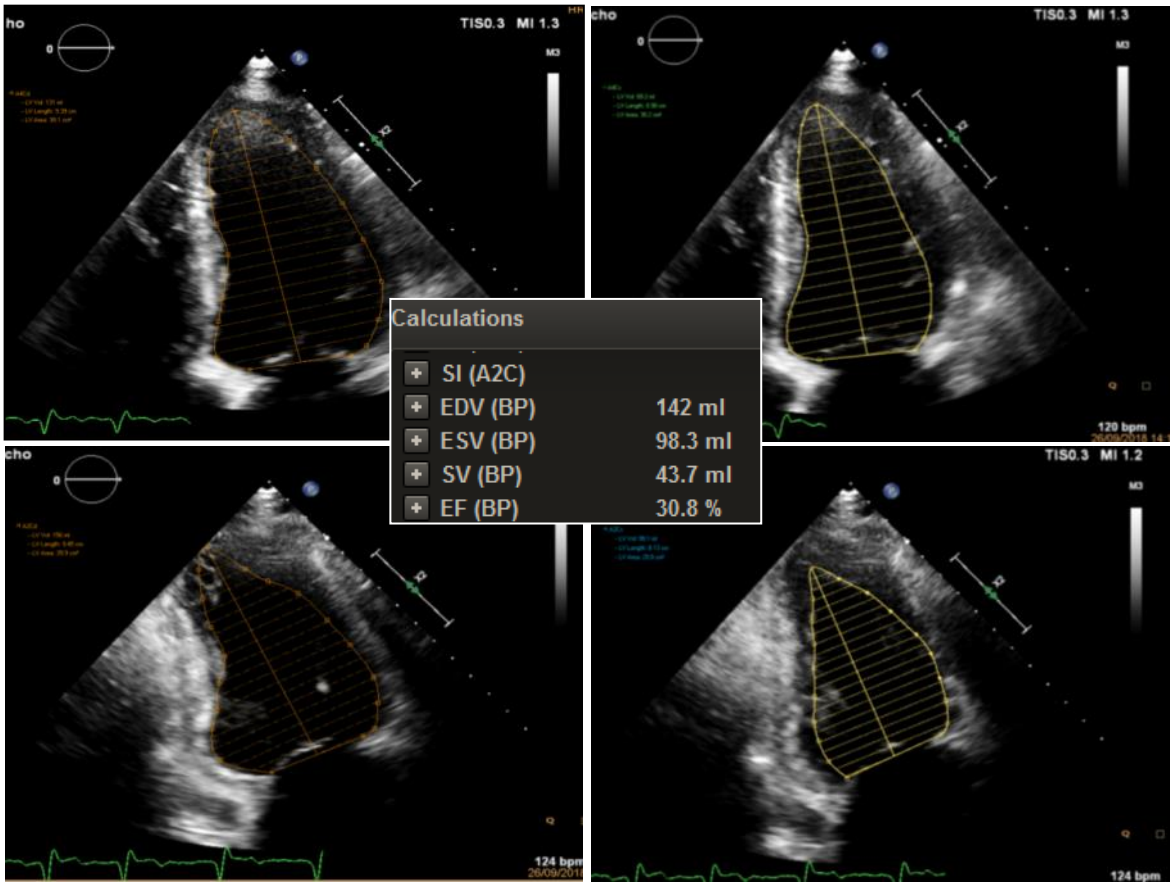
This method relies on correct measurement of the LVOT diameter, which should be measured in mid-systole 0.5-1 cm below the aortic valve's annulus and correct positioning of the pulsed wave Doppler to measure the LVOT VTI (at the point where you measured the LVOT diameter). This measurement is significantly affected by heart rate, afterload and preload, so will vary with irregular cardiac cycle lengths.(26) (27)

Figure 6. Stroke Volume. Measurement of the LVOT diameter (left) and measurement of the LVOT VTI (right) with the equation to calculate stroke volume below



Simpson's Biplane Ejection Fraction **(Figure 7)**. This measurement does not directly measure myocardial function, but instead assesses systolic function according to the change in chamber volume over a cardiac cycle. This method is limited by the geometric assumption that every ventricle is cylindrical and it will not incorporate regional wall motion abnormalities or distortions in other planes. It also relies on good endocardial definition to accurately delineate the size of the cavity in end-systole and end-diastole.(28, 29) As it relies on volume, it will be affected by preload and afterload. In patients with AF, ventricular filling is more dependent on the length of the R to R interval compared to patients in sinus rhythm therefore the end-diastolic volume and so ejection fraction will vary according to the R to R interval.(30)

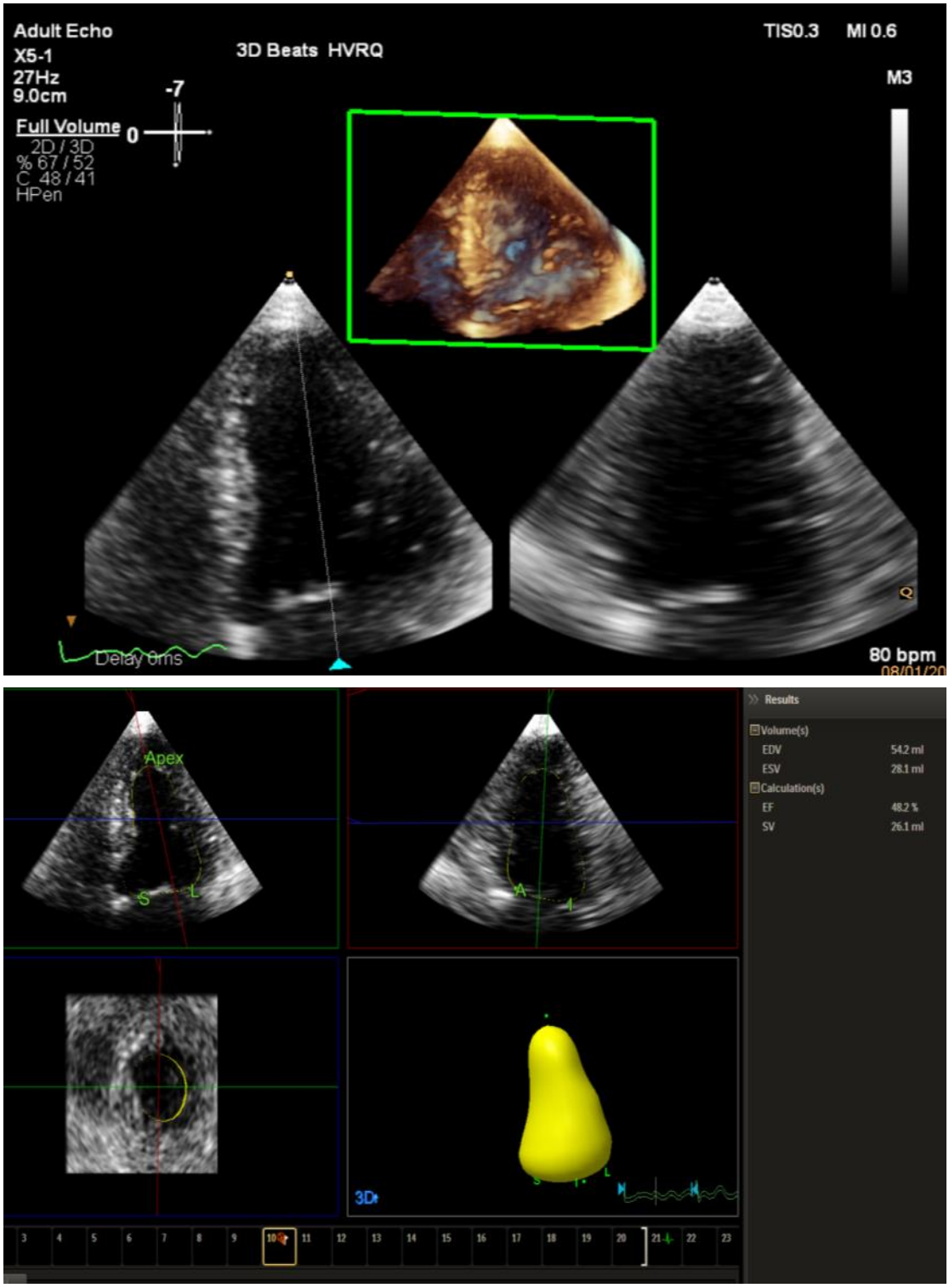
Figure 7. Simpson's Biplane LVEF. Simpson's volume of the ventricle in diastole from the apical 4 chamber (top-left) and apical 2 chamber (bottom-left) and then Simpson's volume of the ventricle in systole from the apical 4 chamber (top-right) and apical 2 chamber (bottom-right)



3-D Volume Ejection Fraction (**Figure 8)**. 3-D This method possesses the advantage of incorporating the entire ventricle in every plane, so that there are no geometric assumptions and the ventricle can be assessed in every plane, including regional wall motion abnormalities and distortions. This method is also semi-automated, which may reduce inter-observer variability. The limitations of this method are firstly that to achieve a 3-D dataset with good spatial and temporal resolution, the sub-volumes of the ventricle may need to be taken over four beats of equal length with minimal cardiac motion. In order for this to be carried out the patient needs to be in a regular heart rhythm and have the ability to hold their breath for a few seconds. For patients with irregular heart rhythms or with breathing difficulties, the dataset will be prone to stitch artefact, which disrupts the acquisition of a 3-D volume. To over-come

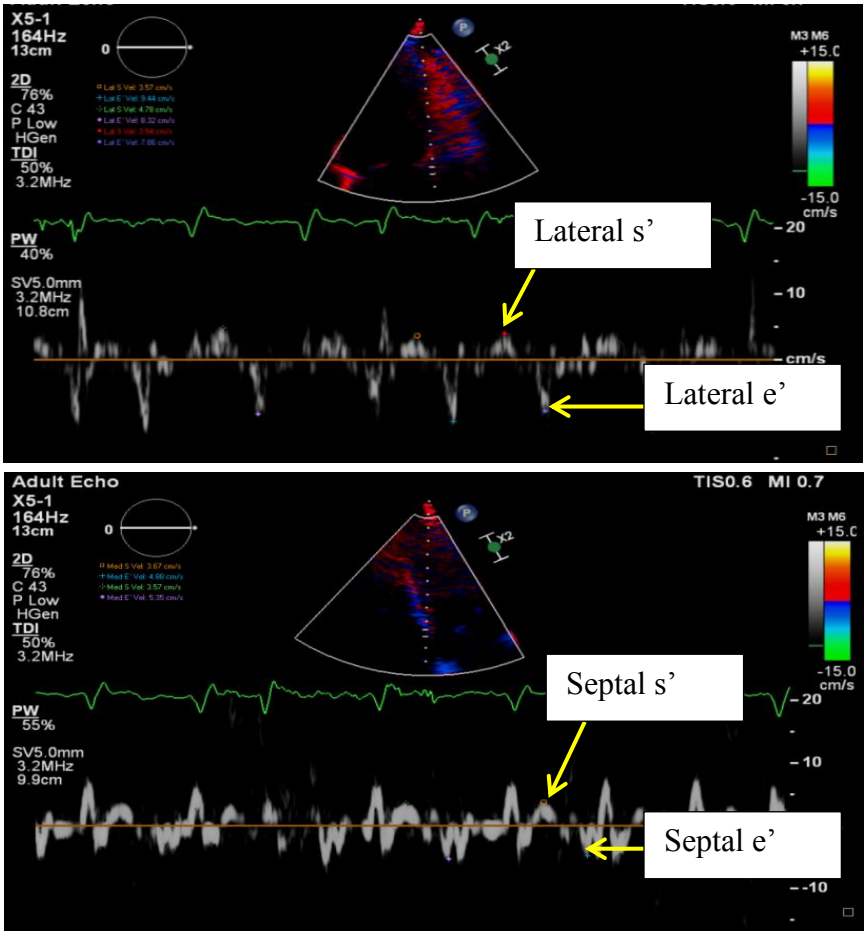
this problem a single-beat acquisition can be used, but the temporal and spatial resolution, as well image quality will be compromised.(31, 32)

Figure 8. 3D volume LVEF with x-plane imaging of the left ventricle (top) and 3D volumes and ejection fraction calculated (below).



Tissue Doppler Indices (TDI) (**Figure 9**). Measurements from this parameter can be used to evaluate both systolic (s') and diastolic function (e'). The normal ranges for tissue Doppler velocities vary with age and sex.

Figure 9. Tissue Doppler Indices (TDI). Lateral annulus (top) and septal annulus (bottom) systolic (s') and diastolic (e') tissue Doppler velocities



The advantage of this method is that it is easy to perform and does not rely on image quality to the same extent as 2D and 3D measurements. It also measures longitudinal function, which tends to deteriorate first in LV dysfunction. However it is limited by its angle dependence; if the angle of incidence is more than 15^{o} there will be a ~4% underestimation in the velocity measured. It is also unable to distinguish areas of normal myocardial contractility from areas of damaged myocardium, which may appear normal due to tethering from other functioning areas. It is also important to be aware that in patients with severe mitral annulus calcification or mitral valve surgery, TDI values will be reduced and so may not represent the longitudinal

function of the ventricle. This method has some load dependency and so with AF patients the variable R to R interval will result in variation in longitudinal function from beat to beat, causing different values of s' from beat to beat (33-35)

Left Ventricular Strain (**Figure 10**). This is a relatively new method and is gradually being incorporated more and more into clinical practice. It provides a quantitative assessment of left ventricular deformation during contraction. There are two methods of assessing strain: speckle tracking and tissue Doppler tracking. Tissue Doppler measures the speed of the myocardium as a marker of function. However it is limited by angulation and noise artefact, which can impact on its accuracy.(94) Speckle tracking works by tracking two points within the myocardium (speckles), as they move away and towards each other. When the speckles move towards each other, this represents myocardial shortening and so contraction, producing a negative value; the more negative the value, the greater the contraction. The advantages of this method is that it assesses all walls, is angle independent and has been shown to be more sensitive at detecting myocardial dysfunction in presence of a normal ejection fraction.(36) The limitations of this method are that in the presence of a high heart rate, low frame rate or poor image quality, tracking of the speckles may deteriorate resulting in inaccurate indices of strain and strain rate. This method is still relatively load dependent and so in AF with longer preceding R to R intervals there will be a greater degree of contractility compared to shorter R to R intervals, resulting in varying strain from beat to beat (37)

Figure 10. Global Longitudinal Strain. Longitudinal strain of the apical 4 chamber (top left), apical 2 chamber (top right), apical 3 chamber (bottom left) and global longitudinal strain displayed as bulls-eye (bottom right)

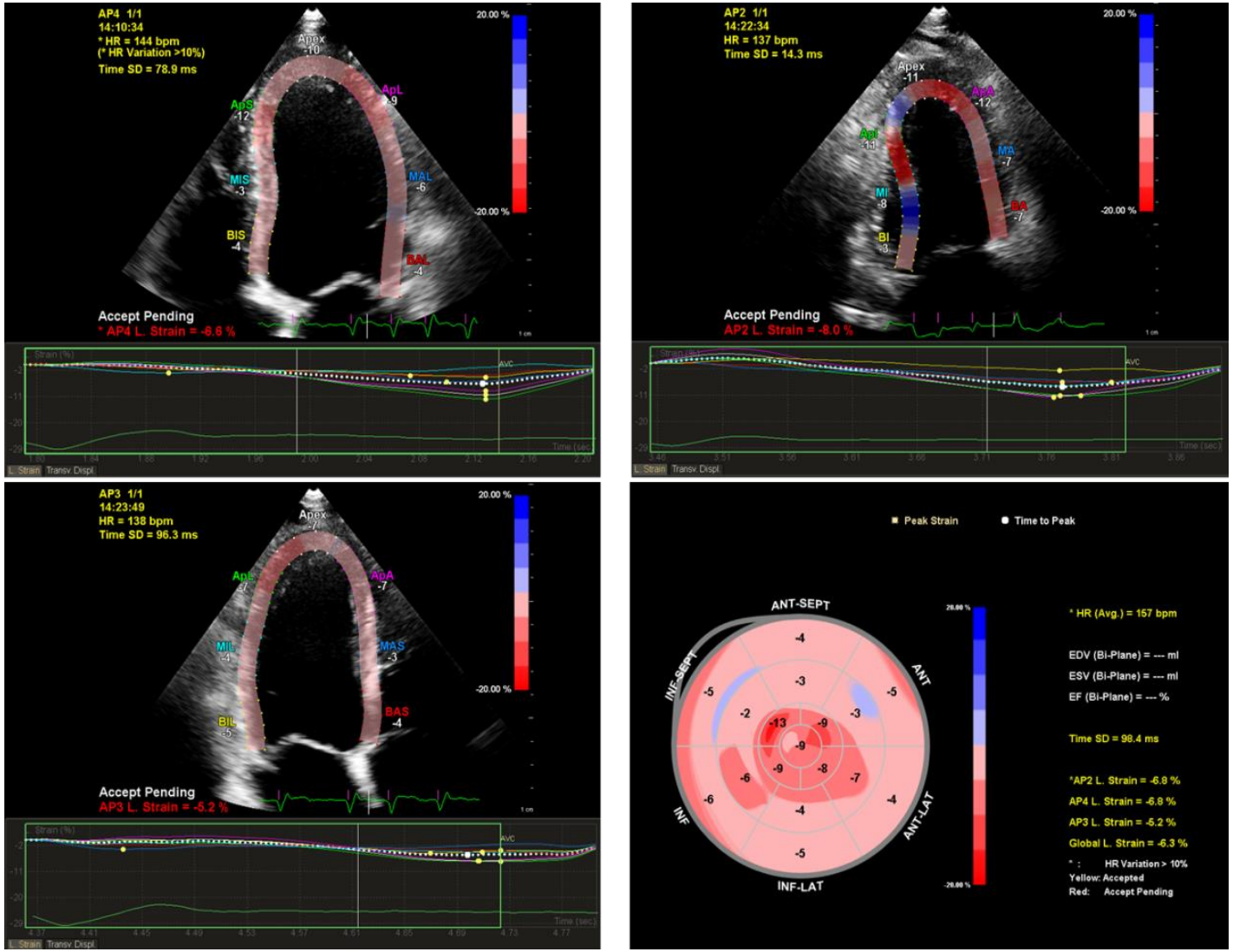


Table 1. Advantages and Disadvantages of measurements used to assess systolic function.

Parameter	Advantages	Disadvantages
Fractional Shortening (%)	Simple High temporal resolution	Single plane Ignores RWMA in other walls M-mode beam must be on axis
Stroke volume (ml)	Provides haemodynamic information	Relies on correct positioning of sample volume (LVOT VTI) and correct measurement of LVOT diameter LVOT is assumed to be circular Cannot be performed with high LVOT velocities (LVOT obstruction)
Simpson's biplane LVEF (%)	Performed in two planes LVEF calculated from volumes instead of diameter	Requires clear endocardial boarder Ignores RWMA in the apical 3 chamber and reliant on geometric assumptions Apex frequently fore-shortened
3D volume LVEF (%)	Assesses volumes in every plane No geometric assumptions Unaffected by foreshortening	Good echo windows are required Lower temporal resolution Difficult in patients with arrhythmias or those unable to breath-hold
Tissue Doppler s' (cm/s)	Measures longitudinal function	Velocities must be parallel to the ultrasound beam Cannot differentiate between active contraction and tethering effects Unreliable if there has been mitral valve surgery or there is heavy mitral annulus calcification
GLS (%)	Can detect early systolic dysfunction before the ejection fraction reduces Angle independent	Strain values differ between vendors Relies on adequate frame rate for speckles to be accurately tracked Load dependent

Abbreviations: 3D= three dimensional; GLS= global longitudinal strain; LVEF= left ventricular ejection fraction; LVOT= left ventricular outflow tract; RWMA= Regional Wall Motion Abnormalities; VTI= velocity time integral

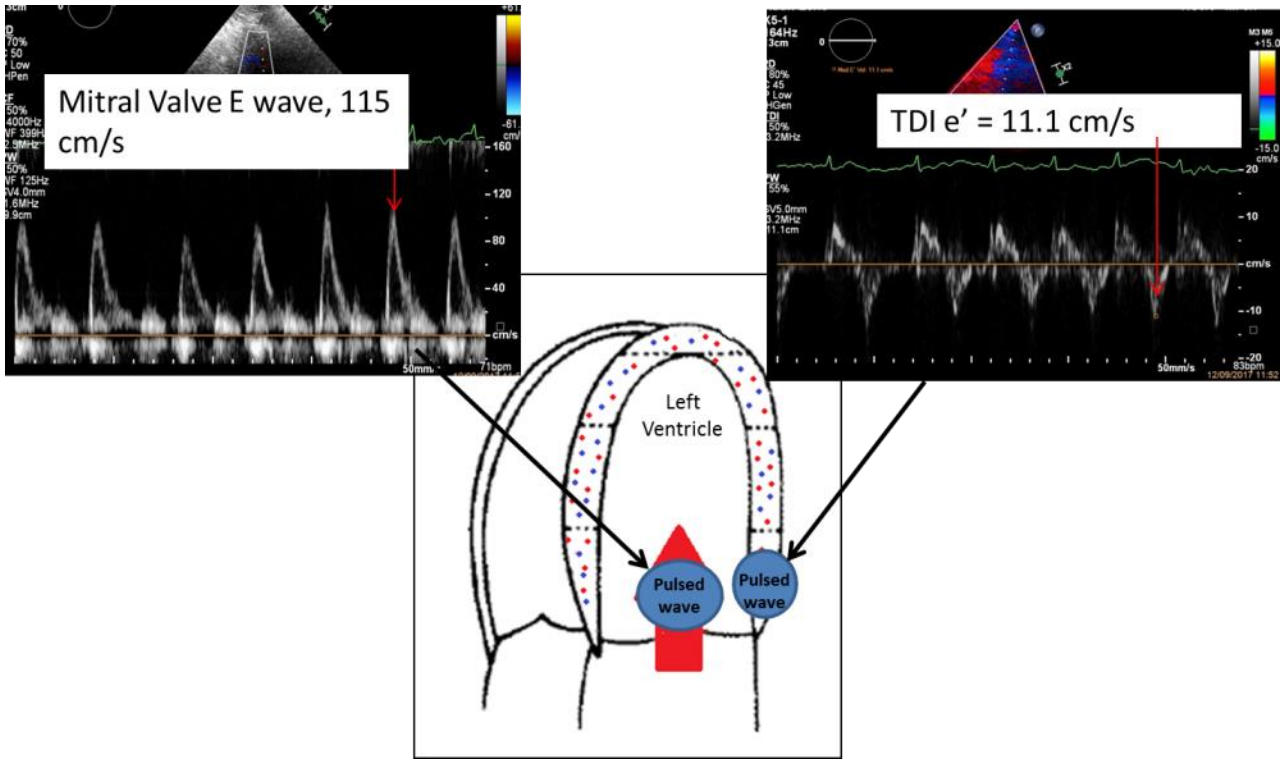
1.3.2 Parameters typically used to assess diastolic function

There are several different parameters which can be used to assess diastolic function in AF patients, all of which have their own advantages and disadvantages, see **Table 2**.

Mitral E wave and deceleration time. The E wave measures the speed of blood as it passes between the left atrium (LA) and LV in early diastole. It represents the filling pressures within the ventricle. As the patient ages, the E wave reduces in velocity and the deceleration time of the E wave profile increases in length; this correlates with a gradual impairment in LV relaxation. It is affected by left atrial pressure and the speed of LV relaxation. Deceleration time of the E wave is affected by how quickly the LV relaxes and the LV diastolic pressure.(36) The variable R to R interval in AF patients will cause a change in filling time from beat to beat, which will result in an inconsistent E wave and deceleration time measured.

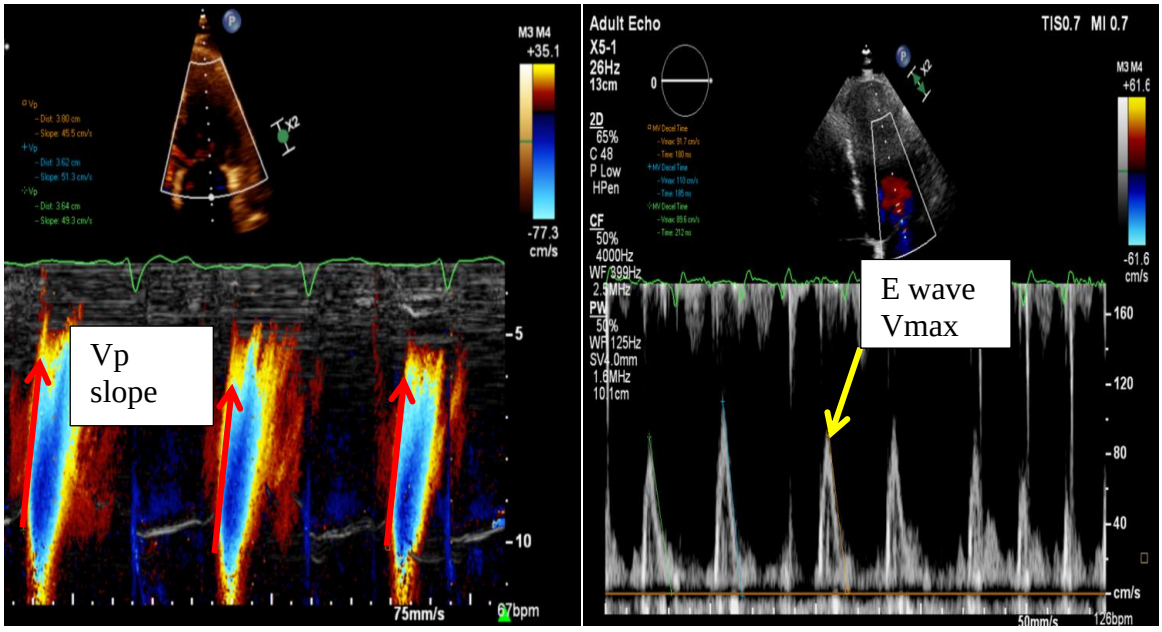
E wave and E/e' (**Figure 11)**. The E/e' ratio is the mitral E wave (described above) divided by the Tissue Doppler Indice (TDI) e'. e' is the speed of the myocardium during diastole; on a TDI trace it is seen as the negative deflection during diastole. E/e' ratio correlates well with pulmonary capillary wedge pressure (PCWP) even in AF patients.(37) A PCWP greater than 12 indicates raised left ventricular end-diastolic pressure (LVEDP).(38) Both the E wave and e' are affected by preload and so with AF the variable R to R interval will result in a variation in E/e' from beat to beat.

Figure 11. E/e'. Measurements of peak mitral valve flow E wave divided by the TDI velocity e' taken from the lateral and septal annulus



E/Vp (**Figure 12)**. This is the E wave divided by the speed of blood propagating from the mitral annulus to the apex (Vp) during early diastole. This is a measure of diastolic function, which correlates with ventricular filling pressure. If the ratio of E/Vp is increased, this will indicate raised ventricular filling pressures.(39) AF will affect the E wave value as this will vary according to the length of the preceding R to R interval.

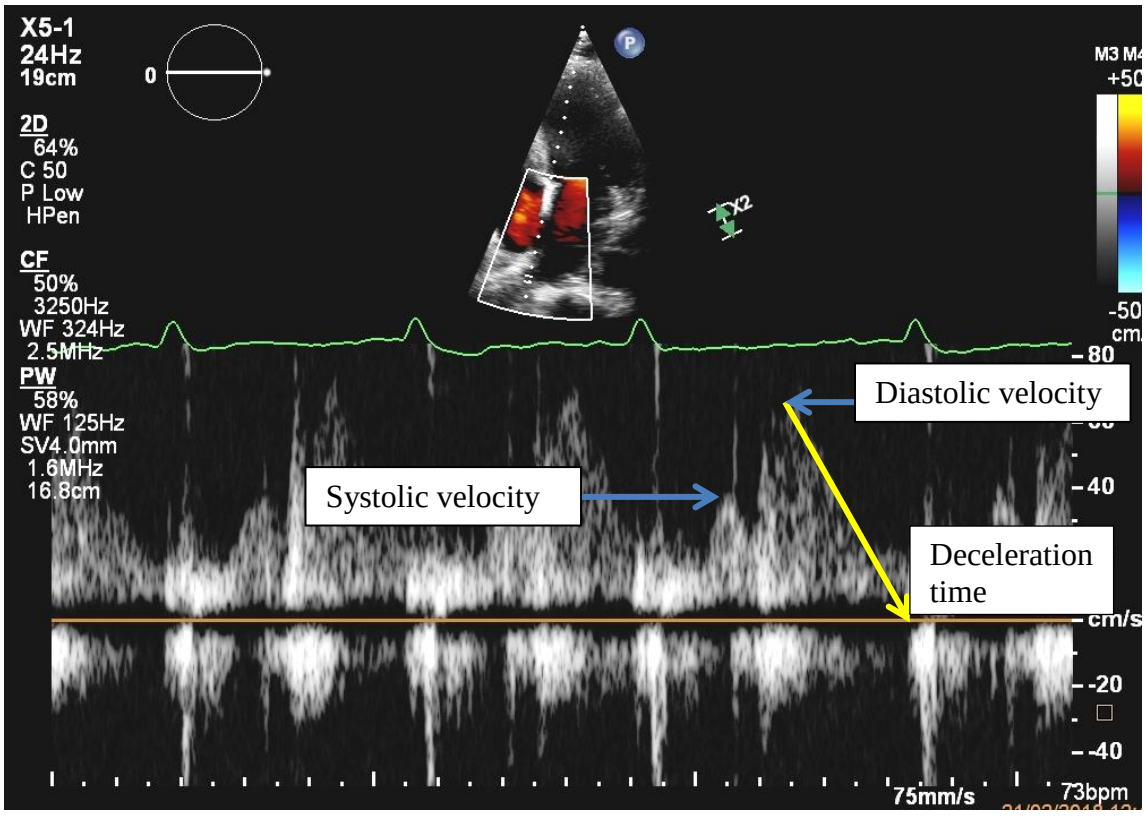
Figure 12. E/ Vp. Peak mitral flow E wave (right) divided by the velocity of blood through the ventricle from base to apex during diastole which is measured by the slope of the blue wave indicated by the red arrows (left).



Pulmonary Venous Doppler (**Figure 13**). In patients with sinus rhythm pulsed wave Doppler will present an S wave which represents atrial relaxation during ventricular contraction, D wave which represents atrial filling, LV relaxation and compliance and the A wave which represents atrial contraction. The ratio of S/D can be used to detect raised left atrial pressures; as LA pressure increases the ratio of S/D. However in patients with atrial fibrillation the A wave disappears and the S wave comes late making it difficult to measure. More recent studies have examined the validity of pulmonary venous diastolic deceleration time. This was compared with invasive end-diastolic pressure and was found to correlate more closely than

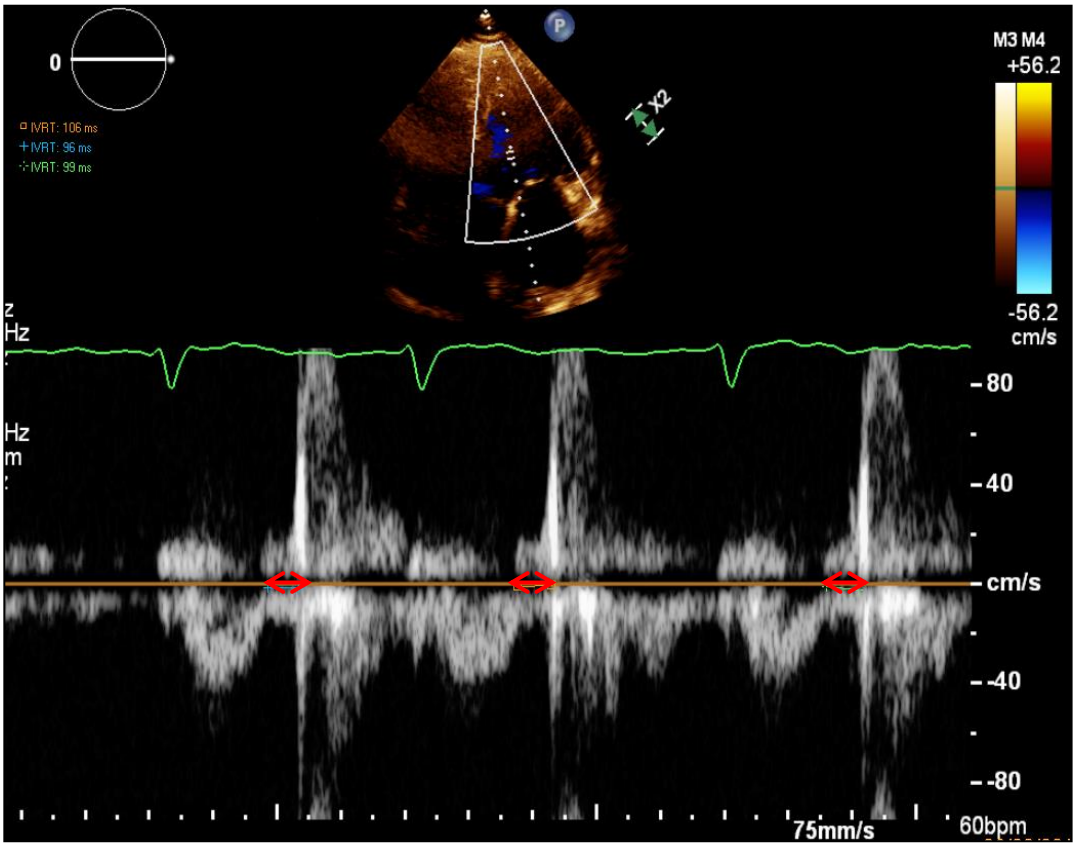
parameters derived from mitral inflow.(40, 41) As with E/e', pulmonary vein deceleration time is associated with invasive filling pressures in patients with AF, although the clinical utility of this measure is currently unknown.(37)

Figure 13. Pulmonary venous Doppler flow with measurements of systolic, diastolic flow and the deceleration time of the diastolic wave.



Isovolumic Relaxation Time (IVRT) **(Figure 14)**. This is a measurement which can be used to detect impaired LV relaxation and raised left atrial pressures. It is the time interval between when the aortic valve closes and when the mitral valve opens. Changes in filling pressures will result in a change in IVRT. If the IVRT is raised, this suggests that there is impaired LV relaxation present. If the IVRT is shortened, this suggests that left atrial pressures are raised and may be indicative of a restrictive cardiac disease. The limitations of this method are that it is affected by heart rate and arterial pressure and so in AF patients with variable R to R intervals the measurement of IVRT varies from beat to beat.(36, 42)

Figure 14. IVRT. Measurements of IVRT indicated as red arrows from the end of systole to the start of diastole.



LA Biplane volume (**Figure 15)**. This is most commonly measured by the Simpson's volume method. The volume of the LA is a marker of the effect of increased LV filling pressures. LA dilatation has been found to be an independent predictor of death, AF, heart failure and ischaemic stroke.(36) The limitation of LA volume is that it relies on good visualisation of the LA wall; as the atria are the furthest away from the transthoracic probe image quality declines making it difficult to accurately differentiate the LA wall, hence intra and inter observer reproducibility has been found to be poor.(43) Using LA size to assess diastolic function is limited in AF patients, as the majority of patients have dilated atria; hence studies have shown a poor correlation with PCWP in AF patients.(44)

Figure 15. LA biplane volume. Volumes of the left atrium measured in the apical 4 and 2 chamber view using the area-length method.

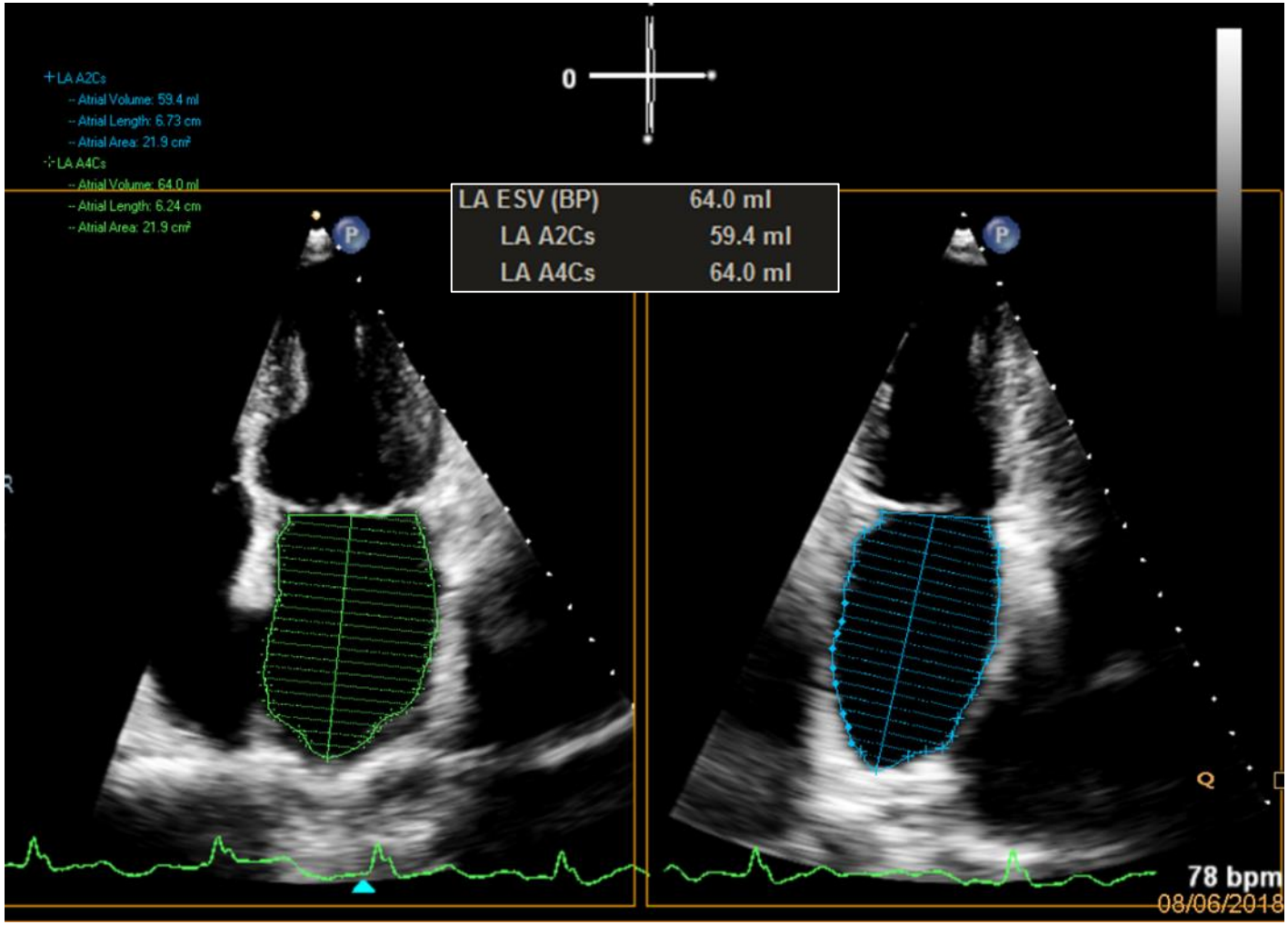


Table 2. Advantages and disadvantages of measurements used to assess diastolic function.

Parameter	Advantages	Disadvantages
E wave (cm/s)	Feasible in most patients In patients with reduced LVEF it correlates better with LV filling pressures, functional class and prognosis than LVEF	Affected by LV volumes and elastic recoil Age dependent Variable with arrhythmias
Deceleration time (ms)	Feasible in most patients A short deceleration time in reduced LVEF indicates increased LVEDP	Unable to measure if there is E and A wave fusion (high heart rates) Not applied in atrial flutter Age dependent Not related to LVEDP in normal LVEF
Tissue Doppler e' (cm/s)	Less load dependent than other parameters Feasible in most patients LV filling pressures have minimal effect on e' in the presence of impaired LV relaxation	Angle dependent Age dependent Need to sample at least two sites Limited accuracy in patients with CAD, regional dysfunction, significant MAC, mitral valve surgery and pericardial disease
E/Vp	Only reliable index of LV relaxation in patients with reduced LVEF and dilated ventricles E/Vp >2.5 predicts PCWP >15 mmHg in patients with reduced LVEF	Relies on accurate angulation of M-mode through colour Difficult to acquire Vp can appear normal in patients with normal LV and LVEF
Pulmonary venous Doppler S/D	Deceleration time of diastolic velocity can be used to estimate mean PCWP in patients with AF S/D <1 suggests increased LA pressures	Difficult to obtain in some patients Limited accuracy in patients with normal LVEF, AF, mitral valve disease and HCM
IVRT (ms)	Overall feasible and reproducible Combined with E/A it can be used to measure LV filling pressures in patients with HFrEF It can be combined with LVEDP to estimate the time constant of	Affected by heart rate and arterial pressure Difficult to measure in the presence of tachycardia Different results according to whether continuous or pulsed

	LV relaxation (τ)	wave Doppler is used
LA biplane volume (ml)	Feasible in most patients Provides diagnostic and prognostic information about LV diastolic dysfunction	Technically challenging in poor image quality and in the presence of a prominent aorta or large interatrial septal aneurysm LA dilatation is seen in well-trained athletes, bradycardia, high-output states, heart transplants, atrial arrhythmias and mitral valve disease despite normal diastolic function

Abbreviations: LVEDP= Left Ventricular End Diastolic Pressure; LVEF=left ventricular ejection fraction; CAD= coronary artery disease; MAC= mitral annulus calcification; HCM= hypertrophic cardiomyopathy; PCWP= Pulmonary capillary wedge pressure; LA= Left atrial

1.4 Practical guide to assessing reproducibility in echocardiography

In this section, I develop the rationale for my reproducibility studies in further chapters. Before considering patients with AF specifically, I have first reviewed methods for achieving reproducible echocardiographic measures in general. *This has been published in Bunting et al., Journal of the American Society of Echocardiography 2019;32(12):1505-15(45). I was the first author for this paper and so carried out the literature searches for the information provided in this review, wrote the manuscript with input from the co-authors. All figures and tables were created by myself and formatted with the help of Dr Kotecha. The concept of the website link and embedded equations were formulated by myself, however the creation of the website was done by Luke Slater.*

Echocardiography is a key cardiac investigation that has contributed to improvements in the diagnosis and management of cardiovascular disease (CVD).(46, 47) The use of echocardiography continues to grow, not only in number, but also in the type of measurements, from M-mode to two-dimensional (2D) imaging, Doppler echocardiography, three-dimensional (3D) imaging and speckle tracking. However, inpatient hospital data suggests that echocardiography continues to be under-utilised in critical CVD conditions, and is an operator-dependent technique that is prone to variable reproducibility.(48) Defining a reproducible measurement from echocardiography is challenging due to intrinsic biological variation, and the difference in measurement and interpretation between operators.

1.4.1 Terminology and clinical need

The term reproducibility covers many overlapping concepts. It is explicitly defined as the variation of the same measurement made on a subject under changing conditions, but in real-life practice also includes changes in measurement method, observer, time-frame, instrumentation, location and/or environment. Repeatability can be separately considered as

the variation in repeat measurements made on the same subject under identical conditions, whereas reliability describes the magnitude of error between measurements.(49) It is inevitable that there will be some degree of error in clinical measurements, and the acceptable amount will depend on particular circumstances.(50-52) The correct statistical tests to determine these forms of reproducibility are often poorly considered, with the potential to mislead and confound clinical decision-making.(52)

As clinical indications for echocardiography increase, it is essential that these measurements can be relied upon for accurate diagnosis and serial assessment of cardiac function.(53, 54) In the following sections I have reviewed the literature on reproducibility, repeatability and reliability in the practical context of echocardiography. In Table 3, I have provided a summary of statistical tests to assess reproducibility, repeatability and reliability. Table 4 highlights the application of these tests, giving examples specific to echocardiography. The aim is to provide echocardiographers and clinicians with the tools to appraise their own measurements, reduce inconsistencies within and between operators, and improve the reliability of echocardiography in clinical practice. To enable assessment in routine clinical care, I have provided an online calculator for key statistical tests and graphs, allowing users to input measurements and easily assess reproducibility: http://sono.lokero.xyz/.

Table 3: Terms of reference. Abbreviations: SD = standard deviation; SEM = standard error of the mean.

Term	Explanation	Examples of practical application in echocardiography	Most valuable statistical tests
Reproducibility	Variation of the same measurement made on a subject under changing conditions or different operators	Comparing measurements of aortic valve peak velocity on the same patient by two different echocardiographers.	Correlation coefficients for association: Pearson or Spearman correlation (r) and linear regression (percentage of variation explained = r^2).
		Comparing the grade of mitral regurgitation by two echocardiographers as none/mild/moderate/severe.	Measure of the agreement between two operators: Cohen kappa (or weighted kappa for degree of disagreement). k=(total number of agreements - total agreements due to chance) / (total observations - total agreements due to chance).
		Comparing the difference in measurement of ejection fraction made by 2D Simpson's biplane and 3D volumes.	Agreement: Bland and Altman limits of agreement = bias (average difference between measurements) ± 1.96 x SD.
		Assessing the correlation of left-ventricular outflow tract diameter measured by multiple operators in the echo department.	Intraclass correlation coefficient (requires complex computation).
Repeatability	Variation in repeat measurements made on the same subject under identical conditions	Assessing the difference in consecutive beats by the same operator for tissue Doppler E/e'.	Repeatability coefficient = within-subject SD x √2 x 1.96.
Reliability	Magnitude of error between repeated measurements	Assess within a department the variation in mitral regurgitation effective regurgitant orifice area between operators.	Minimal detectable change = 1.96 x √2 x SEM. Coefficient of variation = SD/mean x 100. Percentage Change= (2^{nd} measurement- 1^{st} measurement)/ average x 100.

1.4.2 Reproducibility

Reproducibility assesses the degree of variation in a measurement when conditions are changed. In echocardiography, this could be used to assess the variability in different operators, between different echo sessions or across separate patients with the same condition. When assessing reproducibility, statistical tests can assess correlation, bias and agreement; together these are used to form a conclusion as to whether a study is reproducible (see Table 3 for a summary of terms). Correlation is defined as how well one variable can be used to predict the other, bias is whether there is a systematic difference from the expected value (either under- or over-estimated), and agreement is defined as how close two measurements are from each other when on the same scale.(50, 55)

I have explored these three aspects in detail below, along with their limitations, using the example of biplane Simpson's left ventricular ejection fraction (LVEF) assessed by two operators (Figure 16).

Association

Association assesses the relationship between groups of data, with higher values (either positive or negative) suggesting a closer association. The choice of association statistic depends on the type of data available, and below we discuss four main options.

Correlation coefficient

The correlation coefficient (*r*) simply measures the linear relationship between two variables. The most commonly used methods are the Pearson correlation coefficient (for normally distributed variables) and the Spearman correlation coefficient (for skewed variables, using a ranking of the measurements). An *r* value of 0 implies no correlation between the variables at all. If there was a perfect correlation between two variables, the *r* value would equal 1 (or minus 1 if perfectly and inversely correlated).(56, 57) In reality, no clinical variables could

attain this level of correlation, but an *r* value above 0.8 shows very strong correlation and between 0.6 and 0.8 strong correlation.(58) It should be emphasized that correlation is not a good measure of agreement (discussed later), and will depend on the range of the measurement in question.(59) Statistical tests can be used to determine if these correlations are likely due to chance; p-values in this context do not refer to the strength of correlation, but instead indicate whether the sample size is large enough to have confidence in the correlation coefficient. **Figure 16A, B** and **C** demonstrates strong or very strong correlation between the two operators for LVEF, in contrast to **Figure 16D** where correlation is relatively weak. These methods are best used for paired parameters, such as intra-observer variability (the same operator taking an echo measure twice on the same subject and assessing the variation) or inter-observer variability (two operators taking the same measure on the same subject and assessing their variation).

Linear regression

Regression analysis describes how well one variable can be used to predict the value of another, or the strength of their relationship. With enough data points, a "line of best fit" can be created based on the regression equation: VARIABLE 1 = *constant value* + *coefficient* * VARIABLE 2. Given the two variables, the regression model provides the constant value and the coefficient by trying to minimise the difference between the true observed value and the value predicted from the model (also known as the residual). This method requires data that is normally distributed (not skewed) and can be affected by outlying values. It only measures to what extent two variables are linearly related (in many cases, the association can be more complex).(54, 60) The value of linear regression is limited, but can be useful to visualise the association of paired data prior to other statistical tests. As with any statistical measurement, there is some variability. The 95% confidence interval gives us an idea of the bounds of uncertainty around the calculated estimate.

Figure 16A shows a very close relationship between the values from the two operators, with a regression coefficient of 0.90. This means that for every 1.0% increase in LVEF ratings in the future by operator 1, we would expect that the corresponding average LVEF measurement of operator 2 would increase by 0.9%. The confidence interval suggests that if repeated samples are taken, there is a 95% chance that the true regression coefficient will lie in the interval between 0.45 and 1.34. Conversely, **Figure 16D** shows a very variable relationship, with a regression coefficient of 0.15 and a broad confidence interval (from -0.28 to 0.60). This confidence interval includes the value of zero, meaning that there may be no association between the operators at all.

Intraclass correlation coefficient (ICC)

The ICC is often used to determine the reproducibility of numerical measurements organised into groups beyond a simple pairing, for example different operators measuring the same variable in different patients. The formulae for ICC are complex, but essentially they pool data and compare within and across operators based on an analysis of variance. The choice of analysis of variance model will depend on whether the patient is assessed by a random pool of operators (one-way random effects model) or each patient is assessed by the same operators (two-way random effects model).(61) This divides the total variability into actual difference and error, and the ICC is an average of all the correlations based on all the possible pairs of data.(62) ICC can be used to assess variability both within a single operator (intra-observer), between different operators (inter-observer), or across different time points. It possesses the advantage of being able to compare more than two groups of variables (more than two operators) and may be superior to Pearson and Spearman correlation coefficients as it considers systematic differences. Pearson and Spearman correlation is a linearity index measuring to what extent one variable predicts the other variable, whereas ICC is an additivity

index measuring to what extent one variable cane be equated to another(63, 64) The disadvantage of ICC is that it has limited value for comparing reproducibility of results in different populations. As the ICC is a dimensionless value, the outcome will vary according to the dependent variables in the population sampled; data with a wide range of values will generate a high ICC value whereas data with a narrow range of values will result in a low ICC.(56, 61, 65) ICC is unhelpful if the indices show poor agreement, as there is no indication as to the source of the error. Whilst there is no strict ICC value which marks the cut-off for appropriate correlation(52, 57), values between 0.75 and 1.00 suggest excellent correlation, between 0.60 and 0.74 good correlation, and less than 0.4 suggests poor correlation.(66) Interpretation of the ICC is demonstrated when comparing **Figure 16A** and **B**. Whereas the standard correlation coefficient is similar (0.82 and 0.70), the ICC is considerably different (0.90 and 0.48) due to greater variance between the two operators in example **B**. However both are statistically significant in contrast to **Figure 16D**.

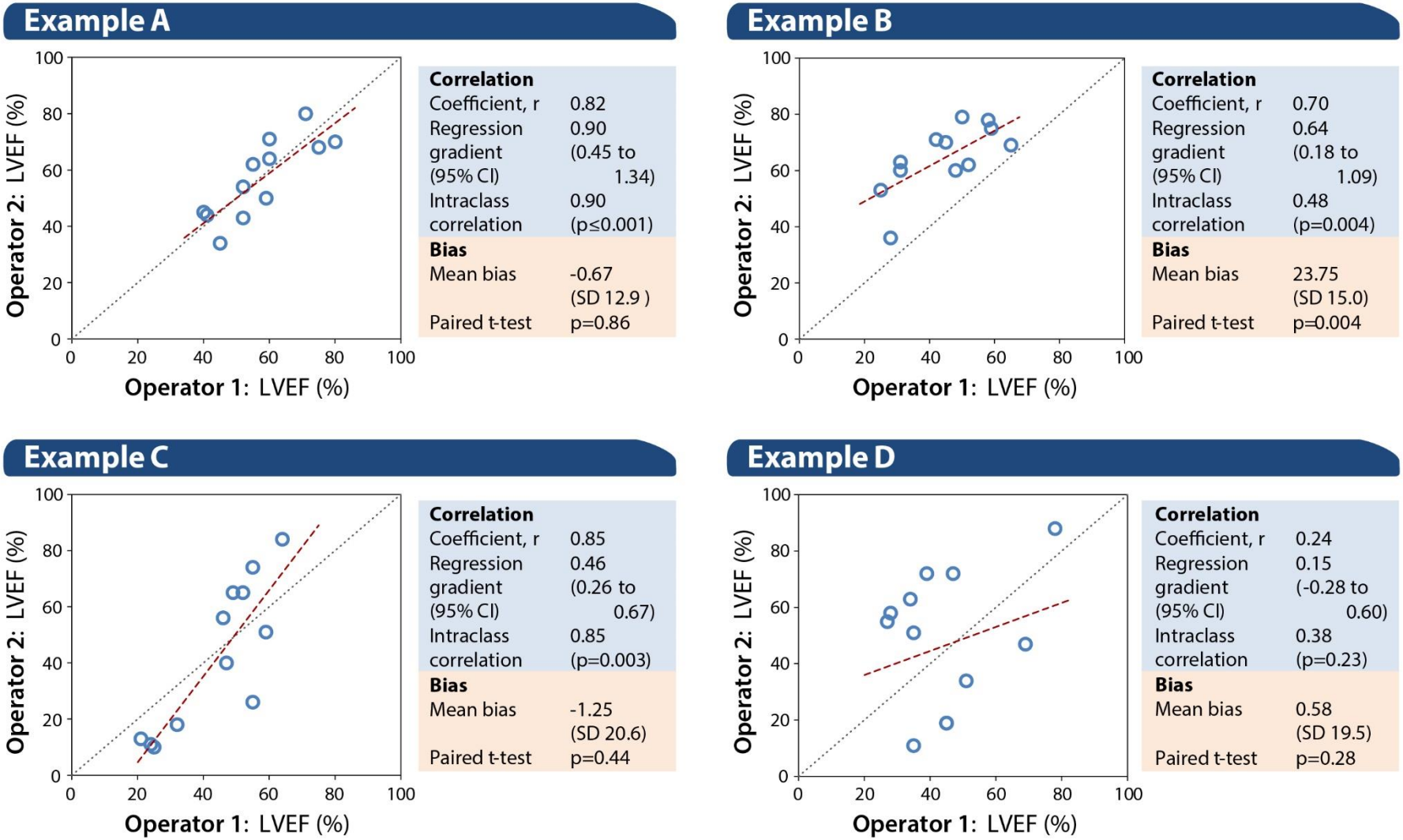
With the online calculator, this method can be more widely used as it allows for the assessment of reproducibility in more than two groups. For example, it can be used to assess inter-observer variability across all members of the echocardiography department.

Bias

Bias indicates to what extent there is a true difference in two data points that has not resulted from chance. These statistical tests can help to determine if there are significant differences in paired data, for example two recordings of left ventricular outflow tract diameter. A small probability (often $p<0.05$, which is less than 1 in 20) suggests there is evidence for a difference in the two measurements (i.e. we reject the null hypothesis which is of no difference in values).(67) It is important to note that the strength of statistical significance is

not related to the extent of bias, but rather whether there is confidence in the rejection of a chance effect. Paired t-tests are used for normally-distributed data and the Wilcoxon test for skewed data. In our example, the bias assessment is not significant for **Figure 16 A** and **D**, whereas there is a systematic bias in **Figure 16B** which is highly statistically-significant at p=0.004 and gives evidence for a true difference between the two operators. If the data points are clustered equally around the line of equality, this suggests that there is no systematic bias. Of note, **Figure 16C** shows a proportional bias, and so a t-test is likely to be inaccurate in this case. Proportional bias occurs when the difference between measurements is dependent on the value of the measurement taken.(68)

Figure 16: Reproducibility assessment between two operators (taken from Bunting KV et al, 2019)(45)



Agreement

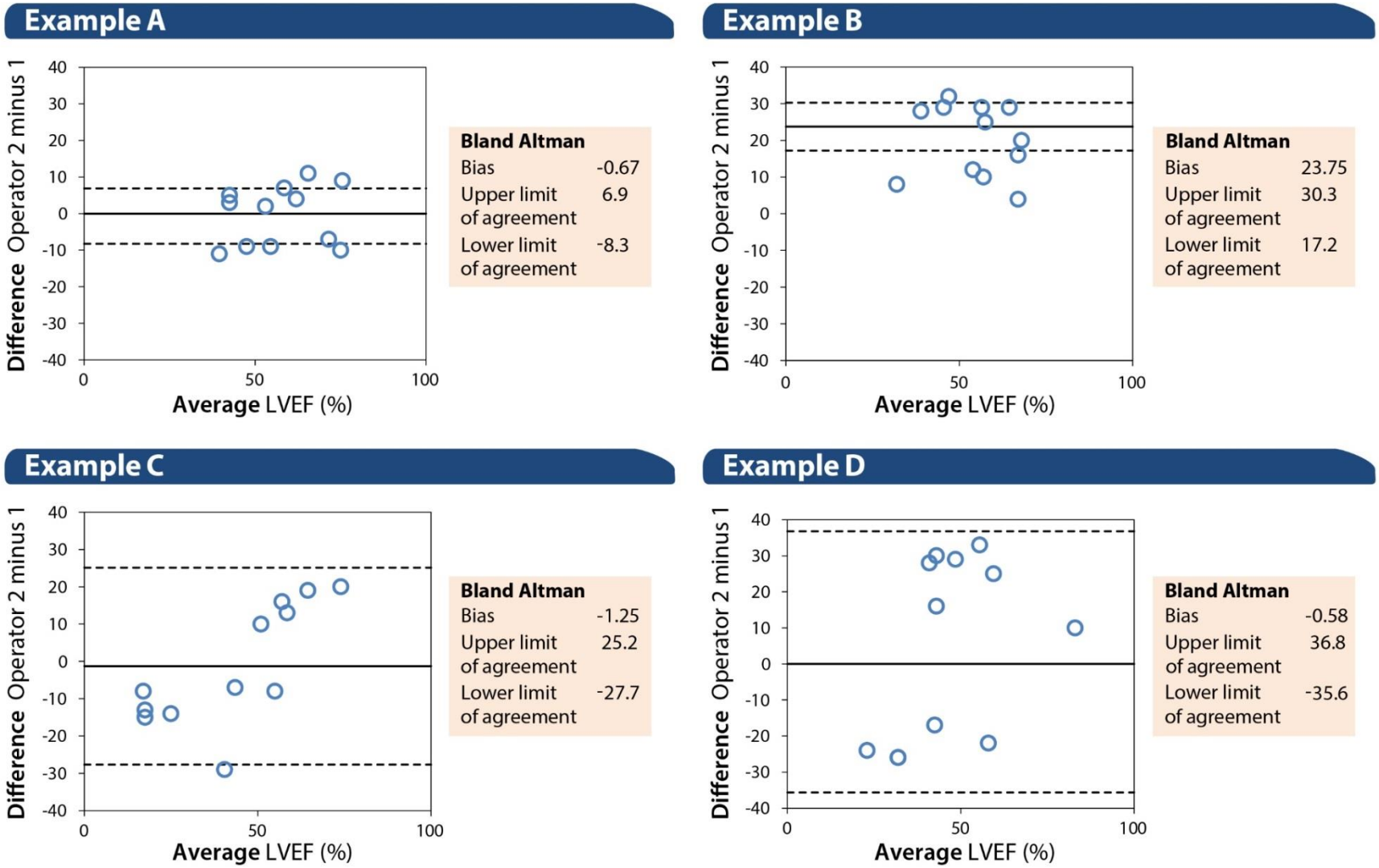
Agreement defines the degree of consensus between different measurements, and different statistical comparisons are available according to whether the data are continuous or categorical.

Bland and Altman plot

The Bland and Altman plot is widely used to visualise the difference in two continuous measurements from the same individual, graphed according to the average value of the two measures. In terms of echocardiography, this is highly valuable to assess measurements taken on the same patient by two different echocardiographers. This method can also be used for assessing two measurements made by the same operator, or two measurements using different techniques or in different environments.

Creating the Bland and Altman plot is straightforward and requires plotting: (1) the difference in the pair of measurements against their mean; (2) the bias (the mean of the differences); and (3) the upper and lower limits of agreement (bias ± 1.96 * standard deviation of difference). The limits of agreement indicate where the true mean (and future measurements) are likely to lie and interpretation will depend on the clinical magnitude of the limits (56, 57, 69) If values are consistently outside the confidence limits, it may indicate a lack of agreement or a true biological difference that is not just due to sampling error.(50, 69, 70) **Figure 17** shows the examples from **Figure 16** constructed into Bland and Altman plots. **Figure 17A** shows a small degree of bias (-0.67) and narrow limits of agreement (-8.3 to 6.9), whereas **Figure 17B** shows a systematically higher LVEF in operator 2 for each measurement. In **Figure 17C** there is evidence of a proportional error, with increasing difference between measurements at both extremes of LVEF. **Figure 17D** shows very wide limits of agreement (-35.6 to 36.8) that are likely to be highly clinically relevant.

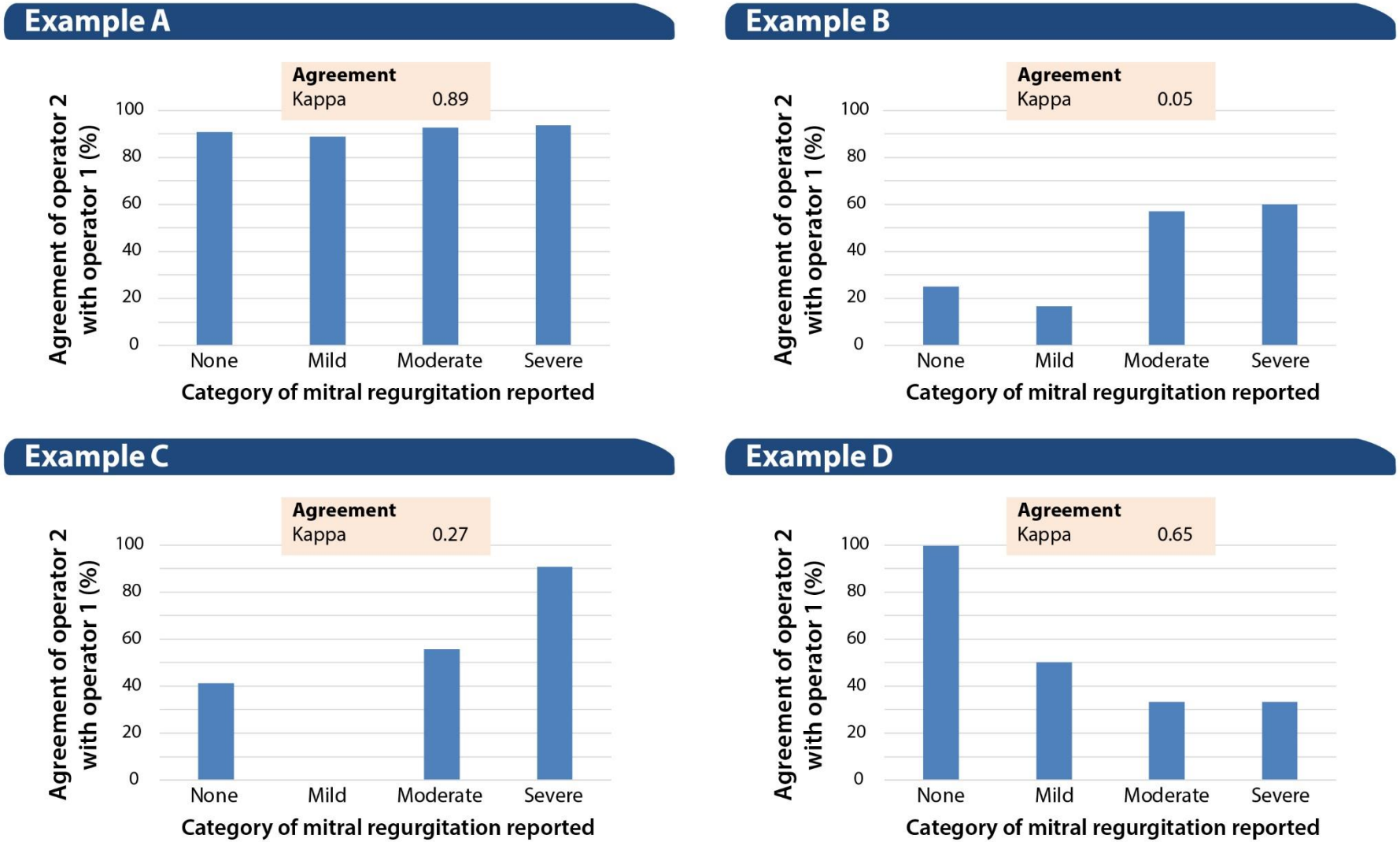
Figure 17: Bland and Altman plots for agreement between two tests or operators (taken from Bunting KV.et al 2019)(45)



Kappa statistics

The Cohen kappa is used to assess the agreement between categorical data (measurements with different levels, such as the severity of valve disease or categories of left ventricular dysfunction). The result ranges from 0 (no agreement) to 1 (perfect agreement), with values <0.6 indicating weak agreement and >0.8 strong agreement. Cohen's kappa takes into account disagreement between the two operators and also agreement by chance. A modified approach, the weighted kappa, can be used to determine the degree of disagreement using a predefined table of weights.(52) **Figure 18A** demonstrates strong agreement between the two observers (k=0.89) as for each case they made a similar grading for the severity of mitral regurgitation in the same patients. In contrast, **Figure 18B** shows almost no agreement between the two observers across the severity of mitral regurgitation, (k=0.05). **Figure 18C** shows that there is reasonable agreement between the two observers for cases at the extreme ends of the categories ("none" and "severe"), but overall the agreement is weak due to a lack of consistent results in those graded with "mild" or "moderate" disease (k=0.27). **Figure 18D** shows overall moderate agreement across all cases (k=0.65) despite there being 100% agreement for patients with no mitral regurgitation. Note that Cohen's kappa is not the only statistic which can be used to assess agreement for categorical data, and other measures are available to address some of its assumptions and shortcomings. These include percent agreement, Scott's PI, Gwet's AC1 and Fleiss's generalized Kappa among others.(71)

Figure 18. Cohen kappa to assess the inter-observer variability of mitral regurgitation assessment by two observers (taken from Bunting KV, 2019)(45)



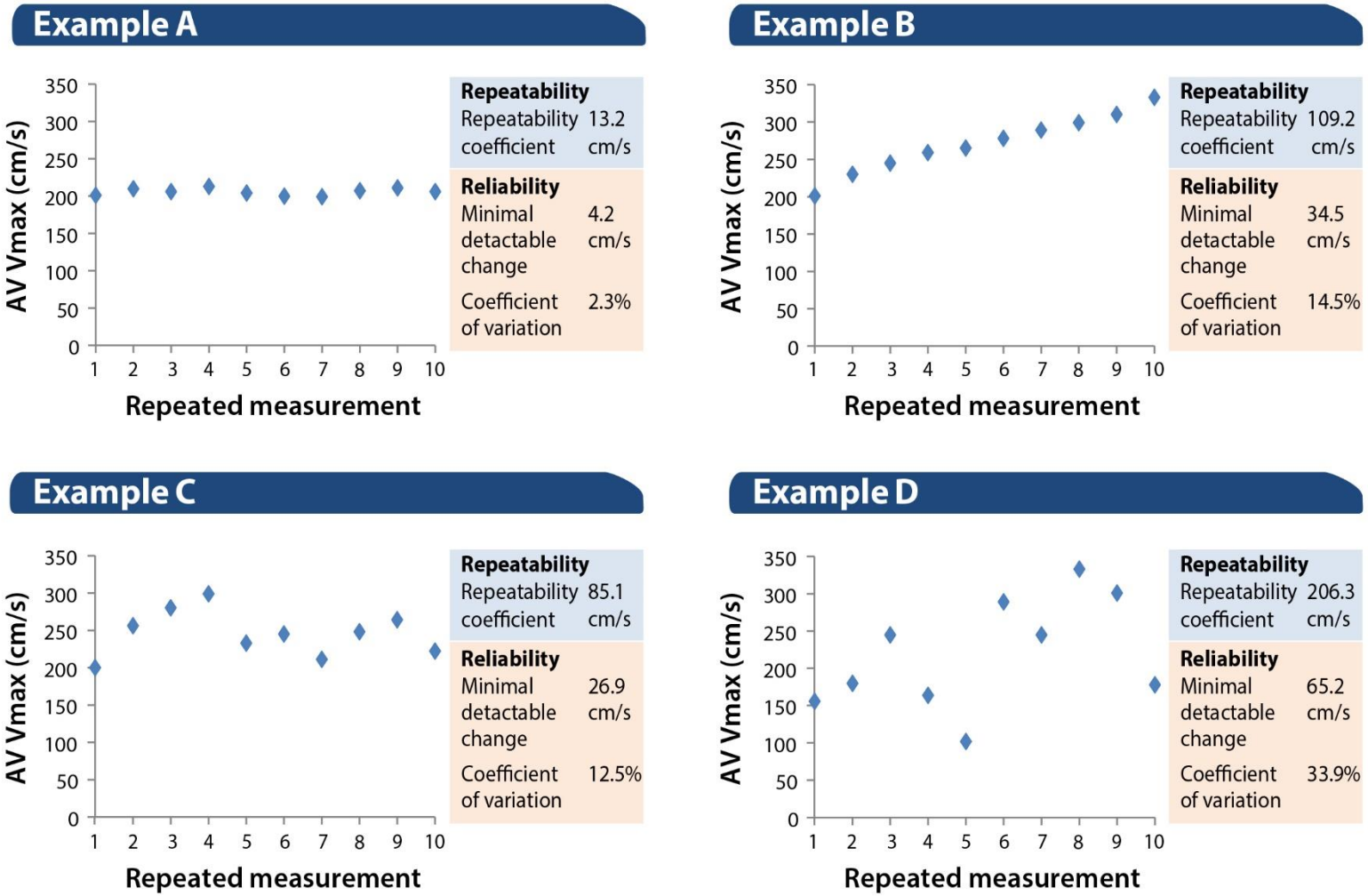
1.4.3 Repeatability

Repeatability studies are used to ensure minimal variation exists when the measurement is retested on the same subject or group - the smaller the variation, the more reliable the results. When carrying out test-retest procedures, if the conditions in which the measurement are taken are kept exactly the same, then any variation detected can be attributed to the accuracy of the measurement. The time interval between repetitions should be short enough to exclude any biological change, but long enough to prevent any interference from the preceding test. The appropriate time interval will vary depending on the situation,(57) however for echocardiography, repeating measurements on the same day with at least a few minutes interval would seem appropriate. For calculations which require multiple echocardiographic measurements for calculation, such as aortic valve area, it is important to obtain measurements under similar haemodynamic conditions. Therefore in the context of any cardiac arrhythmias, similar cardiac cycle lengths should be selected for measurement.(72) Variability of results within a single patient can be assessed statistically by the repeatability coefficient (using the standard deviation of differences), the coefficient of variation (discussed further below), or an ICC. The advantage of the repeatability coefficient is that its value is in the same units as the measurement, allowing easier interpretation to guide decision making.(65)

Figure 19 shows an example for peak aortic valve velocity in four patients undergoing ten consecutive measurements by the same operator for possible aortic stenosis. **Figure 19 A** demonstrates a repeatability coefficient of 13cm/s, meaning that the variation in future measurements for aortic valve peak velocity are small (by that echocardiographer on that particular patient). **Figure 19B** shows proportional bias for velocity to increase in value as the observer takes more measurements, whereas **Figure 19C** displays clinically-relevant

variation (perhaps due to a patient factor like atrial fibrillation). In **Figure 19D** we see major issues in repeatability (for example, due to equipment problems).

Figure 19. Repeatability and reliability assessment (taken from Bunting KV et al, 2019)(45)



1.4.4 Reliability

To be a reliable measurement, the magnitude of the difference between repeated measurements should be within a clinically-acceptable limit. The test should be precise enough to give us confidence that we can differentiate between normal or abnormal in a given population, or between different patients or populations. The minimal detectable change (MDC) can be used to assess reliability when measurements are repeated over a short time interval.(73) It is expressed as a percentage and represents the minimal change required to be sure that the differences observed reflect a real change rather than measurement error (with higher percentages suggesting a less reliable method).(74) The coefficient of variation is a common method to compare reliability between tests. It is calculated as the ratio of standard deviation to mean, with a smaller percentage indicating a more precise method.(54, 75) This would be useful in echocardiography for assessing the variation in parameters within a certain patient population; for example, different measures of left atrial dilatation in the same patients with hypertension, or reliability of averaging different numbers of cardiac cycles in those with atrial fibrillation

Simple assessment of reliability can also be calculated, such as the absolute or percentage change in two measurements. However, these tests have limited statistical power to determine differences, are unable to account for inherent variation, and the results are highly dependent on the value at baseline.(76, 77) Whatever method is used, echocardiographers need to consider whether the change in measurement is due to the reliability of the test, or if a biological change in the patient could explain the difference (for example, worsening of valve disease over the time period).

Table 4: Statistical methods useful in echocardiography.

Statistical Method	Strengths of method	Weakness of method	Examples from published literature
Association			
Correlation coefficient	Options for normally-distributed data (Pearson) and skewed data (Spearman).	Can only account for linear relationships. Sensitive to outlying values.	n=17 with heart failure or dilated cardiomyopathy. Very strong inter-operator association between LVEF and GLS: Pearson's correlation coefficient r= 0.89 for LVEF and r= 0.97 for GLS.(78)
Linear regression	The regression line can be used to predict the value of one variable from another. Analysis of the difference between the observed and predicted values (residuals).	Can only be used if the data are normally distributed. Assumes the same degree of variance across the whole variable. Sensitive to outlying values.	n=31 patients clinically indicated for cardiac CT. Strong correlations seen between different imaging modalities when measuring volumes and LVEF. For CT vs. CMR, linear regression r^2=0.85; regression equation y=0.97*x* -1.3. For 3D TTE vs. CMR, r^2=0.93; regression equation y=0.87*x*+6.3.(79)
Intra-class correlation coefficient (ICC)	Assess how closely variables are related to each other. Best for a large number of observations. Accounts for a change in the mean over time. Independent of the scale of measurement and size of error.	As with other measures above, shows correlation not causation. No fixed clinical interpretation for level of agreement. Cannot be used to compare reliability of measurements between different studies. Effected by the size of the range of data.	n=183 patients with hypertension, comparing two measurements 45 days apart. Excellent correlation between first and second study: ICC 0.90 for indexed LV mass and 0.85 for septal diameter.(80)
Bias			
T-test	Provides a p-value for paired data sets.	For normally distributed data only.	n=88 patients prior to chemotherapy. Differences in intra and inter-observer variability of LVEF and volumes were assessed using a t-test, with p<0.001 considered statistically significant. Non-contrast 3D echocardiography had significantly lower variability than 2D Simpson's method, 2D triplane, or studies using contrast.(81)

Wilcoxon-signed rank/Mann-Whitney test	Can be used for skewed data.	Uses ranking, therefore assessment of raw data needed to interpret the p-value.	n=284 children with evaluation of MAPSE using B-mode and M-mode. M-mode MAPSE had significantly lower variability than B-mode lateral MAPSE for both inter ($p < 0.001$) and intra ($p<0.001$) observer variability (using Wilcoxon signed rank test).(82)
Agreement			
Bland and Altman plot	Demonstrates degree of agreement and depicts outliers. Demonstrates systematic bias.	Unable to detect proportional bias. Assumes normal distribution. Numerical data only. A clinical decision needs to be made as to whether there is good agreement based on the width of confidence limits.	n=50 herceptin patients comparing two scans a minimum of 14 days apart by the same operator, showing better agreement for GLS than Simpson's biplane LVEF. For GLS, bias -0.1 between the two time periods; limits of agreement -1.8 to 1.7. For LVEF, bias 0.5; limits of agreement -11.2 to 12.1.(83)
Cohen's kappa	Measures agreement and takes into account the amount of agreement which is there by chance.	Dependent on the prevalence of a condition. Doesn't account for degree of disagreement.	n=146 enrolled in the Multi-Ethnic Study of Atherosclerosis trial with echocardiography and CMR on the same day. For classification of hypertrophy (normalized for body surface area), there was weak agreement between modalities, albeit statistically significant (Cohen's kappa 0.37; $p<0.001$).(84)
Weighted kappa	Weights the degree of agreement and disagreement between data sets.	Requires a predefined table of weights.	n=80 with clinical aortic stenosis undergoing cardiac CT and TEE. Weak agreement between modalities for grading aortic valve calcification: Weighted kappa 0.34.(85)
Repeatability			
Repeatability coefficient (RC)	Uses the units of the variable.	Assumes normally distributed data. Unsuitable if the extent of agreement depends on the value of the measurement.	n=67 pregnant women with measurement of transabdominal Doppler ultrasound of the ductus venosus at 10-14 weeks of gestation. Intra-observer repeatability was better for pulsatility index for veins (RC 1.27) compared to end diastolic velocity (RC 2.03).(86)
Reliability			

Minimal detectable change (MDC)	To assess reliability of measurements. Simple method to detect change.	Suited more for short intervals between repeated measurements.	n=56 patients referred for echocardiography before beginning Herceptin treatment. Lowest intra and inter-observer variability for assessing LVEF shown with 3D without contrast (MDC= 0.048% and 0.075%) versus other echo methods with and without contrast.(81)
Coefficient of variation (CV)	Optimal method if the standard deviation is proportional to the mean.	Suboptimal method if there is a large difference between the highest and lowest possible values. Limited if the degree of error is not associated with the value of the measurement. Cannot be used if there are both positive and negative values.	n=60 (n=20 with heart failure, n=20 with LVH and n=20 with normal structure). CV values comparing CMR vs. TTE show lower variation with CMR: for LVEF 2.4-7.3% using CMR vs. 8.6-19.4% with TTE; for LVM 2.8-4.8% vs. 11.6-15.7% respectively.(87)
Percentage change	Scale independent. Simple to interpret.	Low statistical power compared to other methods. Does not correct for imbalance between groups.	n=608 with Marfan's syndrome assessing inter-observer assessment of aortic root dimensions. Measurements using a single beat were less reliable than taking the average of 3 beats (percentage error 3.9% ± 3.0 vs. 3.6% ± 2.6%; p=0.0002).(88)

Abbreviations: AoR= Aortic root; CT= Cardiac computed tomography; CMR= Cardiac magnetic resonance; GLS=Global longitudinal strain; HFpEF = Heart failure with preserved ejection fraction; LVEF= Left ventricular ejection fraction; MAPSE = Mitral annular plane systolic excursion; LVH= Left ventricular hypertrophy; LVM= Left ventricular mass; TEE= Transoesophageal echocardiogram.

1.4.4 Discussion

To ensure that the methods we use in echocardiography are useful for clinical decisions, reproducibility, repeatability and reliability should be assessed. Unreliable estimates have the potential to impact on patient management and outcomes, as well as leading to a waste of time and resources. The challenge for the echocardiographer is not only to identify a change in a biological parameter, but then to know whether that change is real or clinically significant. For example, is there a true change in cardiac structure and/or function that would require additional treatment, or is the change inconsistent or accounted for by changes to environment, operator or other factors?(89)

In contrast to clinical practice, there is already awareness in imaging research of the need to quantify intra- and inter-operator reproducibility, thereby providing some idea of generalisability to routine care. Design of research studies that formally evaluate reproducibility, repeatability or reliability should clearly delineate what variation is specifically being assessed, with clear use of terminology to avoid confusion. To accurately measure reproducibility, these data should not be gathered as an accessory to other data, but with a distinct study plan. Similar to other study outcomes, prior ascertainment of required sample size is vital so that a sufficient number of observations are obtained for quantification beyond the play of chance. (90, 91) Other important considerations are the method of subject sampling and whether this is consecutive, random or by convenience (with implications on statistical method and potential inclusion of bias), the degree of blinding possible, and appropriate reporting of all facets of the study.(92)

To identify any significant variability in echocardiographic parameters within a department, intra- and inter-observer variability can be measured.(54, 93) The possibility of measurement

error should be minimized as much as possible by ensuring that all equipment is accurately calibrated, adequate training is given to echocardiographers, and standardised guidelines are followed.(52) In clinical practice, a patient being serially assessed will likely be scanned by different echocardiographers on each occasion, hence the importance of ensuring no significant variation between operators. For numerical data (such as LVEF or Doppler values), the degree of agreement can be assessed by either the Bland and Altman plot or the ICC. Pure measures of association (such as correlation and linear regression) provide limited information, but are essential components of understanding and visualising data to assess for outliers and points which influence the trend of the data. When assessing a categorical result (such as quantifying the severity of mitral regurgitation), a kappa test can be used.(52, 54)

Repeatability and reliability measurements are as important, and give confidence that the values obtained can be used to make clinical decisions. Repeatability coefficients and the coefficient of variation are commonly used and can be calculated without difficulty.(52) For assessment of within-subject variation, three repeat measurements are usually considered appropriate (52, 94), translated into echocardiography as the average of three Doppler indices. This is probably appropriate for sinus rhythm, however in the case of atrial fibrillation, the assessment of reproducibility is even more challenging because of the variation in ejection time and volume between consecutive heart beats. Loss of atrial contraction and irregular ventricular contraction lead to beat-to-beat changes in pre-load, and hence variation in load-dependent echocardiography variables.(95) Although echocardiographers are recommended to average multiple consecutive beats in patients with atrial fibrillation, a systematic review by our group showed that isolating and averaging beats with similar cardiac cycle length (the index beat approach) could improve the overall reproducibility of measurement in atrial fibrillation.(37)

In my thesis, I use the techniques described in this section to explore the reproducibility, repeatability and reliability of the index beat method verses the averaging of consecutive beats.

1.5 Difficulty of assessing systolic and diastolic function in patients with atrial fibrillation

Determining accurate quantitative measurements of systolic and diastolic parameters is difficult in the setting of AF. AF is characterised by an irregular ventricular response, so there is continual haemodynamic variation from beat to beat altering preload, strength of contraction and afterload. This results in different systolic and diastolic parameters from beat-to-beat, due to a continual differing length of the R to R interval. The length of the R to R interval will determine the ventricular pre-load and via the Frank-starling mechanism; with more pre-load there is greater stretch and so in turn a more forceful contraction and also a greater stroke volume. This was investigated by Gosselink *et al.* who sought to determine how the length of the preceding R to R intervals will affect the end-diastolic volume and ejection fraction. Ejection fraction was influenced by not only the preceding cycle length but also the pre-preceding cycle length. Ejection fraction is enhanced when there is a short cycle length followed by a longer cycle length, as a result of post-extrasystolic potentiation.(96, 97)

Patients with AF are also prone to getting AF with an uncontrolled fast ventricular response, which makes the study more difficult. At faster heart rates there is increased beat-to-beat variability,(98) therefore more difficulty in obtaining reproducible results. Also due to reduced filling, as a result of shorter R to R intervals there is a reduced stroke volume. This

results in a general underestimation of LV function, despite normal intrinsic contractility.(98, 99)

1.5.1 Validity of systolic and diastolic parameters in patients with atrial fibrillation

A recent systematic review was carried out by Kotecha *et al.* to assess the validity and reproducibility of echocardiographic systolic and diastolic parameters for patients in AF(37).

There was a lot more information on the validity of diastolic function in AF patients. Several studies have compared invasive pulmonary capillary wedge pressure (PWCP) with diastolic indices derived from echocardiography. E/e' was shown to correlate well with PCWP with r values ranging from 0.46 to 0.79.(100-104) The correlations derived from these studies are similar to studies performed in patients with sinus rhythm, with correlations ranging from r=0.46 to 0.86.(105-107) IVRT has also been found to correlate strongly with PCWP with correlations ranging from r= -0.70 to -0.95.(44, 108-110). Mitral Valve E wave deceleration time has been correlated with PCWP with r values ranging from no correlation found to strong correlations of -0.70.(44, 100, 101, 108, 110-112). E/vp was found to strongly correlate with PCWP with r values ranging from 0.63 to 0.65.(44, 113) The pulmonary venous flow diastolic wave deceleration time had a very strong correlation with PCWP with r values of -0.91 and -0.80(111, 112) and the pulmonary venous S/D had a moderate correlation of r= 0.5.(106) There have also been studies comparing indices of diastolic function with other clinical parameters. An elevated E/e' has been shown to correlate with several factors, which predict a worse patient prognosis.(100) Okura et al carried out a retro-spective study analysing the mortality of patients with a septal E/e' >15 and <15. The patient group with an E/e' >15 had a higher all cause and cardiovascular mortality rate, suggesting E/e' is proportional to risk of mortality.(107) Oyama et al. assessed the relationship between E/Vp and levels of Brain Naturetic Peptide (BNP) using linear regression analysis. It was found

that the E/Vp correlated with levels of BNP; a higher E/Vp (cm/s) predicts higher levels of BNP.(108)

The number of studies assessing the validity of echocardiographic systolic parameters were far fewer. Surprisingly, there have been no studies comparing echocardiographic systolic parameters with other modalities, for example CMR or nuclear imaging. However there have been studies comparing different echocardiographic measurements for patients in AF. For example Thavendiranathan *et al.* assessed the relationship between ventricular volumes and LVEF measured by 2-D Simpson's biplane and 3-D volume imaging in patients with atrial fibrillation. The two modalities correlated highly with each other when both consecutive beats were averaged and on a single-beat basis(114). There have also been comparisons made with other clinical outcomes to determine the clinical utility of echocardiographic systolic measurements(37). Su H.M. *et al* compared global left ventricular strain with cardiovascular events. It was found that reduced longitudinal strain (>-12.5%) was independently associated with an increased risk of cardiovascular events(115).

However there is still a lack of clarity as to whether systolic measurements for patients in AF are valid. An individual patient data-meta analysis has been conducted by the Beta Blockers in Heart Failure Collaborative Group, to determine the effect of beta-blockers on patient prognosis according to the baseline LVEF.(116) As demonstrated in **Table 5,** patients in sinus rhythm have a worse outcome as baseline LVEF falls, with higher risk of all-cause mortality (HR 1.24 per 5% lower LVEF, 95% C.I. 1.21-1.28) and cardiovascular death (HR 1.20 per 5% lower LVEF, 95% C.I.1.22-1.30). In patients with atrial fibrillation on their ECG at randomisation, the association of LVEF with mortality was still significant, but much reduced compared to those in sinus rhythm HR 1.09, C.I. 1.03-1.15 and HR 1.10, C.I. 1.05-1.18 respectively.(117)

Table 5. Baseline LVEF and hazard ratios for all-cause and cardiovascular mortality in patients with sinus rhythm and atrial fibrillation (taken from Cleland JGF., Bunting KV., et al, 2018 (117))

	All-cause mortality		Cardiovascular death	
	Number (events / patients	**HR, 95% CI; p-value**	**Number (events / patients**	**HR, 95% CI; p-value**
Sinus rhythm; per 5% lower LVEF at baseline	2,160 / 14,261	1.24, 1.21-1.28; p<0.0001	1,768 / 14,260	1.20, 1.22-1.30; p<0.0001
Atrial fibrillation; per 5% lower LVEF at baseline	609 / 3,034	1.09, 1.03-1.15; p=0.002	498 / 3,034	1.10, 1.05-1.18; p<0.0001

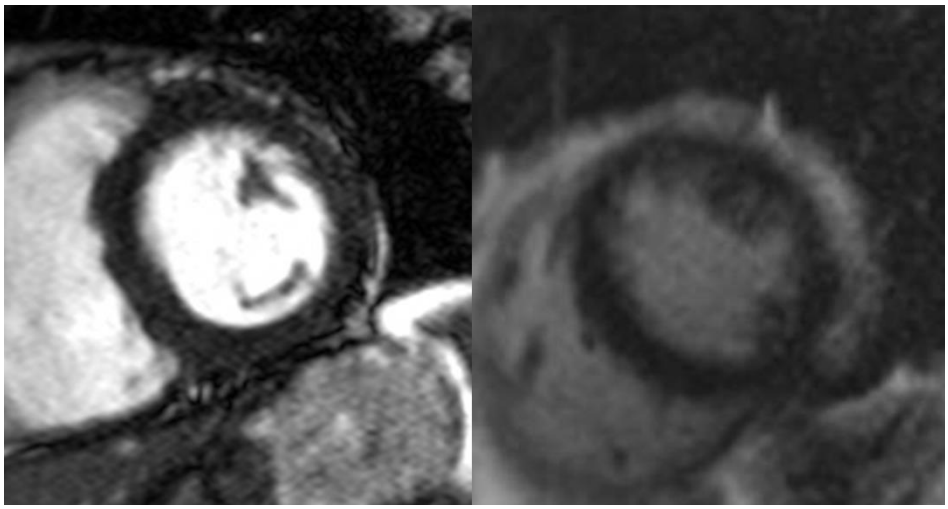
This data suggests that the systolic parameter LVEF is not as strongly associated with patient outcomes in AF, when compared to patients in sinus rhythm. This calls into question whether this is due to a biological property of AF, or whether this can be explained by LVEF lacking reproducibility and validity in the context of AF. Therefore studies need to be carried out to compare systolic measurements derived from echocardiography with other modalities measuring the same parameter in AF. We should not assume that echocardiographic measures designed for sinus rhythm will apply equally to those with irregular cardiac cycles. Parameter values which defined "normal" for patients in sinus rhythm also need to be validated in patients in AF. The reference values for normal LVEF have typically been based on population-based studies which have excluded patients with AF.(117)

1.5.2 Other Imaging Modalities and Atrial Fibrillation

Magnetic Resonance Imaging (MRI)

MRI is considered the gold-standard method for assessing left ventricular function in sinus rhythm.(118) Cardiac MRI delivers an unrestricted field of view with good temporal and spatial resolution without exposing the patient to any ionizing radiation. The standard method of measuring volumes and ejection fraction by MRI is to acquire a series of steady-state free precession cine images (SSFP) from the base to the apex of the heart. These are contiguous slices with minimal or no gap, that are then analysed by drawing the endocardial surface to produce a volume **(Figure 20)**. Cine images are acquired over 10-15 phases, with data from each phase filling k space. In the context of AF, the irregularity of cycle length both varies the extent of filling from a given cardiac cycle, and also leads to 'mis-matching' of data across the stack, so that the diastolic and systolic images may be taken or drawn at different times.(119-121)

Figure 20. SSFP short axis slice of the left ventricle. Image quality of a patient in sinus rhythm (left) verses poorer quality for patient in AF (right)



Computed Tomography (CT)

CT has superior spatial resolution and can rapidly acquire images, however it exposes the patient to ionising radiation. It uses retro-spective or prospective ECG gating to reconstruct images of the ventricle through all phases of the cardiac cycle. Similarly to CMR the endocardial boarders of the LV is traced to quantify LV size and function. In AF image quality of the endocardial and epicardial definition can be compromised due to misregistration artefact, resulting in difficulty in accurately measuring LV volumes and ejection fraction.(118)

Radionuclide Angiography

Also referred to as the multi-gated acquisition (MUGA) scan uses the radioactive compound technetium 99m pertechnetate to label red blood cells. The change in radioactivity between end-diastole and end-systole is measured to determine the LVEF; the greater change in radioactivity, the greater LVEF, as more red blood cells are leaving the heart. Again the acquisition of these images is gated by the patient's ECG, as it averages the acquisitions over time assuming a regular R to R interval; therefore if it measured on short R to R intervals it may underestimate the LVEF over time and vice versa for a longer R to R interval.(122)

This chapter has outlined the need for valid and reproducible echocardiographic parameters to assess systolic and diastolic function in AF patients, to guide clinical decisions in AF patients. Obtaining reproducible measurements using echocardiography is challenging and there is uncertainty of what method should be used to achieve reproducible and valid measurements. The following results chapters explore the validity and reproducibility of systolic and diastolic measurements.

Specifically, in the following results chapter I investigate the validity and reproducibility of systolic parameters across all cardiovascular imaging modalities. Then in **chapter 4** I answer a key clinical question about what is the most reproducible method of measuring systolic and diastolic parameters. This data is from a randomised controlled clinical trial with blinded echocardiography in all-comers with permanent AF, to demonstrate the real-world value of the index beat method verses conventional averaging of consecutive beats. This is followed by **chapter 5** in which I compare the validity of the index beat verses averaging of consecutive beats using NTproBNP and patient-reported quality of life.

Aims and Rationale

Currently when performing an echocardiogram in patients with AF, there is a lack of clarity of how to perform a study to accurately assess ventricular systolic and diastolic function which is both reproducible and clinically valid.

The systematic review by Kotecha *et al* has revealed a lack of validity studies for the assessment of systolic measurements using echocardiography in patients in AF at the time of imaging.(37) To date there has not been a systematic review assessing the validity of systolic measurements using other cardiac imaging modalities. Therefore the first aim is to perform a systematic review of all cardiac imaging studies assessing the validity and reproducibility of systolic measurements derived from patients in AF at the time of imaging.

Current guidelines on how many beats to measure to achieve a reproducible result are derived from minimal evidence. The introduction of the index beat method into routine clinical practice could provide reproducible and time-efficient results. Therefore the second aim is to determine the most reproducible method of obtaining systolic and diastolic parameters by comparing the intra and inter-operator variability of averaging up to 10 consecutive beats with the index beat method.

The validity of the index beat has not been compared with measurements made by conventional averaging of consecutive beats. There are also very few or no studies in which systolic and diastolic parameters have been compared against the clinical biomarkers N-terminal pro-brain naturetic peptide (NTproBNP) and patient symptoms. The third aim is to compare the systolic parameters of LVEF and GLS and the diastolic indice E/e' with NT-pro-BNP and to examine patient reported quality of life, the physical component score (PCS) of

the SF-36 tool and the atrial fibrillation effect on quality of life test (AFEQT) score derived from patient reported quality of life questionnaires will be used.

Hypothesis 1: On systematic review, there have been sufficient studies for cardiac imaging of all modalities for measurements of systolic function to be valid and reproducible in patients in AF at the time of imaging.

Hypothesis 2: Measuring on an index beat is a more reproducible method than averaging several consecutive beats when taking parameters of systolic and diastolic function.

Hypothesis 3: Echocardiographic parameters of systolic and diastolic function in patients with AF correlate with NTproBNP and the physical component score and atrial fibrillation effect on quality of life test score

Chapter 2: Systematic review of imaging methods to assess systolic function in AF patients

2.1 Introduction

As well as impacting on quality of life and increasing the risk of stroke, hospital admission, cognitive dysfunction and mortality, AF is strongly associated with the development and progression of heart failure.(123) Reduction in left-ventricular ejection fraction (LVEF) is a common finding in AF patients, particularly in those with persistent or permanent AF.(124) To enable clinicians to provide appropriate therapy and improve prognosis, it is essential that systolic function can be accurately assessed. In clinical practice, echocardiography, cardiovascular magnetic resonance imaging (CMR), computed tomography (CT), invasive angiography and nuclear scintigraphy are all used to assess systolic function, with each technique possessing advantages and limitations. As discussed in **chapter 1**, cardiac imaging in patients with AF is challenging due to the variation in ejection time, force of contraction and filling period.(124) There is varied susceptibility of each imaging modality to R-R interval irregularity and/or elevated heart rate, with validity and reproducibility reduced by difficulties in acquiring diagnostic-quality images or the interpretation or results. The assumption that parameters used in sinus rhythm to quantify systolic dysfunction have the same validity in AF may not be correct.(37) As outlined in **chapter 1** in heart failure patients with AF, conventional LVEF measurements are significantly associated with all-cause mortality, but with a substantially reduced relationship compared to sinus rhythm.(117)

A systematic review of all studies assessing the validity and/or reproducibility of systolic function measurements, in patients in AF at the time of cardiac imaging was performed. The systematic review synthesised conclusions from all evidence available, minimising bias and at the same time reliably identifying areas for further investigation. The knowledge gaps identified will guide the aim of future results chapters. The aim of this systematic review was to determine if different imaging modalities of systolic assessment have clinical value in patients with AF, to assist in the diagnosis of heart failure and guide optimal management for

patients. To assess this, the evidence for the reproducibility and validity of systolic measurements made in patients in AF, was examined across cardiac imaging modalities.

2.2 Methods

The systematic review of imaging modalities in patients with AF was performed prospectively and published on PROSPERO (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=91674) and reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.

2.2.1 Eligibility criteria & search strategy

All studies reporting validity or reproducibility data on left ventricular (LV) systolic function in AF patients were examined. There was no restriction on study design, however only human populations with AF at the time of imaging were included. Exclusion criteria included case reports, studies that were only published in abstract form, and those in a language other than English. All editorials, commentaries and informal reviews of other literature were also excluded. An online search of PubMed, Embase and MEDLINE through the OVID library (inception to February 2019) was performed, including the broad terms "atrial fibrillation", "angiography", "computed tomography", "cardiac magnetic resonance", "nuclear imaging" and "echocardiography" using MESH headings and title/abstract searches, including syntax variations (see **Table 6**). A manual screening of relevant reviews and reference lists was also conducted.

Table 6: Example of search criteria

Search Operators:

Echocardiography	Computed Tomography	MRI	Nuclear imaging	Systolic function	Ventricle
Echo* Cardiac ultrasound TTE TOE TEE Transthoracic echo* Transoesophageal echo*	CT Computed axial tomography Computer assisted-tomography Computerized tomography CAT scan	Magnetic resonance imaging MR MRI Cardiac MR Functional magnetic resonance imaging fMRI	MUGA scan Technetium heart scan Ventriculography Radionuclide Radionuclide angiography Multi-gated acquisition scan	Ejection fraction Function Contraction Stroke volume Cardiomyopathy Heart failure Strain TDI Tissue Doppler imaging	Left ventricle Cardiac function Heart function Ventricular Chamber

Example of search strategy for Cardiac Magnetic Resonance:

("atrial fibrillation"[MeSH Terms] OR ("atrial"[All Fields] AND "fibrillation"[All Fields]) OR "atrial fibrillation"[All Fields]) AND ((("heart"[MeSH Terms] OR "heart"[All Fields] OR "cardiac"[All Fields]) AND ("magnetic resonance imaging"[MeSH Terms] OR ("magnetic"[All Fields] AND "resonance"[All Fields] AND "imaging"[All Fields]) OR "magnetic resonance imaging"[All Fields] OR "mri"[All Fields])) OR ("Calif Manage Rev"[Journal] OR "cmr"[All Fields]) OR ("magnetic resonance imaging"[MeSH Terms] OR ("magnetic"[All Fields] AND "resonance"[All Fields] AND "imaging"[All Fields]) OR "magnetic resonance imaging"[All Fields] OR "mri"[All Fields]) OR (("heart"[MeSH Terms] OR "heart"[All Fields] OR "cardiac"[All Fields]) AND ("magnetic resonance imaging"[MeSH Terms] OR ("magnetic"[All Fields] AND "resonance"[All Fields] AND "imaging"[All Fields]) OR "magnetic resonance imaging"[All Fields])) OR (("heart"[MeSH Terms] OR "heart"[All Fields] OR "cardiac"[All Fields]) AND ("magnetic resonance spectroscopy"[MeSH Terms] OR ("magnetic"[All Fields] AND "resonance"[All Fields] AND "spectroscopy"[All Fields]) OR "magnetic resonance spectroscopy"[All Fields] OR ("magnetic"[All Fields] AND "resonance"[All Fields]) OR "magnetic resonance"[All Fields]))

2.2.2 Outcomes

The primary outcomes of interest were the validity and reproducibility of LV systolic assessment in AF patients using different imaging modalities. For echocardiography, these included LVEF (measured either by Simpson's biplane method or three-dimensional [3D] volume assessment), fractional shortening, stroke volume derived from left ventricular outflow tract (LVOT) pulsed wave Doppler, tissue Doppler velocities, pre-ejection period derived myocardial performance index (MPI), peak longitudinal systolic strain (PLSS) and global longitudinal strain (GLS). For CMR, this included volume-derived LVEF, GLS using either feature tracking or myocardial tagging, and stroke volume derived from flow mapping in the aortic root. For nuclear medicine, this included measurements of LVEF derived from: radionuclide equilibrium angiography, gated single photon positron emission tomography (SPECT) and gated positron emission tomography (PET). Data was extracted systematically using a standardised extraction form to ascertain: (1) validity against other imaging modalities (external validation); (2) association with clinical or surrogate endpoints; (3) comparison within an imaging modality (internal validity); and (4) measurements of intra- and inter-operator reproducibility.

2.2.3 Data collection and quality assessment

Two investigators independently assessed inclusion at full text level and extracted relevant variables (KB and KO). Disagreements were resolved by consensus review and additional independent adjudication (DK). Variables of interest for validity were strength of association using correlation (r) and intra-class correlation coefficient (ICC), and agreement using Bland and Altman analysis. For association with clinical parameters, hazard ratios, chi-squared tests, area under the curve and Kaplan-Meier analysis were also included. Variables of

interest for reproducibility were agreement using Bland and Altman analysis and mean difference, association measured using correlation coefficients, linear regression (r^2) and ICC, and variability measured using percentage change, coefficient of variation and repeatability coefficient.

Study quality was assessed using Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2).(125) Risk of bias was similarly assessed by two investigators independently with adjudication, covering bias and applicability on the level of patient selection, the index test, reference standard and study flow and timing (**Figure 22**).

2.2.4 Data synthesis and statistical analysis

Baseline demographics were pooled from all studies providing suitable data (including variance where applicable), and are summarized as a weighted mean according to sample size. Outcomes were synthesized qualitatively. Meta-analysis of comparative data between AF and sinus rhythm was not possible due to the limited studies available and a lack of published data on the variance of outcome measures.

2.3 Results

From the search strategy, a total of 7382 papers were identified of which 7058 were excluded mainly due to a lack of relevance to the assessment of systolic function in patients with AF. After the full text was screened, a further 310 studies were excluded leaving a total of 24 studies which were then sorted into each imaging modality (**Figure 21**). Overall risk of bias is presented in **Figure 22**, highlighting concern about patient selection bias. Results of cardiac imaging in AF are categorised according to external validity (**Table 7**), internal validity (**Table 8**) association with clinical or surrogate endpoints (**Table 9**), and reproducibility (**Table 10**). In the text below, results are summarised according to imaging modality (see **Table 11**).

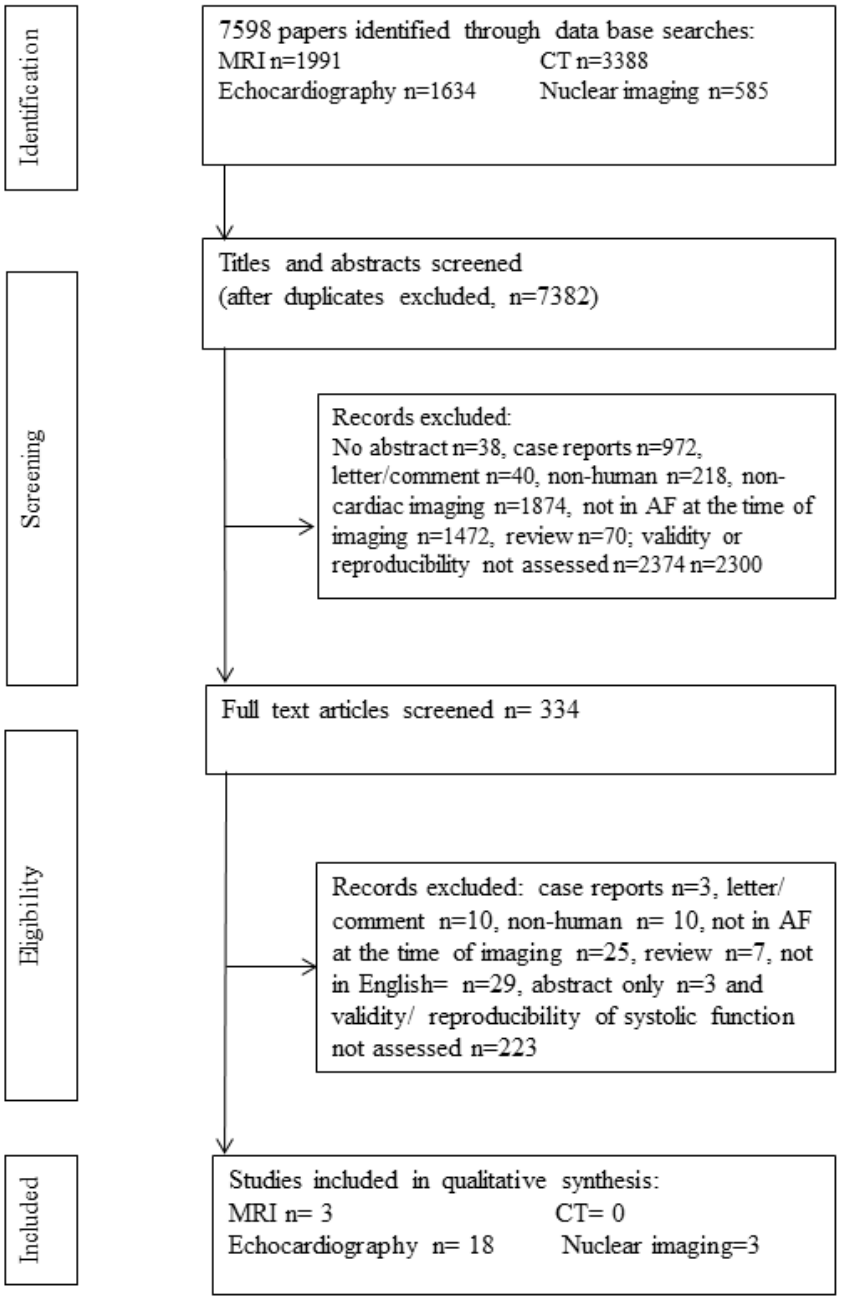
2.3.1 Cardiac Magnetic Resonance Imaging

Three CMR studies were included which either assessed stroke volume or LVEF derived from breath-hold cines with steady-state free precession imaging (SSFP) of the LV to calculate end-diastole and end-systole short-axis volumes. I identified no studies assessing the reproducibility or validity of phase mapping or strain imaging in patients with AF at the time of imaging. The method of patient selection and flow and timing of data obtained was unclear for these studies and so the risk of bias was unclear.

One study externally validated CMR parameters of LVEF and stroke volume against invasive catheter angiography in 13 AF patients; three of the patients were excluded due to frequent ventricular ectopy, frequent need to void and data corruption. CMR-derived LVEF was shown to correlate strongly with left ventriculography ($r=0.85$, with a mean difference of 0, SD 0.08; $p= 0.37$). CMR-derived stroke volume correlated strongly with both left

ventriculography (r=0.90, with a mean difference of 4 ml SD 13 ml; p= 0.24) and thermodilution techniques (r= 0.95, with a mean difference of -5 ml SD 10; p= 0.06).(126)

Figure 21. Systematic review flowchart. Flow chart to show the number of papers included and excluded at each stage of the screening process.



Abbreviations: AF= atrial fibrillation; CT= computed tomography; MRI= magnetic resonance imaging

One study internally validated LVEF by comparing compressed sensing and parallel imaging with conventional SSFP in 20 patients with AF. A strong correlation was observed between LVEF measured by this method and conventional SSFP (ICC=0.97, 95% CI 0.93-0.99, p=0.14) with a small mean difference between methods (-4%± 11%), although heart rate at the time of LV assessment was not stated.(127)

Two studies examined the reproducibility of systolic parameters using CMR. LVEF inter-observer reproducibility was higher using CMR when compared to angiography; for CMR the standard error was 8% versus 14% with left ventriculography. This was also shown for stroke volume; a standard error of 9mL for CMR versus 24mL with left ventriculography.(126) Heart rate was not stated. The reproducibility of LVEF using SSFP was examined in 10 patients with permanent AF and a mean heart rate of 82 bpm (range from 57-109), in which intra-observer reproducibility was good with r^2= 0.97, repeatability coefficient was 3.8 and a Bland and Altman bias of -1.9 % 2SD 4.2. Inter-study reproducibility was also good with r^2= 0.99, repeatability coefficient 1.3 and Bland and Altman bias of 0.5 % 2SD 3.(128)

2.3.2 Nuclear Imaging

No studies were identified in which systolic parameters were externally validated or correlated with other clinical parameters in patients with AF. Three nuclear imaging studies were included that addressed reproducibility. The method of patient selection and degree of blinding to the index and reference test was not stated clearly in these studies, making the risk of bias unclear.

Gating errors are a well-known limitation of SPECT imaging in patients with AF, and in one study of 35 AF patients with suspected coronary artery disease, gating errors from AF were simulated and compared with a control group of 35 patients in AF. AF gating errors

significantly affected the measurement of wall thickening (60% ± 299%) and myocardial perfusion (76% ± 352%). This study also showed that gated SPECT had a strong correlation with equilibrium radionuclide angiocardiography (r= 0.89, p=<0.0001), however LVEF measured by SPECT was consistently lower by 3-4%.(129)

In gated pool studies, cycle length windowing is used as a way to overcome the altering cardiac cycle length in patients with AF. In a study of 20 AF patients, LVEF values from the windowed studies were slightly higher compared to non-windowed, but this was not statistically significant (p=0.16) and the correlation between the two methods was very strong (r= 0.97).(130) The reproducibility of measuring volumes and LVEF was assessed in 115 patients with AF using myocardial perfusion gated SPECT, with low inter and intra observer variability and low variation between two consecutively taken studies (inter-assay) using two different quantitative parameters.(131)

2.3.3 Echocardiography

Eighteen echocardiography studies were included, of which 15 examined validity either against external modalities, clinical parameters or internal measures, and 8 studies assessed reproducibility. There were no studies identified which directly compared measurements of systolic function with another imaging modality. The method of patient selection for most echocardiography studies incurred a high risk of bias, due to the exclusion of patients with inadequate echocardiographic windows.

Two studies externally validated echocardiographic systolic parameters against dP/dt derived from invasive angiography, with GLS found to have a strong correlation with averaged dP/dt (r=0.94; p<0.001).(132) Tissue Doppler s' was shown to correlate strongly with dP/dt (r=0.88, p<0.0001) which was accentuated in AF patients with heart failure (r=0.90, p<0.0001).(133)

Nine studies compared echocardiographic indices of systolic function with clinical parameters or surrogate biomarkers. In 1293 AF patients who had suffered a myocardial infarction, lower LVEF (estimated using an echocardiographic wall motion score) was associated with an increase in the risk of 30-day mortality (8% for patients with LVEF >50%, 10% for LVEF 36-50%, 24% for LVEF 26-35% and 40% for LVEF <25%). However, lower LVEF (<0.25) did not affect long-term mortality in AF patients.(134) Reduced GLS was associated with adverse CV events in two studies of 196 and 204 AF patients, (135, 136) with similar results seen with global circumferential strain and when GLS was corrected for R to R interval.(137) Myocardial performance index was associated with cardiovascular events in 196 patients with a hazard ratio of 1.10 per 0.1 unit increase (95% CI 1.03-1.18; p= 0.004).(138) In 104 AF patients, LVEF derived from Simpson's biplane correlated weakly with B-type natriuretic peptide (r= -0.25; p= 0.07).(139) In 67 patients with AF, LVEF derived from the Teichholz formula was shown to weakly correlate with atrial natriuretic peptide (r=-0.42, p=0.01).(140)

Four studies have internally validated systolic parameters with other echocardiographic parameters (**Table 8**), showing strong correlation of real-time 3D full-volume and Simpson's biplane LVEF in 24 patients on both a beat-to-beat level (r=0.92; p<0.001) and patient level (r=0.91; p<0.001)(141), and reasonable correlation of M-mode mitral annulus motion with LVEF (20 patients) (142) and LVOT stroke volume with fractional shortening (18 patients).(99) Myocardial performance index derived from pre-ejection period was found to correlate moderately with LVEF (r= -0.586, p<0.001) and TDI s' (r=0.601, p=<0.001).(143)

There have been no echocardiographic studies comparing the reproducibility of systolic parameters directly with other imaging modalities. A variety of small studies have demonstrated low levels of intra and inter-observer variability for LVEF, GLS and myocardial performance index when reassessing systolic function in AF patients using echocardiography (**Table 10**). 3D measurement of LVEF was shown to be more reproducible when calculated

using a single-beat analysis compared to 4-beat averaging (intra-observer variability 4.8% versus 8.3%; inter-observer 5.6% versus 17.9%).(144) An index beat approach, whereby measurement is made following two R to R intervals of similar length results in lower intra and inter observer variability compared to conventional averaging of consecutive beats (132, 135, 145)

2.3.4 Computed Tomography

There were no studies assessing validity, association with clinical endpoints or reproducibility of systolic function in patients with AF.

Figure 22. Risk of bias overall studies according to QUADAS-2 assessment. **Bar chart (left panel) to display the proportion of studies with low, high or unclear bias according to the categories work flow, reference test, index test and patient selection. Bar chart (right panel) to display the proportion of studies with low, high or unclear concerns of applicability according to the categories reference test, index test and patient selection.**

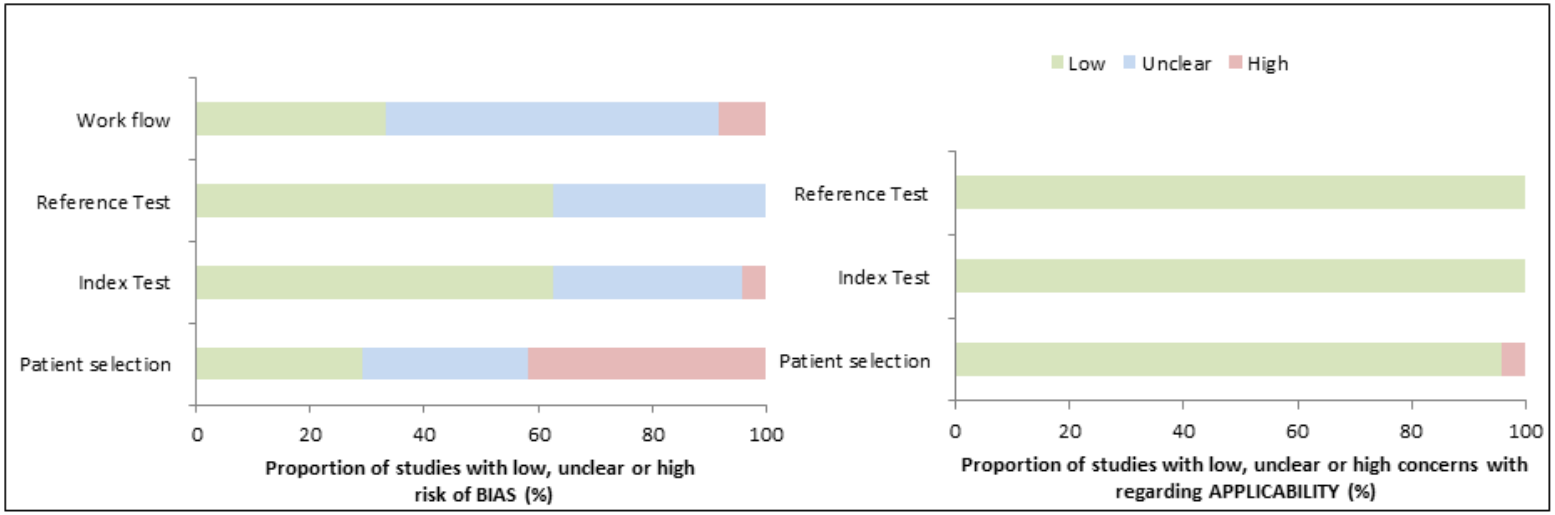


Table 7. External validity of systolic parameters against another modality in AF

Parameter	Study	Number of patients	Mean heart rate ± SD (bpm)	Blood pressure ± SD (mmHg)	Imaging modality	Validated against	Validity results
LVEF (%)	Hundley (1996)(126)	10 patients with AF (3 were excluded) & 13 patients in sinus rhythm	[not stated]	[not stated]	Gradient echo CMR	Invasive catheter angiography	In AF patients $LVEF_{MRI}$ vs $LVEF_{cath}$ r= 0.85; mean difference= 0% SD 0.08%, p= 0.37
	Kusunose (2012)(132)	25 AF patients with dyspnoea, angina or LV asynergy	74 (± 15)	131/ 76 (±16/12)	TTE	Invasive LV peak pressure (dP/dt)	$LVEF_{TTE}$ vs dP/dt r=0.49, p=0.013
Stroke Volume (ml)	Hundley (1996)(126)	10 patients with AF (3 were excluded) & 13 patients in sinus rhythm	[not stated]	[not stated]	CMR	Invasive catheter angiography and thermodilution	SV_{MRI} vs SV_{Thermo} r= 0.9; mean difference= -5ml SD 10ml, p=0.06 ; SV_{MRI} vs SV_{cath} , r = 0.95, mean difference= 4 ml SD 13ml, p= 0.24
GLS (%)	Kusunose (2012)(132)	25 AF patients with dyspnoea, angina or LV asynergy	74 (± 15)	131/ 76 (±16/12)	TTE	LV peak pressure (dP/dt)	Index beat LS_{TTE} with peak +dP/dt (r = 0.73, p < .001).
TDI systolic wall motion (cm/s)	Oki (1999)(146)	39 AF patients with no significant valve disease or regional LV wall synergy	Lone AF 78 (±18) AF with a dilated LV 80 (±15)	AF only MBP 92 (±8) Dilated MBP 90 (±11)	TTE	LV peak pressure (dP/dt)	S'_{TTE} vs dP/dt, r=0.88, p= <0.0001.
	Kusunose (2012)(132)	25 AF patients with dyspnoea, angina or LV asynergy	74 (± 15)	131/ 76 (±16/12)	TTE	LV peak pressure (dP/dt)	S'_{TTE} vs dP/dt r=0.56, p=0.03

Abbreviations: AF= atrial fibrillation; CMR= cardiovascular magnetic resonance imaging; GLS= global longitudinal strain; HR= hazard ratio; LS= longitudinal strain; LV= left ventricular; LVEF= left ventricular ejection fraction; MBP= mean blood pressure; SD= standard deviation; SV= stroke volume; TDI= Tissue Doppler imaging; TTE= Transthoracic Echocardiography;

Table 8: Internal validity of systolic parameters in AF

Parameter	Study	Number of patients	Mean heart rate ± SD (bpm)	Blood pressure ± SD (mmHg)	Imaging modality	Validated against	Validity results
LVEF (%)	Goebel (2017)(127)	20 patients with persistent AF	[not stated]	[not stated]	SPARSE-SENSE cine CMR	Cine SSFP CMR	ICC comparing both sequences, for LVEF ICC= 0.90, 95% C.I.= 0.93 to 0.99) and SV ICC= 0.80, 95% C.I.= 0.75 to 0.96
	Nichols K (1999)(129)	36 AF patients with suspected coronary artery disease	[not stated]	[not stated]	ERNA nuclear imaging	SPECT	r= 0.89, p<0.0001.
	Wallis, (1991)(130)	20 AF patients	94 (58-124)	[not stated]	Non-windowed scintigraphy	Windowed scintigraphy	Windowed LVEF slightly higher than non-windowed LVEF. r= 0.97, standard error of the estimate= 3.5
	Thavendiranathan, (2012) (141)	24 AF patients. Excluded for poor echocardiographic image quality	82 ± 19	[not stated]	3D RT-VTTE	Simpson's biplane LVEF	r =0.92 at a beat-to-beat level; at patient level r= 0.91 (p<0.001). Bland and Altman analysis bias (± limits of agreement)= -2 (±4%), p>0.05
Mitral annulus motion (mm)	Emilsson, (2000)(142)	20 AF & 20 sinus rhythm patients. Excluding poor image quality	83 ±15	[not stated]	TTE	LVEF Simpson's Biplane method	LVEF vs MAM, AF r= 0.66, p= <0.01 vs SR r=0.84,p<0.001. Conversion factor from LVEF to MAM, AF=7,.2 (±1.8) vs SR= 5.1 (±0.9), p=0.001.
LVOT peak	Ko, (2005)(147)	18 AF patients.	Normal LV	Normal 119.4/	TTE	Fractional	Fractional shortening vs

velocity (cm/s)		Excluded those with R-R intervals outside 0.6 and 1s	function: 76.9 (±10.2) Impaired LV function: 80 (±8.6)	73.9 (±18.6/7.4) Impaired: 115/71.7 (±16.6/7.5)		shortening	the LVOT peak velocity (where RR1= 1 second) r= -0.6, p= 0.008 and vs LVOT peak velocity (where RR2= 1 second) r=0.62, p=0.006.
Myocardial Performance index	Su (2011) (143)	54 patients with permanent AF	80 ± 13	133/ 81 (±18/12)	TTE	Modified Simpson's LVEF and Sa	Vs LVEF: r= -0.586, p<0.001 & β= -0.26 p=0.024. Vs Sa r=0.601, p=<0.001, β=-0.141, p=0.336.

Abbreviations: 2D= two dimensional; 3D-RT-VTTE= real-time full-volume 3-dimensional transthoracic echocardiography; AF= atrial fibrillation; CMR= cardiovascular magnetic resonance imaging; C.I.= confidence interval; ERNA= Equilibrium Radionuclide Angiocardiography; ICC= intra-class correlation coefficient; LVEF= left ventricular ejection fraction; LVOT= left ventricular outflow tract; MAM= mitral annulus motion; MBP= mean blood pressure; MRI= magnetic resonance imaging; RR1= preceding R to R interval; RR2= pre-preceding R to R interval; Sa= peak systolic mitral annular velocity; SPARSE-SENSE =compressed sensing and parallel imaging ; SPECT= single-photon emission computed tomography; SR= sinus rhythm; SV= stroke volume; SV= stroke volume; TTE= Transthoracic Echocardiography; Vpe= Left ventricular peak ejection velocity

Table 9. Clinical associations of systolic parameters in AF

Parameter	Study	Number of patients	Mean heart rate ± SD (bpm)	Blood pressure ± SD (mmHg)	Imaging modality	Validated against	Validity results
LVEF (%)	Kim, (2007)(148)	104 with chronic AF	[not stated]	127.4/78.5 (±13.8/8.9)	TTE	BNP(pg/l)	r=-0.25,p= 0.065
	Su, (2013)(135)	196 AF patients. Exclusion: severe valve disease and inadequate echo windows.	83 (±20)	132/76.5 (±21/12)	TTE	CV events (death, non-fatal stroke & hospitalisation for heart failure)	Univariate analysis of HR= 0.97 (0.95 to 0.99), p=0.001
	Wozakowska-Kaplon, (2005)(149)	67 patients with persistent AF. Excluded if: NYHA IV, LVEF= <45%, uncontrolled AF, untreated hypertension, unstable angina, myocardial infarction within the preceding 3 months, anaemia, renal or liver insufficiency, respiratory failure, and malignancy.)	84.3 ± 8.4	SBP: 117 (±15)	TTE Teichholz formula LVEF	ANP	Univariate analysis r=-0.42, p=0.01 Multivariate regression r=0.22
	Pedersen, (2005)(134)	6232 patients who had suffered a myocardial infarction. 1293 with AF and 4953 without AF	[not stated]	[not stated]	TTE LV wall motion index	Mortality	In patients with LVEF <0.25 presence of AF increased risk of in hospital mortality, OR= 1.8 (1.1-.3.2, p <0.05) but no effect on long term mortality. In patients with LVEF 0.25 to

Parameter	Study	Number of patients	Mean heart rate ± SD (bpm)	Blood pressure ± SD (mmHg)	Imaging modality	Validated against	Validity results
							<=0.35 the presence of AF increased risk of in-hospital mortality, OR = 1.7 (1.3-2.3, p<0.001) and 30 day mortality OR= 1.7 (1.3 – 2.2, p<0.001).
GLS	Dons (2018)(136)	204 patients in AF	90 ± 21	[not stated]	TTE	Adverse outcome (all-cause mortality, incident heart failure, stroke and myocardial infarction)	Reduced GLS increased risk of adverse outcome. Unadjusted GLS per 1% increase= HR 1.14 (1.07-1.21, p=<0.001); GLS/√(RR) per 1%/sec increase= HR 1.13 (1.07-1.2, p= <0.001)
	Modin,(2018)(137)	151 AF patients with HFrEF	80.3 ± 20.4	MAP 93.4 (±14.2)	TTE	All-cause mortality	R-R corrected GLS (GLSc) and GCS (GCSc) predicts all-cause mortality. GLSc: HR= 1.19 (CI 1.06-1.33) per 1% decrease, p= 0.003 and GCSc: HR=1.17 (C.I. 1.05-1.31) per 1% decrease, p=0.005.
	Su, (2013)(135)	196 AF patients. Exclusion: severe valve disease and inadequate echo windows.	83 (±20)	132/76.5 (±21/12)	TTE	CV events (death, non-fatal stroke & hospitalisation for heart failure)	Multivariate analysis showed a lower GLS increased risk of CV events HR= 1.12, CI 1.02 to 1.23, p<0.014. Kaplan-Meir GLS >-12.5% predicts increased CV events.
TDI s'(cm/s)	Su, (2013)(135)	196 AF patients. Exclusion: severe valve disease and inadequate echo windows.	83 (±20)	132/76.5 (±21/12)	TTE	CV events (death, non-fatal stroke & hospitalisation for heart failure)	Univariate analysis HR 0.680 (0.560 to 0.826), p<0.001.

Parameter	Study	Number of patients	Mean heart rate ± SD (bpm)	Blood pressure ± SD (mmHg)	Imaging modality	Validated against	Validity results
PEPa derived MPI	Chu, (2015)(150)	196 patients with persistent AF. Excluding significant valve disease and inadequate echo windows	83 (±20)	132/77 (±12/20)	TTE	CV events (CV death, nonfatal stroke & hospitalisation for heart failure)	PEPa-derived MPI ≥0.72 increased cardiovascular events. Per 0.1 increase in PEPa-derived MPI increase CV events by HR: 1.44 (C.I. 1.09 to 1.90), p=0.011).
LVOT velocity (cm/s)	Lee, (2009)(151)	107 Patients in AF. Exclusion: Patients with most RR intervals <0.6 or >1.0 second, hemodynamically significant mitral stenosis or aortic stenosis	76.9 (±11.7)	[not stated]	TTE	Heart failure	Areas under the receiver operating characteristics curve of slope/Vpe-1 for identifying heart failure were 0.72 (95% confidence interval 0.63 to 0.82, p<0.000) and 0.74 (95% confidence interval 0.62 to 0.85, p <0.001) in all patients and in patients with normal LV size and without significant regurgitation, respectively

Abbreviations: 2D= two dimensional; 3D-RT-VTTE= real-time full-volume 3-dimensional transthoracic echocardiography; AF= atrial fibrillation; ANP= atrial natriuretic peptide; BNP= brain natriuretic peptide; C.I.= confidence interval; CMR= cardiovascular magnetic resonance imaging; CV= cardiovascular; ERNA= Equilibrium Radionuclide Angiocardiography; HFrEF= heart failure with reduced ejection fraction; HR= hazard ratio; GCS= global circumferential strain; GLS= global longitudinal strain; LVEF= left ventricular ejection fraction; MAM= mitral annulus motion; MAP= mean arterial pressure; MRI= magnetic resonance imaging; NYHA= New York Heart Association; OR= odd's ratio; PEPa-derived MPI= Pre-ejection period derived myocardial performance index; SD= standard deviation; SPECT= single-photon emission computed tomography; TTE= Transthoracic Echocardiography; Vpe= Left ventricular peak ejection velocity

Table 10: Reproducibility of systolic measurements in AF

Parameter	Study	Number of patients	Mean heart rate ± SD (bpm)	Blood pressure ± SD (mmHg)	Imaging modality	Acquisition method	Reproducibility results
LVEF (%)	Goebel (2017)(127)	20 patients with persistent AF	[not stated]	[not stated]	CMR	SSFP and real-time SPARSE CMR	Bland and Altman for intra observer SSFP = -0.6% (-6.0 to 4.8) and real-time SPARSE = 0% (-3.8 to 3.8). Inter observer: SSFP= 0.4% (-17.2 to 18.1) and real-time SPARSE= -1.1% (-15.9 to 13.6)
	Hundley (1996)(126)	13 patients with AF & 13 patients in sinus rhythm	[not stated]	[not stated]	CMR	Gradient echo MRI	n= 10 in AF (3 excluded). Inter-observer variability (standard error): 8%
		13 patients with AF & 13 patients in sinus rhythm	[not stated]	[not stated]	Angiography	Average of 3 measurements	n= 10 in AF (3 excluded). Inter-observer variability (standard error): 14%
	Therkelsen, (2005)(128)	19 permanent AF patients	82 (57-109)	148/86 (111-186)/(61-117)	CMR	15 beats per slice	n=10 AF in analysis, Intra-observer variability: LV EF: R^2= 0.97, RC= 3.8 and bias= -1.9 ± 4.2 2SD. Inter-study variability: LV EF: R^2= 0.99, RC= 1.3 and bias= 0.5 ± 3 2SD.
	Aguade-Bruix, (2010)(131)	115 with chronic AF referred for myocardial SPECT	Gated SPECT 1: 74.9 (±15.2) Gated SPECT 2: 73.0(±15.57)	[not stated]	Gated SPECT	QGS and ECT	SPECT Inter-observer variability: 0.47% (0.19-1.14) &intra-observer variability: 0.22% (0.08-0.94) Inter-session variability between first and second SPECT study, using QGS r=0.948 (C.I. 0.926-0.964) and ECT r=0.951 (C.I. 0.930-

Parameter	Study	Number of patients	Mean heart rate ± SD (bpm)	Blood pressure ± SD (mmHg)	Imaging modality	Acquisition method	Reproducibility results
							0.966)
	Egami, (2010)(152)	27 hypertensive patients with persistent AF who had previously been cardioverted	[not stated]	118/76 (±18/9)	TTE	Not specified	N= 10 randomly selected AF patients. Average difference in measurements, inter-observer= -0.12% (r=0.97) and intra observer variation= -0.09% (r=0.83)
	Henrard, (2013)(153)	59 AF patients taking part in the AF-CHF echocardiographic sub-study	Rhythm: 69.2 (±13.6) Rate: 73.2 (±17)	Rhythm: 110.8/65.4 (±17.9/11.1) Rate: 110.6/65.3 (16.9/9.4)	TTE	Modified Simpson's biplane LVEF averaged over 3-5 beats	N=20 patients randomly selected. ICC intra-reader for two observers 0.96 and 0.98 and for inter-reader was 0.9.
	Shahgaldi, (2010)(144)	23 AF patients and 55 patients with sinus rhythm	97 (±27)	[not stated]	TTE	3D	Single beat vs 4 beat 3D analysis: Intra observer variability: 4.8% vs 8.3 % (p<0.001). Inter observer variability: 5.6% vs 17.9% (p<0.001).
Stroke Volume (mL)	Hundley, (1996)(126)	13 patients with AF & 13 patients in sinus rhythm	[not stated]	[not stated]	CMR	8-12 frames per cardiac cycle using phase contrast CMR	n= 10 in AF (3 excluded).Inter observer: Standard error= 9mL
		13 patients with AF & 13 patients in sinus rhythm	[not stated]	[not stated]	Angiography	Average of 3 beats using thermodilution	n= 10 in AF (3 excluded).Inter observer: Standard error= 24mL.
	Goebel (2017)(127)	20 patients with persistent AF	[not stated]	[not stated]	CMR	SSFP and real-time SPARSE	Bland and Altman for intra observer SSFP= -0.5 (-9.7 to 8.7) and real-time SPARSE = -

Parameter	Study	Number of patients	Mean heart rate ± SD (bpm)	Blood pressure ± SD (mmHg)	Imaging modality	Acquisition method	Reproducibility results
							0.1 (-6.0 to 5.8). Inter observer: SSFP= 7.2 (-17.4 to 31.8) and real-time SPARSE= 4.3 (-22.4 to 31.1)
Longitudinal Strain (%)	Lee, (2012)(154)	98 Patients with persistent or permanent AF and resting ventricular rates ≤ 105 bpm	76 (±13)	135/ 79 (±24/11)	TTE	Index beat vs 15 average beats	N= 15 randomly selected patients. The intra-observer and inter-observer mean percentage errors for PLSSavg: 2.4 ± 1.4% and 2.7 ± 1.7%; and for PLSSindex 3.5 ± 2.9% and 4.0 ± 2.9%
	Kusunose, (2012)(132)	25 AF patients with dyspnoea, angina or LV asynergy	74 (± 15)	131/ 76 (±16/12)	TTE	average over 10 seconds	N= 10. The intra-observer variability for mean percentage error of LS was 6.6 ± 8.8%, and the inter-observer variability was 7.2 ± 9.1%.
	Dons, (2018)(136)	204 patients in AF	90 ± 21	[not stated]	TTE	indexed the strain measurements with the square root of the RR-interval	N=20 randomly selected patients. Intra and inter-observer variability for GLS/√(RR had a mean difference ±1.96 SD: −0.12±2.37 and −1.36±3.87. GLS/√(RR) had the lowest variability with a coefficient of variation of 13% for intra- and 15% for inter-observer variability.
	Su, (2013)(135)	196 AF patients. Exclusion: severe valve disease and inadequate echo	83 (±20)	132/76.5 (±21/12)	TTE	The index beat	N=30 randomly selected patients. Mean percent errors for intra-observer= 5.3 ± 3.5% and for inter-observer= 6.2 ± 3.8%.

Parameter	Study	Number of patients	Mean heart rate ± SD (bpm)	Blood pressure ± SD (mmHg)	Imaging modality	Acquisition method	Reproducibility results
		windows.					
PEPa-derived MPI	Su, Ho-Ming, (2011) (143)	54 Patients with permanent AF Exclusion: LBBB, mitral annular calcification, presence of prosthesis valve, severe mitral regurgitation, lateral myocardial infarction or inadequate echocardiographic windows	80.4 (±13.7)	133/81 (±18/12)	TTE	Average of 13 beats	N=13 randomly selected patients. Intra-observer and inter-observer mean percent errors 5.2 ± 3.1% and 7.3 ± 3.3% respectively.

Abbreviations: 3D= three dimensional; AF= atrial fibrillation; CMR= cardiac magnetic resonance; ECT= Emory Cardiac Toolbox; GLS= global longitudinal strain; LBBB= left bundle branch block; LV= left ventricular; LVEF= left ventricular ejection fraction; PEPa-derived MPI= Pre-ejection period derived myocardial index; PLSS= peak longitudinal systolic strain; QGS= Cedar-Sinai quantitative gated SPECT ; RC= repeatability coefficient; SD= standard deviation; SSFP= Steady-state free precession cine images; SPECT= single-photon emission computed tomography; TTE=transthoracic echocardiography

2.4 Discussion

This is the first systematic review of the validity and reproducibility of systolic measurements made using standard cardiovascular imaging modalities for patients in AF at the time of assessment. The data comparing validity and reproducibility between different imaging modalities in AF are extremely limited, meaning that measurements of systolic LV function in common usage cannot reliably be interchanged. The data on external validation against clinical events or surrogate outcomes are also lacking, meaning that the clinical utility of measurements of systolic function in AF are uncertain. To clarify, assessment of systolic function in patients with AF is performed in every cardiac centre globally, and yet the use of these techniques is unsupported by scientific data on measurement quality or validity.

A lack of validation hampers clinical application of imaging results in AF. Most of the studies included in this systematic review addressed echocardiography, with limited examination of other modalities. Even with echocardiography however, there is a clear lack of external validation. CMR is generally considered the gold-standard method for assessing systolic function in terms of volume derived ejection fraction(155), however in terms of measuring contractility directly the gold-standard is considered to be the end-systolic pressure volume relation obtained from a high fidelity pressure catheter in the left ventricle.(156) There have been no studies externally validating LVEF in AF patients, which is a concern given that this measurement is used as key parameter to guide patient management.(3) In patients with sinus rhythm, LVEF is closely related to clinical outcomes, with each 5% lower LVEF increasing the risk of all-cause mortality by 24% (n=14261 patients ; 95% CI 21-28%; $p<0.0001$).(117) However, in patients with AF, the relationship of LVEF with clinical outcomes is less substantial, with a 9% increase in mortality per 5% lower LVEF (95% CI 3-15%; $p=0.002$),

likely reflecting higher variability in AF patients. LVEF thresholds guide management decisions for patients; for example an LVEF ≤35% is used as a cut-off value to consider implantation of a cardiac resynchronization therapy device(157), and a value of <40% determines the choice of rate and rhythm control therapy in AF patients.(3) This highlights the importance of understanding the accuracy and validity of systolic function assessment in patients with AF; unfortunately the review suggests that this is far from secure.

2.4.1 Reproducibility in patients with AF

The reproducibility of LVEF appears to be reasonable in these AF studies, with low levels of intra and inter observer variability. However, the patients included were selected for good quality imaging (158, 159) and reproducibility assessment did not include the full range of testing (for example, repeatability and reliability).(45) These studies are unlikely to represent the AF population scanned in routine practice, as AF patients usually have multiple co-morbidities such as obesity and airways disease limiting image quality. Moreover, the same images were often re-analysed, rather than the study itself repeated, thereby excluding the inter-session variability in measurements that would be expected in clinical practice. Recommended calculation of parameters in patients with AF typically involves averaging large numbers of consecutive beats, which is time-consuming and is often not completed in routine care.(138) In contrast, the use of an index beat has been shown to be reproducible and could have advantages over averaging beats in AF which each have a different volume and ejection time.(136, 144, 145)

2.4.2 Value of imaging parameters and acquisition methods to identify systolic dysfunction

AF patients often suffer with heart failure with preserved ejection fraction, presenting as a normal ejection fraction and impaired diastolic dysfunction, or features of reduced longitudinal function that may be a precursor to overtly impaired ejection fraction.(160) In echocardiography, GLS has been shown to predict CV events in those with AF(135), but other indices of longitudinal LV function such as mitral annulus motion are more strongly associated with LVEF in patients with sinus rhythm compared to AF.(142) There were very few studies in which systolic measurements have been compared using CMR and nuclear imaging. Both modalities usually rely on the R wave to trigger image acquisition. In CMR, the presence of AF makes acquisition challenging due to the irregular R to R interval, causing artefact when reconstructing the images. Despite this, the intra and inter observer reproducibility has been shown to be high. Nuclear gated blood pool studies to assess LVEF sum the blood counts of a representative cardiac cycle, therefore assuming that all R-R intervals are similar in length. (161, 162) Although internal validity of nuclear imaging seems reasonable in patients with AF (130), there have been no studies providing external validation. Finally, in all studies where heart rate was reported, values were within a well-controlled range of 60-90 beats per minute. There have been no studies assessing the validity or reproducibility of systolic parameters when heart rates are outside this range.

2.4.3 Outlook and Limitations

There is a clear need for external validation of systolic measurements in patients with AF and also inter-operator/inter-session studies to better assess reproducibility. Data on the validity of measurements in CMR, nuclear imaging and CT was extremely limited, making it difficult to draw any conclusions. A major limitation of the reproducibility studies was the lack of blinding of observers, making the risk of bias for work flow, index and reference values uncertain. Moving forward, we urgently need prospective, blinded comparison studies in AF

patients, with imaging not restricted to a selected patient group with high quality images. Hence, in the following chapters the echocardiographic study performed as part of a randomised controlled trial in which all echocardiograms were blinded and no exclusions were made for patient entry according to image quality. This means that the outcome will apply to all AF patients regardless of imaging quality and observer bias will be minimised.

This chapter has highlighted the limited information we have on the validity and reproducibility of systolic measurements we use every day to assess systolic function in cardiac imaging. There remains a significant lack of evidence for the other imaging modalities, which require future studies. However, for purpose of this thesis the focus is initially on echocardiography, as this is generally used in clinical practice echocardiography as a first-line imaging tool to direct management in AF patients (and is real time).

<u>Figure 23. Summary of findings from each imaging modality.</u> CMR still of a mid-short axis slice acquired by SSFP retrospective gated imaging (top left panel); TTE three-dimensional imaging of the left ventricle in the apical window (bottom left panel); radionuclide ventriculography imaging of the left ventricle with contours drawn mapping the left ventricle (top right panel); cardiac CT image of the left ventricle (bottom right panel). Abbreviations: CMR= cardiac magnetic resonance; SSFP= standard steady state free precession; TTE= transthoracic echocardiography; CCT= cardiac computed tomography

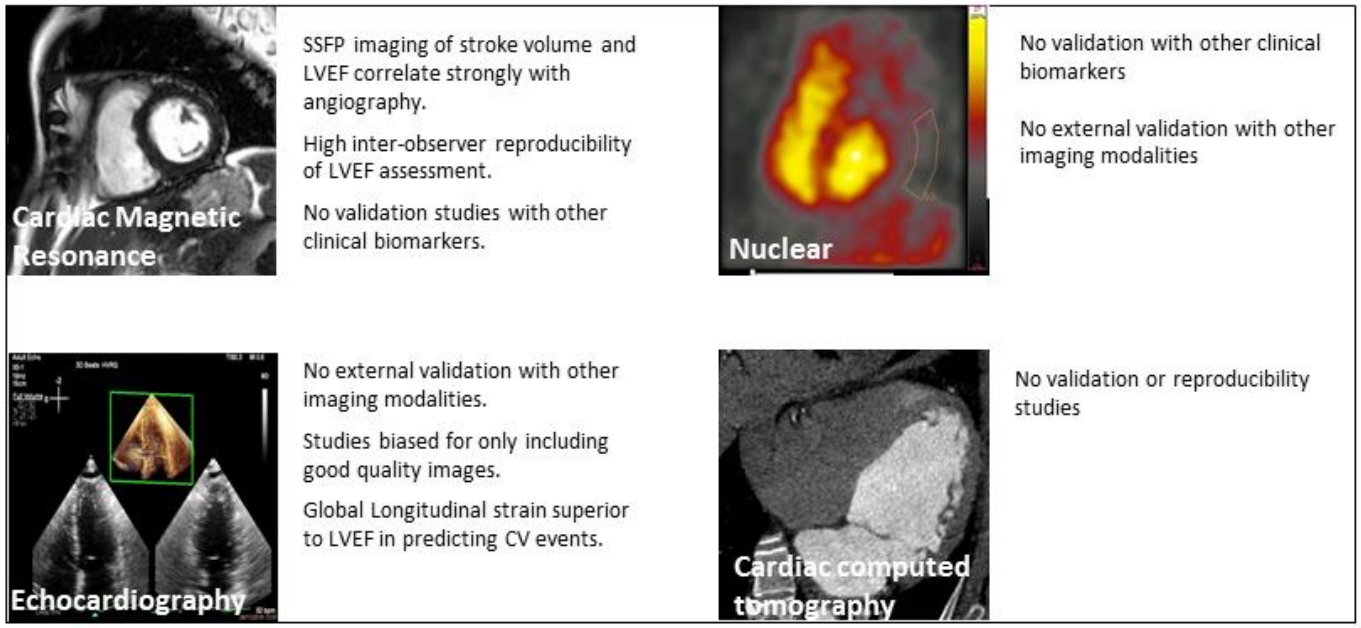


Table 11: Summary of included studies

Study	Number with AF	Population	Assessment	Aims and methods	Main findings related to AF
Nuclear Imaging					
Aguade-Bruix, (2010)(131)	115	Patients with chronic AF	Reproducibility	To assess the reproducibility of EDV, ESV and LVEF using gated SPECT in patients with AF.	Inter and intra observer variability was very low, with small bias and narrow limits of agreement.
Nichols, (1999)(129)	36	Patients referred for evaluation of coronary artery disease	Validity	To compare SPECT and ERNA derived LVEF in AF type gating errors and to determine percentage change in LV volumes, LVEF, wall thickening and myocardial perfusion according to gating error type	ERNA correlated highly with SPECT when measuring LVEF. Gating errors significantly affected wall thickening and myocardial perfusion.
Wallis, (1991) (130)	20	Patients with AF at the time of their resting gated blood pool study	Validity	Assess differences in LVEF with and without windowing	High correlation between windowed and non-windowed LVEF, with no significant difference.
Echocardiography					
Chu, (2015) (150)	196	Patients with persistent AF. Excluding significant valve disease and inadequate echo windows	Validity	To examine the ability of PEPa-derived MPI to predict CV events outcome using an index beat method.	Increased PEPa-derived MPI was associated with increased risk of CV events; cut off-value for PEPa-derived MPI was 0.72.
Dons (2018) (136)	204	Patients in AF at time of echocardiogram	Validity	To evaluate whether GLS predicts risk of CV events (all-cause mortality, incident heart failure, stroke and myocardial infarction).	Reduced GLS increased risk of CV events
Egami, (2010) (152)	27	Hypertensive patients with persistent AF who had previously been successfully cardioverted	Reproducibility	Intra-observer and inter-observer variabilities of LADd and LVEF assessed in 10 randomly selected patients	High intra and inter-observer reproducibility for measurement of LVEF.

Study	Number with AF	Population	Assessment	Aims and methods	Main findings related to AF
Emilsson, (2000) (142)	20	20 AF, 20 SR patients. Exclusion: pacemaker insitu, left/right bundle branch block, cardiac surgery hx or septal/posterior wall thickness>14mm, poor image quality for endocardial definition	Validity	To investigate the relationship between LVEF measured by Simpson's biplane and mitral annulus motion (MAM) in patients with AF.	Patients with AF had a reduced MAM when compared to SR group. MAM correlated better with LVEF in the SR group compared to the AF group.
Henrard, (2013) (153)	59	AF patients taking part in the AF-CHF echocardiographic sub-study	Reproducibility	To assess intra and inter-observer reproducibility of LVEF measured by the modified Simpson's method.	The Intra and inter observer reproducibility for LVEF was very high.
Kim, (2007) (148)	104	Patients with chronic AF	Validity	LVEF was derived from the Simpson's biplane method and correlated with plasma BNP levels	LVEF correlated weakly with BNP.
Ko, (2005) (147)	18	Patients with AF. Excluded if R-R intervals didn't fall between 0.6 and 1s.	Validity	The relationship between RR-1 and RR-2 with the LVOT peak ejection velocity (Vpe) was determined. This was then correlated with fractional shortening.	Fractional shortening correlated strongly with when the ratio of the slope of Vpe to RR-1=1 second and when the slope of Vpe to RR-2= 1 second.
Kusunose, (2012) (132)	25	AF patients	Validity and reproducibility	PLSS measured using averages of instantaneous LS over 10 sec and index-beat. These variables were compared with simultaneously measured LV pressure parameters using invasive catheterisation.	Index beat LS was correlated strongly with the maximal positive derivative of LV pressure (peak +dP/dt)
Lee, (2012) (154)	98	Patients with persistent or permanent AF and resting ventricular rates ≤ 105 bpm.	Reproducibility	Validation of the LV PLSS index against LV PLSS avg. LV systolic strain was obtained from two-dimensional speckle tracking echocardiography. 15 patients were randomly selected for interobserver and intraobserver variability.	LV PLSS index significantly correlated with LV PLSS avg, with only a small difference between them. Similar levels of intra-observer and inter-observer variability between PLSSavg and PLSSindex measurements.

Study	Number with AF	Population	Assessment	Aims and methods	Main findings related to AF
Lee, (2009) (151)	107	Patients in AF. Exclusion: Patients with most RR intervals <0.6 or >1.0 second, hemodynamically significant mitral stenosis or aortic stenosis	Validity	Vpe with RR-1 interval was determined to form the parameter slop/Vpe1 (the ratio of the slope of Vpe co-ordinates measured when RR-1 is 0.6-1 second at 1 second). Variables of heart failure were correlated with slope/Vpe1.	The parameter slope/Vpe-1 is significantly associated with occurrence of heart failure.
Modin, (2018) (137)	151	HFrEF patients with AF	Validity	Evaluate the predictive value of GLS, GLSc (GLS corrected for r to R interval), GCS and GCSc (GCS corrected for R to R interval) in predicting all-cause mortality.	Per 1 % decrease in both GLS and GCS predicted an increase in risk of all-cause mortality.
Oki, (1999) (146)	39	Included if: simultaneous cardiac catheterization and TDI can be performed, presence of AF, no significant valve disease, absence of regional LV wall asynergy.	Validity	TDI systolic LV posterior wall motion velocity was measured along the long and short axes (Sw1 and Sw2). Simultaneous recording of LV pressure curve dP/dt using invasive catheterisation.	Sw1 & sw2 correlated highly with dP/dt.
Pedersen, (2005) (134)	1293	Patients who had suffered and acute myocardial infarction	Validity	To determine the impact of presence of AF on in hospital, 30 day and long term mortality according to LVEF measured by the wall motion score index stratified in to <0.25, 0.25≤LVEF≤0.35, .35<LVEF≤0.50 and LVEF>0.50.	In patients with LVEF <0.25 in hospital mortality risk was increased in AF patients but no effect on long term mortality
Shahgaldi, (2010) (144)	23	23 AF patients and 55 patients with sinus rhythm	Reproducibility	To compare single-Beat with four-beat full volume 3DE acquisition for the inter- and intraobserver assessment of LV volumes and LVEF.	Lower intra and inter-observer variability in measuring LVEF when single beat 3D volume is used instead of 4 beat 3D volumes.
Su, (2013) (135)	196	AF patients. Exclusion: severe valve disease and inadequate echo windows.	Validity and reproducibility	To determine the relationship between GLS as a predictor of CV events (CV death, non-fatal stroke and hospitalisation due to heart failure) in patients with AF	A lower GLS was the highest predictor of CV events and Kaplan-Meir analysis showed that a GLS >-12.55% predicted increased risk of CV events

Study	Number with AF	Population	Assessment	Aims and methods	Main findings related to AF
Su, (2011) (143)	54	Permanent AF Exclusion: LBBB, mitral annular calcification, presence of prosthesis valve, severe mitral regurgitation, lateral myocardial infarction or inadequate echocardiographic windows	Reproducibility and validity	To determine whether PEPa-derived MPI can be used to evaluate systolic and diastolic LV function by comparing with systolic mitral annular velocity and LVEF measured using the modified Simpson's method. Intra and interobserver variability of PEPa-derived MPI was assessed in 13 patients.	PEPa had a moderate negative correlation with Sa and LVEF, with a high level of intra and inter-observer reproducibility.
Thavendiranathan, (2012) (141)	24	AF patients >18 years. Excluded if poor image quality.	Validity	To compare LVEF and LV volumes measured by Real Time full-volume 3-dimensional Echocardiography with the 2D biplane Simpson method	RT-VTTE LVEF correlated highly with vs 2D Simpson's biplane LVEF with small bias and narrow limits of agreement.
Wozakowska-Kaplon, (2005) (149)	67	Persistent AF. Excluded if: NYHA IV, LVEF= <45%, uncontrolled AF, untreated hypertension, unstable angina, myocardial infarction within 3 months, anaemia, renal or liver insufficiency, respiratory failure, and malignancy.	Validity	To evaluate the relationship between ANP levels and LVEF	LVEF correlated weakly with ANP
CMR					
Goebel, (2017)(127)	20	Persistent AF	Validity	To determine whether free-breathing SPARSE-SENSE CMR can reliably assess LV volumes and function in comparison to SSFP	SPARE-SENSE CMR correlated highly with SSFP in measuring LVEF

Study	Number with AF	Population	Assessment	Aims and methods	Main findings related to AF
Hundley, 1996(126)	10	AF patients with no significant valve disease or exclusion criteria for CMR	Validity	To assess the utility of CMR in measuring LV volumes, EF and cardiac output in patients with AF by comparing with left heart catheter derived LVEF and stroke volume using thermodilution and left ventriculography.	LVEF derived from CMR correlated highly with measurements derived from invasive catheterisation. CMR derived SV correlated highly with both thermodilution and left ventriculography. CMR had higher inter-observer reproducibility for measurement of LVEF and SV.
Therkelsen, (2005)(128)	79	19 healthy volunteers, 19 with permanent AF and 60 with persistent AF.	Reproducibility	To evaluate intra and inter study reproducibility of LVEF	N=10 Low intra and inter-study variability for LVEF assessment

Abbreviations: 3D= three dimensional; AF= atrial fibrillation; ANP= atrial naturetic peptide; BNP= brain naturetic peptide; CHF= congestive heart failure; CMR= cardiac magnetic resonance; CV= cardiovascular; LoA= limits of agreement; EDV= end diastolic volume; ERNA= Equilibrium Radionucleotide Angiography; ESV= end systolic volume; GCS= global circumferential strain; GLS= global longitudinal strain; HF= heart failure; ICC= intraclass correlation coefficient; LADd= left atrial dimension at end-systole; LV= left ventricular; LVEF= left ventricular ejection fraction; LVOT= left ventricular outflow tract; LS= longitudinal strain; MAM= mitral annulus motion; NYHA= New York Heart Association; PEPa-derived-MPI= Pre-ejection period derived myocardial index; PLSS= peak longitudinal systolic strain; SPARSE-SENSE= compressed sensing and parallel imaging; SPECT= single-photon emission computed-tomography; sw1= first peak systolic TDI waveform; sw2= second peak systolic TDI waveform; SR= sinus rhythm; SSFP= steady-state free precession imaging; TDI= Tissue Doppler Index; Vpe= peak left ventricular outflow tract ejection velocity

Chapter 3. General Methods

3.1 RAte control Therapy Evaluation in permanent Atrial Fibrillation (RATE-AF) trial

All data was collected from patients taking part in the RATE-AF trial; the baseline data was used for the results in this thesis.(163)

3.1.1 Rationale

The majority of patients with AF will require some form of rate control, with 40-50% being unsuitable for rhythm control and are instead indicated for long-term rate control.(164) However currently the choice of rate control medication is based on low-quality evidence(165) and in clinical practice medication is chosen according to expert consensus and a physician's individual preference. There are no randomised clinical trials assessing long-term rate control in patients with AF and there is very limited data on how choice of rate control effects quality of life and functional outcomes. The RATE-AF trial aimed to compare the efficacy of beta-blockers verses digoxin in symptomatic permanent AF patients, aged 60 years and over, by assessing quality of life, functional capacity, systolic and diastolic LV function and biomarkers of treatment response.

3.1.2 Ethics

The RATE-AF trial has been approved by the East Midlands—Derby Research Ethics Committee (16/EM/0178) (see (NCT02391337) and received approval from the National Health Service Health Research Authority (IRAS project ID: 191437).

3.1.3 Trial Team

The Birmingham Clinical Trials Unit (BCTU) at the University of Birmingham managed the trial and visits took place in the NIHR/Wellcome Trust Clinical Research Facility based at the Queen Elizabeth Hospital, Birmingham. The trial management group consisted of: Dr Dipak Kotecha (chief investigator), Dr Michael Griffith (principal investigator at site Queen

Elizabeth Hospital , Birmingham), Professor Paulus Kirchhof (principal investigator at site Birmingham City and Sandwell hospital), Prof Gregory Y H Lip (principal investigator at site Birmingham City and Sandwell hospital), Prof Jonathon Townend (principal investigator at site Queen Elizabeth Hospital , Birmingham), Dr Rick Steeds (principal investigator at site Queen Elizabeth Hospital , Birmingham), Prof Melanie Calvert, Dr Susan Jowett, Dr Jonathon Mathers, Prof Jon Deeks, Gemma Slinn (team leader of trials management), Dr Rebekah Wale (trial manager) and Samir Mehta (statistician). The trial oversight committee was chaired by Prof John Camm and Dr Kazem Rahimi.

The research assistant and PhD fellow Karina Bunting (KB) screened all cardiology out-patient clinics and diagnostic referrals for potential subjects at University Hospital Birmingham between December 2016 and September 2018. The research nurse (Patience Domingos) based at City and Sandwell hospital, also assisted in the screening of potential subjects from City and Sandwell hospital and Heartland's hospital. KB was responsible for recruiting and consenting all patients, for arranging and performing all study visits, reporting any serious adverse events and with the assistance of the research nurse for performing all study visit procedures as stated in the protocol with the exception of procedures and decisions related to medical management (performed by Dr Dipak Kotecha and Dr Simrat Gill).

KB also maintained all the regulatory documents and was responsible for updating the site file with the ethics committee amendments and attending Data monitoring and Trial Steering committee meetings.

3.1.4 Patient and public involvement (PPI) panel

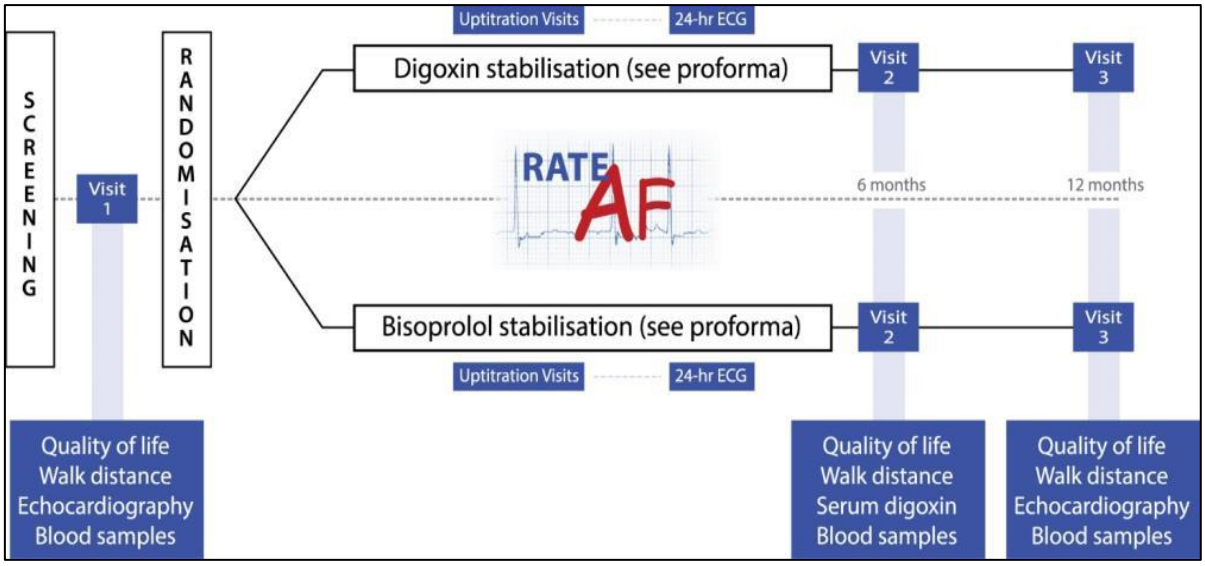
The PPI was responsible for carrying out the qualitative research to assess the utility of the quality of life (QoL) questionnaires in assessing patients' symptoms. This was carried out using patient focus groups of around 10 participants from each treatment arm. Qualitative

data was gathered to assess QoL questionnaires difficulty in completion, relevance, reasons for non-completion and other feasibility issues from the patient's perspective.

3.1.5 Summary of trial design

The trial sponsor was the University of Birmingham and it was funded by the National Institute of Healthcare Research (NIHR). This was a Clinical Trial of an Investigational Medicinal Product trial, designed as a Prospective Open-labelled Blinded End-point trial to determine the effectiveness of beta-blockers verses digoxin in patients with permanent atrial fibrillation. The primary end-point of the study was patient-reported quality of life using the Short Form (36) Health survey (SF-36) at 6 months. The secondary end-points included changes in cardiac diastolic and systolic function, functional status, global and AF specific quality of life scores and cardiovascular biomarkers such as heart rate and changes in N-terminal B-type Natriuretic peptide (NTproBNP) levels at 6 months (163), see **Figure 24** for the trial schema.

Figure 24. RATE-AF trial schema



The full protocol can be accessed online using the link listed in **appendix 1**. Please also see the following link for the short film promoting the RATE-AF trial made by the chief

investigator (Dipak Kotecha) and a member of the patient representative group: https://www.youtube.com/watch?v=4oxe8AcVo0E.

3.2 Recruitment

Recruitment of patients began in December 2016 until the last patient was recruited in October 2018. Patients were screened for eligibility across the Queen Elizabeth Hospital (Birmingham), City and Sandwell Hospital (Birmingham) and Heartlands Hospital (Birmingham). General Practitioner (GP) practices across the Birmingham area were also invited to act as patient identification sites, to refer appropriate patients. The trial was promoted at the Research Site Initiative Practice event at Edgbaston cricket ground on 9th February 2017, in which the trial was presented to GPs attending the event.

The inclusion criteria were as follows:

- Adult patients aged 60 years or older
- Permanent AF, characterised (at time of randomisation) as a physician decision for rate-control with no plans for cardioversion, anti-arrhythmic medication, or ablation therapy
- Symptoms of breathlessness (New York Heart Association Class II or more)
- Able to provide written informed consent

The exclusion criteria were as follows:

- Established clinical indication for beta-blocker therapy, e.g. myocardial infarction in the last 6 months
- Known contraindications for therapy with beta-blockers or digoxin, e.g. a history of severe bronchospasm that would preclude use of beta-blockers, or known intolerance to these medications
- Baseline heart rate <60 bpm

- History of second or third-degree heart block
- Supraventricular arrhythmias associated with accessory conducting pathways (e.g. Wolff-Parkinson-White syndrome) or a history of ventricular tachycardia or fibrillation
- Planned pacemaker implantation (including cardiac resynchronisation therapy), pacemaker-dependent rhythm or history of atrioventricular node ablation
- Decompensated heart failure (evidenced by need for intravenous inotropes, vasodilators or diuretics) within 14 days prior to randomisation
- A current diagnosis of obstructive hypertrophic cardiomyopathy, myocarditis or constrictive pericarditis
- Received or on waiting list for heart transplantation
- Receiving renal replacement therapy
- Major surgery, including thoracic or cardiac surgery, within 3 months of randomisation including patients with severe valve disease being considered for surgery
- Severe, concomitant non-cardiovascular disease (including malignancy) that is expected to reduce life expectancy

Suitable patients were screened for with the following methods: patients attending cardiology outpatient clinics, all 24-hour ECG ambulatory monitor reports, all ECGs taken within the department and all direct GP echocardiogram referrals for new AF. Patients, identified as having a history of AF, were further screened using clinical letters to look for any reason to exclude the patient. Once satisfied with the initial screening of the patient, patients were telephoned to ensure there were not any other reasons to exclude. If at that stage patients met criteria, they were invited to take part in the study and a patient information leaflet was sent out to them (see **appendix 2**). Suitable patients were also directly referred by GP practices, and from Birmingham City and Sandwell Hospital and Heartlands Hospital.

3.3 Informed Consent

Having completed Good Clinical Practise and Informed consent training, KB was predominantly responsible for carrying out the consent process for all patients wishing to enrol in the trial. Time was taken to ensure that the patient fully understood the trial and what was expected of them and the trial team. Once satisfied that the patient was adequately informed the patient was asked to complete the consent form (see **appendix 3**). The patient also had the option to take part in additional studies listed on the optional consent form (see **appendix 4**).

3.3 Baseline visit

3.3.1 Randomisation

When patients came in for their baseline visit, initially a 12-lead Electrocardiogram (ECG) was performed to ensure the patient was still in AF. The rest of the eligibility criteria was then systematically checked with the use of the randomisation form (see **appendix 5**).

All patients had to provide informed consent before enrolling in the trial. Once satisfied that the patient understood the trial and what was expected of them, informed consent was obtained. The patient was then enrolled in the trial and randomised to either digoxin or a beta-blocker using a minimised randomisation protocol managed by BCTU. As part of the randomisation process the patient was also given a study identification number which would be used to identify the patient on all trial related paperwork.

3.3.2 Medical history and clinical examination

The patient's current medication was recorded in their file and specified any anticoagulants, antihypertensives, antiplatelets or inhalers for airways disease on the baseline case report form (CRF) see **appendix 6**.

The patient was also physically examined by the consultant cardiologist and any signs of heart failure were recorded in the baseline CRF; these included: abnormal heart sounds, raised jugular venous pressure, peripheral oedema and lung crepitations.

3.3.3 Physiological measurements

A 12-lead electrocardiograph (ECG) was performed during the randomisation process adhering to standard operating procedures as described by the Society for Cardiological Science and Technology.(166) This was carried out to primarily ensure the patient was in AF and there were no other ECG features, which would exclude the patient from the study. Heart rate (bpm), QRS duration (ms) and QT duration (ms) were recorded in the baseline CRF. The ECG was performed with the patient in the supine position and care was taken to allow the patient to rest for one to two minutes before recording the ECG, in order to obtain an accurate resting heart rate.

The blood pressure was measured, using two consecutive blood pressures taken from brachial position using a validated oscillometric blood pressure machine. In cases in which the automated machine was unable to accurately measure the blood pressure, a manual blood pressure was taken using a sphygmomanometer and stethoscope. The blood pressure was taken at rest, before the walk test to ensure an accurate measurement of resting blood pressure was obtained. Heart rate was measured using the radial pulse and by listening to the apex beat using a stethoscope. These measurements were obtained consecutively in the same order to minimise any ascertainment bias.

Anthropometric measurements of weight (kg) using digital stand-on weighing scales, height (cm) using a portable stadiometer and waist circumference using a body tape measure, were

recorded. To ensure a consistent position for waist measurement, all waist measurements were taken just above the hipbones in expiration.

3.3.4 Echocardiogram

All patients underwent an echocardiogram at baseline, which were all carried out by myself (BSE accredited). All echocardiograms were carried out on a Phillips EPIQ 7 with an X-3 transducer. The structure and function of the heart was assessed according to the British Society of Echocardiography's normal protocol.(167) In the presence of pathology for example valve disease, I took extra measurements as described by the BSE protocol accordingly. Extended loops (up to10 beat per loop) and multiple frames were obtained as described in **Table 12**, so that variability analysis could be carried out. Intra-operator and inter-operator reproducibility of the index beat verses the averaging of 3, 5 and 10 consecutive beats was demonstrated using the measurement of GLS and E/e'. For intra-operator reproducibility at the end of the initial protocol the patient was asked to re-position and the first operator took a second set of acquisitions, with at least ten available loops or traces to measure GLS and E/e' using a single index beat and an average of 3, 5 and 10 consecutive beats. For inter-operator reproducibility a second operator acquired at least ten available loops or traces to measure GLS and E/e'.

All images obtained were optimised by:

- Using maximal frequency transducer to increase axial resolution
- Reducing sector width to area of interest in order to increase frame rate
- Reducing depth to increase the size of the image on the screen
- Bringing the focus to the point of interest to increase lateral resolution
- Optimize compression to achieve optimum grey-scale range

- Adjusting Time Gain Compensation’s in order to optimize the distribution of gain at different penetration depths.
- Optimizing gain and resolution to identify endocardial boarders and structures.
- Asking the patient to inhale or exhale in order to optimise image and reduce motion artefact

Table 12. The baseline echocardiogram protocol

View	Modality	Image acquisition	Number of beats per loop	Number of repetitions	Sweep speed (mm/s)/ colour scale(cm/s)	Post processing measurement
PLAX	2D	LV, AV and MV	3	1	n/a	IVSd and LVIDs
	2D zoom	LVOT and Aortic root	3	1	n/a	LVOT diameter and root dimensions
	M-mode	Optimised on-axis LV	5	6	50 mm/s (slow)	LVIDd and LVIDs
		Optimised on-axis AoR and LA	5	6	50 mm/s (slow)	LA dimension
	Colour	Colour over MV	3	1	60 cm/s	*quantify any MR
		Colour over AV	3	1	60 cm/s	*quantify any AR
PLAX RV inflow	2D	TV and RV inflow	3	1	n/a	n/a
	Colour	Colour over TV	3	1	60 cm/s	*quantify any TR
	CW	TV inflow and any regurgitation	n/a	1	75 mm/s (med)	*TR Vmax
PLAX RV outflow	2D	PV and RV outflow tract	3	1	n/a	n/a
	Colour	Colour over PV	3	1	60 cm/s	*quantify any PR
	CW	PV inflow and any regurgitation	n/a	1	75 mm/s (med)	*quantify any PR or PS
	PW	PV inflow	3	1	75 mm/s(med)	PV Vmax
PSAX	2D	Aortic valve level	3	1	n/a	n/a

View	Modality	Image acquisition	Number of beats per loop	Number of repetitions	Sweep speed (mm/s)/ colour scale(cm/s)	Post processing measurement
		Basal level	3	1	n/a	n/a
		Mid-level	3	1	n/a	n/a
		Apical level	3	1	n/a	n/a
A4C	2D	Optimised RV	3	1	n/a	RVIDd and RA area
		LA	10	3	n/a	LA volume, LA transverse dimension and LA longitudinal dimension
		Optimised LV	11 (/6- depending on need for breath hold)	3 (/6- depending on need for breath hold)	Adjust speed/res to maximise frame rate	Longitudinal Strain and Simpson's single plane end-diastolic and end-systolic volume **
	2D x-plane	Optimised LV	6	2	n/a	Simpson's biplane end diastolic and end-systolic volume
		Optimised LA	6	2	n/a	LA biplane volumes
	3D HVR	Optimised LV	8	2	n/a	3D end-diastolic and end-systolic volumes
	3D volume	Optimised LV	4	3	n/a	3D end-diastolic and end-systolic volumes
	TDI and PW	Lateral tissue Doppler velocity spectrum	10	3	25 mm/s (min)	s' and e' velocities ***

View	Modality	Image acquisition	Number of beats per loop	Number of repetitions	Sweep speed (mm/s)/ colour scale(cm/s)	Post processing measurement
		Septal tissue Doppler velocity spectrum	10	3	25 mm/s (min)	s' and e' velocities ***
	PW	Mitral valve inflow	10	3	25 mm/s (min)	E and E deceleration time
		Pulmonary venous flow	3	10	50 mm/s (slow)	Systolic and diastolic velocity and diastolic deceleration time
	Colour m-mode	Flow through the mitral valve	5	6	50 mm/s (slow) Colour baseline 40 cm/s	Vp
	M-mode	Motion through RV base	10	3	25 mm/s (min)	TAPSE
	Colour	Colour over Tricuspid valve	3	1	60 cm/s	*quantify regurgitation
		Colour over Mitral valve	3	1	60 cm/s	*quantify regurgitation
A5C	Colour	Colour over aortic valve	3	1	60 cm/s	*quantify regurgitation
	CW	Aortic valve flow	n/a	1	75 mm/s (med)	AV Vmax **
	PW	LVOT flow	5	6	50 mm/s (slow)	LVOT Vmax and LVOT VTI ***
		LVOT and MV flow	3	10	75 mm/s (med)	IVRT

View	Modality	Image acquisition	Number of beats per loop	Number of repetitions	Sweep speed (mm/s)/ colour scale(cm/s)	Post processing measurement
A2C	2D	Optimised LV	11 / (6- depending on need for breath hold)	3 / (6- depending on need for breath hold)	n/a	Simpson's single plane end-diastolic and end systolic volume and Longitudinal strain
A3C	2D	Optimised LV	11 / (6- depending on need for breath hold)	3 / (6- depending on need for breath hold)	n/a	Longitudinal strain
Subcostal 4C	2D	4 chambers of the heart	3	1	n/a	n/a
Subcostal SAX	2D	IVC	3	1	n/a	IVC diameter
		IVC collapse with respiration	Suprasternal	1	3	IVC collapse with respiration
Suprasternal	2D	Arch	3	1	n/a	Arch dimensions
	Colour	Colour over Desc Ao	3	1	60 cm/s	n/a
	CW	Flow down Desc Ao	n/a	1	75 mm/s (med)	n/a
	PW	Flow at prox Desc Ao	n/a	1	75 mm/s (med)	n/a
Patient sits up and operator gets up and leaves the room before returning to do the measurements to test intra-operator variability. All following loops should be labelled "IOV1"						
A4C	2D	Optimised LV	11/ (6- depending on need for	1 / (2- depending on need for breath	n/a	Longitudinal strain **

View	Modality	Image acquisition	Number of beats per loop	Number of repetitions	Sweep speed (mm/s)/ colour scale(cm/s)	Post processing measurement
			breath hold)	hold)		
	TDI and PW	Lateral tissue velocity spectrum	10	1	25 mm/s (min)	s' and e' velocities ***
		Septal tissue velocity spectrum	10	1	25 mm/s (min)	s' and e' velocities ***
	PW	Mitral valve inflow	11	1	25 mm/s (min)	E and E deceleration time
A2C	2D	Optimised LV	11/ (6- depending on need for breath hold)	1 / (2- depending on need for breath hold)	n/a	Longitudinal strain
A3C	2D	Optimised LV	11 / (6- depending on need for breath hold)	1 / (2- depending on need for breath hold)	n/a	Longitudinal strain
On every 8 patients a second operator should take the following acquisitions and all loops should be labelled "IOV2"						
A4C	2D	Optimised LV	11 / (6- depending on need for breath hold	1 (2- depending on need for breath hold)	n/a	Longitudinal strain
	TDI and PW	Lateral tissue velocity spectrum	10	1	25 mm/s (min)	s' and e' velocities ***
		Septal tissue velocity spectrum	10	1	25 mm/s (min)	s' and e' velocities ***

View	Modality	Image acquisition	Number of beats per loop	Number of repetitions	Sweep speed (mm/s)/ colour scale(cm/s)	Post processing measurement
	PW	Mitral valve inflow	10	1	25 mm/s (min)	E and E deceleration time
A2C	2D	Optimised LV	11 / (6- depending on need for breath hold	1 (2- depending on need for breath hold)	n/a	Longitudinal strain
A3C	2D	Optimised LV	11 / (6- depending on need for breath hold	1 (2- depending on need for breath hold)	n/a	Longitudinal strain

Abbreviations:, 3D= three dimensional; A4C= Apical 4 Chamber; A2C= Apical 2 Chamber, A3C= Apical 4 Chamber; AoR= Aortic root; AR= aortic regurgitation; AV= Aortic Valve; CW= continuous wave; Desc Ao= descending aorta; IVC= inferior vena cava; IVRT= isovolumic relaxation time; IVSd= Inter-ventricular septum diameter, LA= Left atrium; LVIDd= left ventricular internal diameter in diastole; LVIDs= left ventricular internal diameter in systole; LV= left ventricle; LVOT= Left Ventricular Outflow Tract; LVPWd= Left Ventricular Posterior Wall diameter; MR=mitral regurgitation, MV=mitral valve, MR= mitral regurgitation; RV= right ventricle, PLAX= Parasternal Long Axis; PR= pulmonary regurgitation; PS= pulmonary stenosis, PSAX= parasternal short axis PV= pulmonary valve; PW= pulsed wave; RA= right atrium; RVIDd= right ventricle internal diameter in diastole; TAPSE= tricuspid annular plane systolic excursion; TR= tricuspid regurgitation; TV= tricuspid valve; Vmax=maximal velocity; Vp= propagation velocity; VTI= velocity time integral.

All measurements were carried out post-process using the Philips Q-station analysis software (version 2014, 4535 617 07481 Rev A).

Anonymization of echocardiograms

All echocardiogram studies were given a code separate to the patient's study identification number, so that the analyser was blinded to the patient details when analysing the scans a minimum of 6 months following the echocardiogram. This excluded observer bias, as the echocardiogram was not identifiable at the point of analysis.

Parameters used to assess systolic function

Simpson's Biplane Ejection Fraction. This method calculates the ejection fraction by measuring the end-diastolic volume and end systolic volume in the plane of the 2-chamber and 4-chamber view. Volume is calculated using the disc summation method with the assumption that the LV is ellipsoid in shape.(28, 29) To measure a Simpson's biplane firstly an optimised loop of the LV in the apical 4 and 2 chamber was obtained. The loop was scrolled to end-diastole when the ventricle cavity was at its largest (usually on the R wave); the endocardial boarder starting from the annulus to the apex was traced to summate the end diastolic volume using the disc summation method. Then the loop was scrolled to end-systole, when the ventricle cavity was at its smallest (usually at the end of the T wave); then again the endocardial boarder was traced to summate the end-systolic volume. As described in **chapter 1** the volumes are used to calculate the LVEF: (EDV-ESV)/EDV x100.

Left ventricular speckle tracking strain.

Optimised 10 beat loops of the left ventricle in the apical 4, 2 and 3 chamber view were taken, ensuring a frame rate between 40 and 90 frames/ second by reducing the sector width and optimising the depth, whilst still ensuring the entire myocardial wall was well seen.(168) Automated cardiac motion quantitation analysis (aCMQ) was selected to initiate the speckle

tracking process. First the loops were scrolled back to ensure that analysis was started on the first cardiac cycle. Next, the apical window strain was being assessed in was selected and then by using the "draw" function three anatomical points were marked out: two on the mitral annulus and one on the apex. This enabled the speckles to align with the myocardium; the speckles could be manually adjusted where necessary to ensure they were tracking the myocardium correctly. Once satisfied that the longitudinal strain value had been correctly measured, the value was accepted. The next beat was then selected for longitudinal strain analysis.

3-D volume ejection fraction. 3-D imaging can be performed with a matrix-array transducer to acquire an image of the ventricle sampling from every plane, to form a pyramidal dataset. From the images a 3-D end-diastolic and end-systolic LV volume can be calculated, which is then used to determine the ejection fraction. The image of the left ventricle in the apical 4-chamber view was optimised and then 3D "full volume" software was initiated so that a 3D pyramidal view of the ventricle could be acquired. Sector width was adjusted to ensure that it was wide enough that the entire ventricle can be viewed in both planes and narrow enough so that the frame rate was maximised. The acquisition setting was changed to 3D HVR so that 10 single 3D loops could be acquired without the issue of stitching artefact.

Analysis was carried out using the Q-station 3D full volume analysis. The first cycle was selected by using the "previous R wave" instruction to scroll the images back to the start of the 10 beat acquisitions. The end-diastolic volume frame was selected and then the axis were aligned to ensure the image of the ventricle was optimised in all planes. The same process was carried out for end-systolic volume. The anatomical markers were next selected beginning with the septal annulus, followed by the lateral annulus, anterior annulus, inferior annulus and the apex. When satisfied that the markers were correct, 3D sequence analysis was selected which used the anatomical markers to track the endocardial boarder throughout

the cardiac cycle. If unsatisfied with the automated endocardial tracking this could be adjusted using the "draw endocardial boarder" setting. Once satisfied with the endocardial boarder tracking, 3D sequence analysis was run again. The End-systolic volume, end-systolic volume, stroke volume and LVEF were measured. Then the next R wave was selected to begin measuring on the sequential beat.

Tissue Doppler Indices (TDI). The Tissue Doppler imaging was activated to allow the speed of the myocardium to be visualised on a colour scale. Pulsed wave Doppler was then placed at the lateral and septal annulus to detect low velocity, high amplitude signals from the moving myocardium. TDI measurements were taken from the lateral and septal annulus. Sequential frames were taken to ensure that at least 10 measurements were obtainable. The s' was measured at the upward deflection following the R wave and e' was measured at the initial downward deflection between the T wave and R wave.

Fractional shortening (FS). For images in which the LV was on axis, M-mode was run through the width of the LV, ensuring that it was parallel to the mitral annulus to avoid over-estimating the size of the internal cavity. The LVIDd was measured on the R wave (at the point when the internal diameter was at its widest) and the LVIDs was measured at the end of the T wave (at the point when the internal diameter was at its narrowest). In cases where the LV was off-axis the measurements were drawn on a 2-D image. Fractional shortening was then calculated using the below equation:

FS= LVIDd- LVIDs/ LVIDd x 100

Parameters used to assess diastolic function

E wave, deceleration time and E/e'. The E wave is the measurement of the peak velocity of the mitral valve inflow. It is obtained by measuring the speed of blood through the mitral valve, using pulsed-wave Doppler at the mitral valve tips. The peak of the E wave is

measured as the E Vmax and the downwards slope of the E wave Doppler trace is measured as the deceleration time. To calculate E/e', the E Vmax is divided by the TDI derived e', which is obtained as described above.

E/Vp. Vp is a measure of the speed of blood as it goes from mitral valve to apex. This was obtained by placing colour Doppler with the Nyquist limit baseline brought up to 40 cm/s, over the left ventricle and mitral valve. Colour M-mode was then passed through the mitral valve to the apex, with the sweep speed set to 100 mm/s, so that speed of colour through the left ventricle was demonstrated as a colour m-mode trace. The slope of the blue element was measured, which determined the speed of blood flow in early diastole from the mitral tips to the apex. The E Vmax peak was then divided by the Vp slope to obtain E/Vp.

Pulmonary Venous Doppler. An optimised image of the left atrium was obtained and then the probe was angled to bring the pulmonary vein's orifices into view, this was facilitated with colour Doppler. Pulsed wave Doppler was then applied to the orifice of the pulmonary veins. This generated a trace in which if available the initial upwards wave was measured as systolic flow (usually at the point of the T wave) and the second upwards deflection as diastolic flow (usually just before the R wave during diastasis). The downwards slope of the diastolic wave was measured as the diastolic deceleration time.

Isovolumic Relaxation Time (IVRT). This was obtained by placing the sample volume for pulsed wave Doppler where the LVOT blood flow and mitral valve inflow, so that the LVOT and E wave Doppler trace could be seen on the same acquisition. The sweep speed was extended to 100 mm/s to make it easier to measure the interval more easily. IVRT was measured as the time between the offset of the LVOT trace and inflow of the mitral valve E wave.

LA biplane volume and left atrial ejection fraction. Images of the left atrium in the apical 2 and 4 chamber were optimised, ensuring to not fore-shorten its size. The image was then frozen and the frame was scrolled back to end-systole (just before the mitral valve opens), so that the left atrium was at its biggest. Then using the Simpson's area-length volume method, the internal boarder of the left atrium was traced using planimetry which generated a volume. To measure left atrial ejection fraction (LAEF), the frame was scrolled to end-diastole (just after the mitral valve closes), when the LA is at its smallest. LAEF was then calculated using the equation: LAEF= (LA volume$_{(end\text{-}systole)}$ – LA volume $_{(end\text{-}diastole)}$)/ LA volume$_{(end\text{-}systole)}$ x 100.

3.3.5 NTproBNP and other blood tests

At baseline, 6 months and 12 months all patients had their NTproBNP (ng/l) measured. This is a biomarker used to assess heart strain and so elevated levels are indicative of heart failure. Venous peripheral blood was taken and NT-proBNP was measured on the Abbott Alinity analyser, in a UKAS accredited clinical laboratory following manufacturer's standard operating procedure biochemistry laboratory for analysis. Other blood biomarkers recorded at baseline were: potassium, sodium, urea, creatinine, eGFR, calcium, phosphate, magnesium, albumin, haemocrit, haemoglobin and INR (if the patient was taking warfarin).

3.3.6 Quality of life assessment

The patient was questioned on how their AF and heart failure affected their daily life; from this it was possible to classify their European Heart Rhythm Association (EHRA) and New York Heart Failure Association (NYHA) class. EHRA score was used to determine how the symptoms of AF (palpitations, breathlessness, dizziness and fatigue) affect the patient's quality of life:

1: None; AF does not cause any symptoms

2a: Mild; normal daily activity not affected; patient not troubled by symptoms

2b: Moderate; normal daily activity not affected; patient troubled by symptoms

3: Severe; normal daily activity affected by symptoms relating to AF

4: Disabling; normal daily activity discontinued

The severity of breathlessness was determined by the NYHA functional class score:

I: No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnoea.

II: Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation or dyspnoea.

III: Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation or dyspnoea.

IV: Unable to carry out any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Patients were asked to complete the quality of life questionnaires: SF-36, EQ-5D-5L & AFEQT (**appendices 7-9**). The SF-36 questionnaire assesses general health (**appendix 7**). It is divided in to the following domains: Physical functioning (10 questions), role limitations due to physical health (4 questions), role limitations due to emotional problems (3 questions), Energy/fatigue (4 questions), Emotional well-being (5 questions), Social functioning (2 questions), Pain (2 questions) and General health (5 questions). Each answer to the question has a weighted value which is transformed to a percentage. The overall score is calculated on a scale of 0-100; a higher percentage suggests a better level of health.(169)

EQ-5D-5L also assesses general health (**appendix 8**). It consists of a descriptive system of questions divided into: mobility, self-care, usual activities, pain/discomfort,

anxiety/depression. Each question has five possible answers, of which the patient must only choose one defined as: (1) "no problems", (2) "slight problems", (3) "moderate problems", (4) "severe problems", and (5) "extreme problems". It also has an analogue scale which asks the patient to score their health out of 0-100; 0 being the "worst health you can imagine" and 100 being the "best health you can imagine".

The Atrial Fibrillation Effect on QualiTy-of-life (AFEQT) questionnaire aims to assess the impact of atrial fibrillation on patients' quality of life (**appendix 9**). The questionnaire is split into four sections: questions 1-4 assesses patient symptoms, 5-12 assesses effect on daily activities and questions 13-18 assesses treatment concerns. Each question has multiple choice answers on a scale of 1-7 (1 being "not at all" and "7" being extremely). Scores are transformed as follows into a score out of 100; the higher the transformed the score the less AF affects the patients' quality of life (**Table 13**).

Table 13. Transformation of raw scores from AF-EQT questionnaire

Raw scale (1-7)	Transformed scale (0-100)
1	100
2	83.3
3	66.7
4	50
5	33.6
6	16.7
7	0

3.3.7 Functional and cognitive assessment

To assess the patient's cognitive function the patient was asked a series of questions and tasks to perform from the mini-mental state examination (**appendix 10**). The functional capacity was assessed by asking the patient to attempt the 6 minute walk test and also by completing a the IPAQ scoring system(170) in which the patient was asked:

- Number of minutes they spend sitting down during a week day based on the last 7 days

- Number of days they have walked for more than 10 minutes at a time in the last 7 days
- Total number of minutes spent walking in the last 7 days
- Number of days they have done moderate physical activity in the last 7 days, defined as "making them breathe somewhat harder than normal and may have included carrying light loads, bicycling at a regular pace, or doubles tennis"
- Total number of minutes spent doing moderate physical activity in the last 7 days
- Number of days they have done vigorous physical activity in the last7 days, defined as "activities that made them breathe much harder than normal and may include heavy lifting, digging, aerobics, or fast bicycling.
- Total number of minutes spent doing vigorous physical activity

6 minute walk test

All baseline patients attempted the 6 minute walk test to measure exercise tolerance. The patients were asked to walk up-and-down between two points measuring 30 metres apart for up to 6 minutes. The patient was instructed to continue walking until told to stop at 6 minutes, unless the patient felt they no longer could continue, at which point the stopwatch was stopped and the distance and duration of walking at that point was measured. As soon as the test ended, the patient's heart rate was measured by taking a manual radial pulse to get the peak heart rate on exertion. The following information was recorded:

- Time walking (minutes:sec)
- Distance travelled (metres)
- Peak heart rate (beats per minute)
    - (if applicable) Reason for wanting to stop before 6 minutes:
        - Breathless

- Fatigue
- Claudication
- Chest pain
- Other pain e.g. joint pain
- Other (please specify)

1

3.4 Up-titration Visit and 24hr ambulatory ECG

Following the patients baseline visit up to four weeks later the patient came back for their up-titration visit. The aim of this visit was to assess the patient's heart rate and symptoms to see whether the patient's rate control medication dose needed to be adjusted. The following procedures were carried out:

1. Assessment of any adverse events: A consultation with the patient to determine whether they have had any adverse symptoms related to the medication, which was recorded in the Up-titration CRF (**Appendix 11**) In the case of a serious adverse event, this was reported using the serious adverse event form (**Appendix 12**) and sent to the sponsor (Birmingham Clinical Trials Unit) within 24 hours.
2. Compliance assessment: Patients were asked if they had taken their medication as directed on a daily basis. If the patient had not been compliant, the percentage compliance was calculated according to how many doses the patient recalls missing.
3. Vital signs and patient demographics: As described at baseline an ECG was performed, patient's weight, two consecutive blood pressures and a radial and apical pulse rate assessment were measured. For patients taking digoxin a blood test was taken to record their digoxin level.
4. Quality of Life and functional capacity questionnaires were given to the patient to complete as described at baseline.
5. A symptom directed physical examination was carried out by the consultant cardiologist.
6. Medications were reviewed by the consultant cardiologist and adjusted accordingly. A sequential up-titration appointment was arranged if medication was changed at their up-titration visit.
7. Once the patient was on the optimal medication for rate control, a date was arranged to fit a 24hr ambulatory ECG to them.

3.5 6 month Protocol

At the patient's 6 month visit the following procedures were carried out:

1. As described at baseline the patients answered quality of life questionnaires and had a cognitive and functional capacity assessment.

2. As described at up-titration any adverse events were recorded in the CRF (**appendix 13**) and serious adverse events reported to the sponsor.

3. As described at baseline the patient's current medication and rate-control medication were recorded.

4. Blood samples were taken as described at baseline with the addition of digoxin level

5. Vital signs and patient demographics: As described at baseline an ECG, two consecutive blood pressures and a radial and apical pulse rate assessment. The patient's weight and waist circumference were also measured. The consultant cardiologist carried out a physical examination and recorded any signs of heart failure in the CRF.

6. As described at their baseline visit the patient underwent a 6 minute walk test

7. Any visits the patient had to their GP practice and whether or not it was cardiovascular or AF related were recorded

3.6 12 month Protocol

At the patient's 12 month visit the same procedures as stated at 6 months were performed, with the addition of an echocardiogram. All patients at their 12 month visit underwent an echocardiogram to assess for any changes in systolic or diastolic function. The same protocol listed in **Table 12** was carried out with the exception of extra measurements taken for intra and inter-operator reproducibility. At the end of the visit the patient was thanked for their contribution in the trial and the consultant cardiologist wrote to their GP giving advice on

how to continue their treatment for atrial fibrillation. At the time of writing of this thesis, all 160 patients had completed their 12-month visits and the final database for the RATE-AF trial was locked in preparation for data analysis by the BCTU statistics team. All results in this thesis relate to the baseline trial data.

3.7 Analysis Plan

All echocardiographic data were stored in Excel (version 2010) and all statistical analysis was carried out in STATA (version 14). A summary of all statistical tests used are summarised in **Table 14.**

3.7.1 The index beat vs averaging consecutive beats

i) To assess the variability within index beats vs averaging 3, 5 and 10 consecutive beats

This will be assessed in the following echocardiographic parameters: Simpson's biplane LVEF, GLS and E/e'. As stated in the protocol, a minimum of 30 measurements will be taken for each parameter. From this data three index beats will be measured and then sets of 3, 5 and 10 consecutive beats. A coefficient of variation using the formula: $\sqrt{\exp(\sigma 2)-1} \times 100$ (with σ = the standard deviation) will be used to assess the variability within the beats measured. The measuring method with the lowest coefficient of variation will have the lowest variability. To test for differences in coefficient variation between the measuring methods a Wilcoxon signed rank test will be used with a p value ≤ 0.05 considered statistically significant.

ii) To assess the inter and intra-operator reproducibility of the index beat vs averaging 3, 5 and 10 consecutive beats

This will be assessed in the following parameters: E/e' and GLS. For intra and inter-operator reproducibility the first measurement taken using the a single index beat and the average of 3, 5 and 10 beats, will be compared with the operators second set of measurements taken using a single index beats and the average of 3, 5 and 10 beats. Bland and Altman analysis will be

used to assess the agreement between the two sets of: index beats and average of 3, 5 and 10 beats.

Further analysis will be carried out using a mixed effects multi-level linear regression model adjusting for the patient and measurement time. From this the intra class correlation coefficient will be derived along with 95% confidence intervals for each of the four measurement methods.

iii) Time taken to measure on an index beat verses averaging consecutive beats

Time was measured in seconds for the total amount of time taken to measure E/e' using a single index beat and average of 5 and 10 consecutive beats. The mean time taken for each measuring method was calculated and differences in time were compared using a paired t-test.

3.7.2 The Validity of systolic and diastolic parameters measured by the index beat

(i) NTproBNP/AFEQT/PCS vs Systolic and diastolic parameters measured using the index beat and average of 3, 5 and 10 beats

Baseline NT-pro-BNP/AFEQT/PCS will be correlated with LVEF, GLS and E/e' measured by the average of three index beats and the average of three, five and ten consecutive beats using a Spearman's correlation coefficient. Histograms were plotted to identify variables that were not normally distributed; skewed variables were transformed to their Log2 value. Univariate linear regression analysis was carried out initially, followed by step-wise multi-variate linear regression. Co-variables with a p value <0.1 were included in the model.

ii) Difference in validity between the index beat and conventional averaging of 3, 5 and 10 beats

To determine whether there was a significant difference in the strength of correlation between the different measuring methods (average of three index beats verses average of 3, 5 and 10

consecutive beats) the difference in correlation coefficients was tested using the corcor function in STATA. A two-sided p value of ≤0.05 was considered to show a statistically significant difference.

Table 14. Summary of all statistical tests used

Results chapter	Statistical test	Where it was used?
Chapter 4	**Mean (±standard deviation)**	The patient demographics and time taken to obtain measurements
	Median (IQR)	The patient demographics
	Coefficient of Variation	Variability within index beats vs average of 3, 5 and 10 consecutive beats
	Bland and Altman analysis	Inter and intra observer variability of index beats vs average of 3, 5 and 10 consecutive beats
	Mixed effects multi-level linear regression analysis	Inter and intra observer variability of the index beat vs average of 3, 5 and 10 consecutive beats, adjusting for the patient.
	Paired T-test	To test difference between time taken to obtain measurements
Chapter 5	**Spearman's Correlation**	Correlation between systolic parameters and diastolic parameters vs NT-pro-BNP and physical component score
	Linear regression	To determine the beta coefficient of how LVEF, GLS and E/e' predicts NTproBNP, AFEQT score and the PCS.
	Step-wise multiple variable linear regression	To determine the beta coefficient of how LVEF, GLS and E/e' predicts NTproBNP, AFEQT score and the PCS, when adjusting for the co-variables
	Correlation of correlation coefficients	To assess whether there is a significant difference between correlations made using the index beat, average of 3, 5 and 10 beats with NTproBNP and patient symptoms

Chapter 4. A simple method to improve the reproducibility of echocardiography in patients with atrial fibrillation

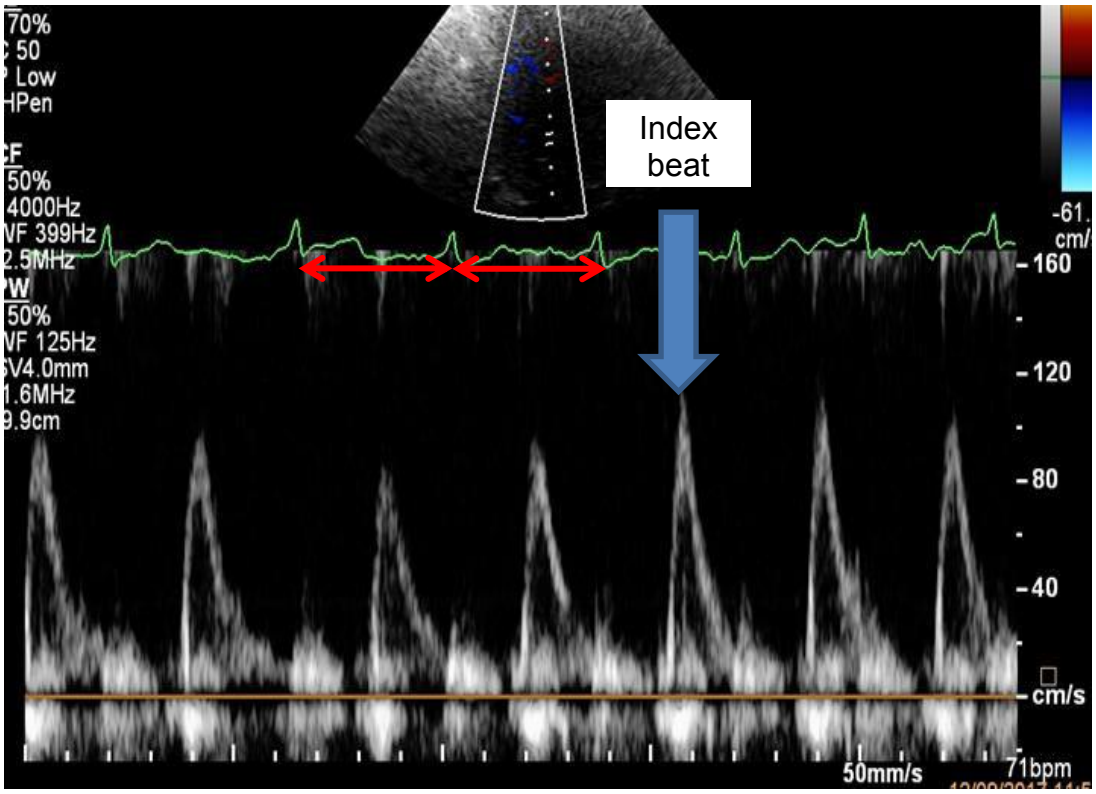
4.1 Introduction

Echocardiography is an important component of atrial fibrillation (AF) management, including stratification of stroke risk, rate and rhythm control, and the identification of heart failure.(3) Around 50% of patients with AF have or will develop heart failure (21, 22), but assessment of systolic and diastolic function are challenging in AF due to the irregular R to R interval. Current guidelines recommend averaging 5 to 10 consecutive beats (171-173), although there is no evidence-base behind this decision and multiple beat analysis is time consuming and may not be appropriate in the context of AF.(37) Accurate and reproducible measurement of systolic and diastolic function is essential so that heart failure can be correctly classified and managed appropriately.

The index beat method has been suggested as a more physiological approach for echocardiography in the context of AF for many decades, (12) (154) following small animal and human studies beginning in the 1970's. It was found that there was a relationship between the length of R to R interval and left ventricular systolic function and contractility.(174) It was found that the preceding R to R interval (RR1) is positively correlated and the pre-preceding R to R interval (RR2)is negatively correlated to contractility as measured by end-systolic LV maximal elastance (E_{max}). Therefore the length of RR1 and RR2 were found to contribute significantly to the E_{max}, whereas the R to R intervals preceding RR1 and RR2 were found to not contribute significantly.(175) The influence of the R to R interval on contractility is believed to be caused by preload (as a result of the Frank Starling mechanism) and uptake of calcium during the relaxation phase. Calcium is released in response to an action potential, which is taken up by the contractile elements activating mechanical contraction. Relaxation occurs when the calcium is removed from the cell by

either being transported across the membrane out of the cell or taken up into storage compartments. This is assumed to be a time dependent process and so the longer the R to R interval the more time for calcium to be taken up and so more would be released in response to the sequential action potential, triggering a greater force of contraction.(176) As ventricular filling and stroke volume for a particular beat are determined by the previous two R to R intervals, the index beat method selects a cardiac cycle for analysis where the preceding (RR1) and pre-preceding (RR2) R to R interval are of similar duration (that is, the ratio of these intervals is approximately one), see **Figure 25** for an example of an index beat.

Figure 25. Measurement of Mitral E wave Vmax on an index beat (blue arrow) by selecting the beat which follows a preceding and pre-preceding R to R interval within 60 ms of each other (red arrows)



However, current guidelines continue to recommend averaging of 5 to 10 consecutive beats.(171-173) The aim of this study was to systematically compare the reproducibility of an index beat approach compared to conventional averaging of three, five and ten beats. There was complete blinding of patients and measurements, and without any pre-selected exclusion

of patients for image quality as is typical in other studies. It was hypothesised that the index beat method would be more reproducible and efficient, facilitating better management of patients with AF.

4.2 Method

4.2.1 Patient population

All patients enrolled in the RAte control Therapy Evaluation in permanent AF (RATE-AF) randomised controlled trial were included after written informed consent (NCT02391337). The trial has received favourable ethical review from the UK Heath Research Authority (East Midlands - Derby Research Ethics Committee; 16/EM/0178) and has oversight from a Trial Steering Committee and Data Monitoring Committee with independent chairs. Rationale and methods for the RATE-AF trial have previously been described in **chapter 3**(163); in brief, patients in the National Health Service aged 60 years or older with permanent AF and symptoms of heart failure (New York Heart Association class II or above) were randomised to digoxin or beta-blockers for initial rate control of AF. Permanent AF was defined as a physician decision for rate control and no plans for any antiarrhythmic drugs or intervention. Patients were excluded if their heart rate was less than 60 beats/min, or had prior evidence of second or third degree heart block. Other exclusion criteria were minimised to enable generalisable 'real-world' results. The trial was publically funded by the UK National Institute for Health Research (NIHR).

4.2.2 Echocardiography

12-lead electrocardiograms confirmed the presence of AF. All patients then underwent transthoracic echocardiography using a Philips EPIQ 7 and X5-1 transducer. All echocardiograms were performed by an experienced echocardiographer accredited with the British Society of Echocardiography. Patients were positioned in the left lateral decubitus position and images were acquired during quiet respiration according to an echocardiography

protocol written and ratified prior to the trial commencing (the full protocol is described in **chapter 3**).

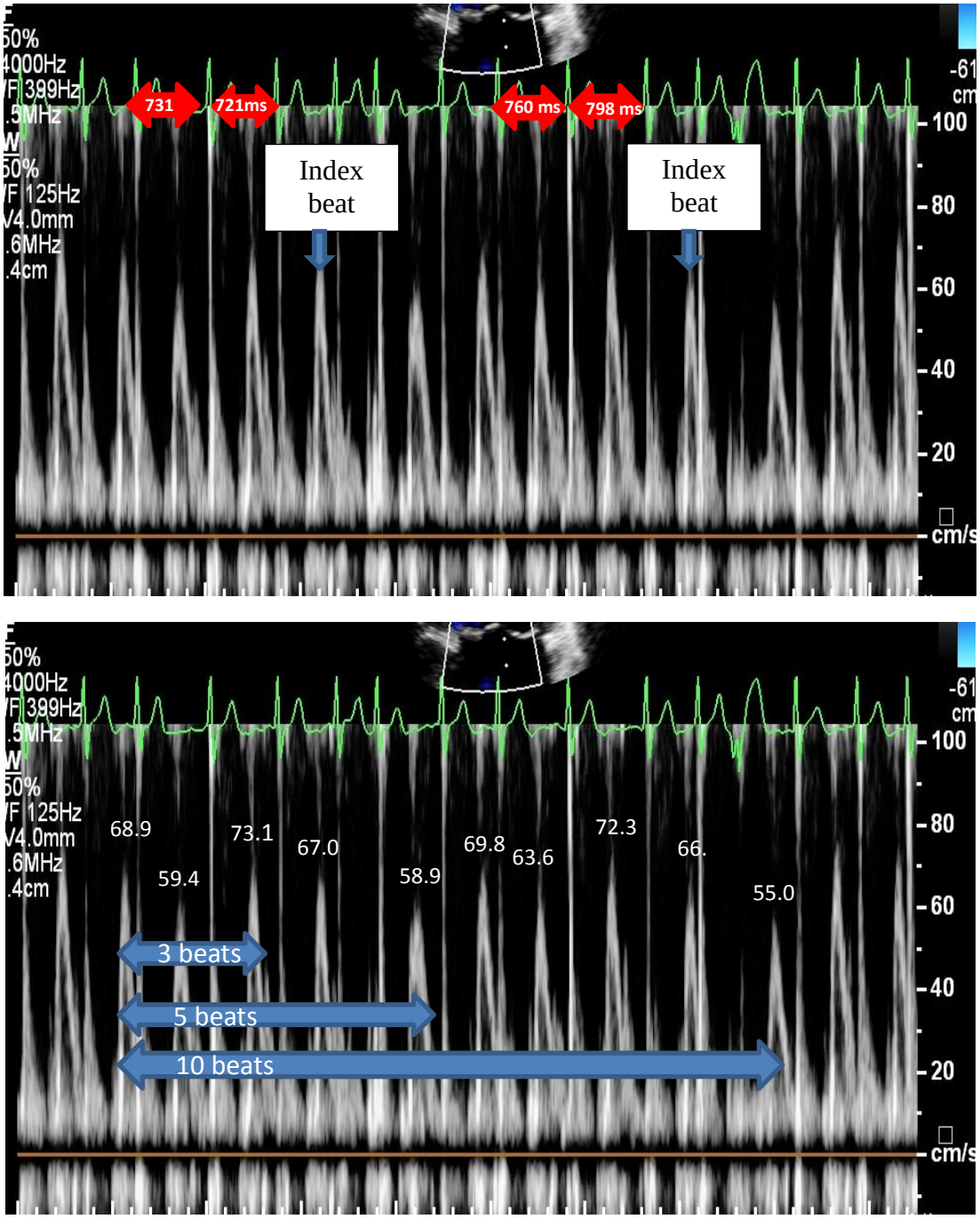
A minimum of 30-beat loops were obtained of the apical 2, 3 and 4-chambers. All images were optimised to maximise frame rate while still ensuring all left ventricular segments were visible. A minimum of 30 traces of Tissue Doppler derived lateral and septal e' were obtained; care was taken to ensure that the lateral and septal annulus was aligned perpendicular to the ultrasound beam in order to minimise the angle of incidence. A minimum of 30 traces of mitral inflow using pulse wave Doppler were also acquired, with colour Doppler used to ensure the sample volume was placed at the level of the mitral leaflet tips within the inflow. The recorded images were unlabelled and had no identifiable features.

All measurements were analysed offline by the same operator a minimum of 6 months after the scan date. The operator was blinded to any identifiable patient, trial or clinical details by a process of assigning each echocardiogram a unique random code. There were no predefined exclusions made for quality of imaging; all patients were included to minimise selection bias. All analyses were performed on Philips Q-station (version 3.5; Philips Healthcare, Andover, Massachusetts). For left ventricular ejection fraction (LVEF), Simpson's biplane LVEF was measured from the apical 4 and 2-chamber views. Longitudinal strain was taken from the apical 2, 3 and 4-chamber views and then averaged to generate overall global longitudinal strain (GLS). The mean frame rate for GLS acquisition was 57 Hertz (SD 7.0). For E/e', mitral valve peak E velocity was measured and then divided by the tissue Doppler imaging (TDI)-derived e' (averaged from the lateral and septal walls).

4.2.3 Index beat and conventional averaging method

The index beat was identified as the cardiac cycle which followed a preceding and pre-preceding R to R interval of similar duration (within 60 ms of each other; **Figure 26**).

Figure 26. Measuring the mitral valve E max using conventional averaging of consecutive beats verses the index beat method. **Mitral valve inflow E max measured on the index beat (top); the beat with similar preceding and pre-preceding R to R intervals indicated by the red arrows and using the average of 3, 5 and 10 consecutive beats (bottom)**



R to R intervals were measured using a calliper in the reporting software and according to the velocity of acquisition of the corresponding electrocardiogram (1cm was equal to 200ms). The index beats were selected consecutively from the beginning of each set of echocardiogram data to avoid any selection bias. Conventional analysis involved using consecutive beats to obtain the average of 3, 5 and 10 cardiac cycles.

4.2.4 Intra-operator reproducibility

At the end of the echocardiogram the same operator immediately afterwards, repositioned the patient and took a second set of 10 images of the left ventricle in the apical 2, 3 and 4 chamber and second set of 10 traces of mitral valve peak E velocity and the TDI-derived e' (averaged from the lateral and septal walls). These images (using methods described above) were then analysed to measure GLS and E/e' using a single index beat and average of 3, 5 and 10 beats. These measurements were compared with the operator's initial measurements of GLS and E/e' using a single index beat and average of 3, 5 and 10 beats to assess intra-operator reproducibility.

4.2.5 Inter-operator reproducibility and time comparison

Similar to the intra-operator protocol, a second accredited operator obtained a second set of 10 images of the left ventricle in the apical 2, 3 and 4 chamber and second set of 10 traces of mitral valve peak E velocity and the TDI-derived e' (averaged from the lateral and septal walls. The second operator's measurements of GLS and E/e' using a single index beat and average of 3, 5 and 10 beats were compared with the operator's initial measurements of GLS and E/e' to assess inter-operator reproducibility.

A second accredited operator re-analysed the E/e' images in 18 randomly selected patients for assessment of inter-operator reproducibility. The operator was blinded to the previously recorded measurements as well as all clinical details of each echocardiogram. The time taken

for the second operator to select and measure E/e' using a single index beat and guideline-recommended 5 and 10 consecutive beats was recorded, with time commencing from the first visualisation of Doppler images.

4.2.6 Statistical analysis

Summary results are presented as percentage, mean with standard deviation or median with interquartile range (IQR; displayed as 25th to 75th quartiles). All echocardiographic measurements were transformed to their natural log value to assess within beat variability. The coefficient of variation within three index beats and within each set of consecutive beats (3, 5 and 10) was calculated using the following formula $\sqrt{\exp(\sigma^2)}-1 \times 100$, where σ is the standard deviation within the set of beats. A Wilcoxon signed rank test was used to compare the differences in coefficient of variation between the index beat method and 3, 5 and 10 consecutive beats. Statistical analysis was performed using Stata (version 14.2; StataCorp, Texas, USA); a 2-tailed p value of ≤ 0.05 was considered statistically significant. For intra- and inter-operator reproducibility, Bland and Altman analysis was carried out to obtain the mean bias and the limits of agreement. A mixed effects multi-level linear regression model was also used for intra and inter-operator reproducibility; adjusting for the random effects of the patient and measurement time. From the model the intraclass correlation (ICC; with 95% confidence interval) was calculated at the patient level for each measurement method. The average time taken to measure E/e' (SD) was calculated and paired t-test was used to compare the time taken between measuring methods; a p-value ≤ 0.05 was considered significant.

4.3 Results

One hundred and 60 patients were included, with median age of 75 years (IQR 69-82), heart rate of 96 beats/minute (86-112) and blood pressure of 134/84 mmHg (IQR 123/76-148/93), see **Table 15**.

Table 15. Baseline Demographics of patients at baseline echocardiogram

Characteristic	n= 160
Age, median years (IQR)	75 (69-82)
Women, n (%)	74 (46.3%)
Years in AF, mean years (SD)	3.8 (6.2)
EHRA score 3/4, n (%)	77 (48.1%)
Previous heart failure clinical diagnosis, n (%)	59 (36.9%)
Signs of heart failure at randomisation, n (%)	84 (52.5%)
NYHA class III/IV, n (%)	61 (38.1%)
Previous myocardial infarction, n (%)	13 (8.1%)
Previous stroke, n (%)	19 (11.9%)
Previous TIA, n (%)	15 (9.4%)
COPD, n (%)	29 (18.1%)
Diabetes mellitus, n (%)	38 (23.8%)
Previous rhythm control, n (%)	23 (14.4%)
Heart rate, median bpm (IQR)	96 (86-112)
Systolic BP, median mmHg (IQR)	134 (123-148)
Diastolic BP, median mmHg (IQR)	84 (76-93)
Body mass index, median kg/m^2 (IQR)	30 (26-34)
NTproBNP, median pg/mL (IQR)	1057 (744-1522)
Estimated GFR, median mL/min (IQR)	67 (55-77)
Anticoagulant medication, n (%)	135 (84.4)
Antiplatelet medication, n (%)	9 (5.6%)
Antihypertensive medication, n (%)	116 (72.5%)
Inhalers for airways disease, n (%)	40 (25.3%)

Abbreviations: AF= atrial fibrillation; BP= blood pressure; COPD= chronic obstructive pulmonary disorder; EHRA= European Heart Rhythm Association; GFR= glomerular filtration rate; NTproBNP= N-terminal pro-B type natriuretic peptide; NYHA= New York Heart Failure Association functional classification; TIA= transient ischaemic attack

Median LVEF was 59% (IQR 52-64), GLS -14 (IQR -12 to -15) and E/e' 9.4 (IQR 7.8-11.7); 18 patients had insufficient image quality for LVEF measurement and 21 patients for GLS, this was predominantly due to patient body habitus (mean BMI= 38 kg/m2) and COPD (33%, n=6). Other echocardiogram parameters of interest are summarised in **Table 16**.

Table 16: Echocardiography parameters

Echocardiographic measurement	Baseline
Left ventricular end diastolic volume, median ml (IQR)*	76 (57-99)
Left ventricular end systolic volume, median ml (IQR)*	30 (22-42)
Stroke volume, median ml (IQR)*	55 (45-64)
Left ventricular ejection fraction, median % (IQR) *	59 (52-64)
Global longitudinal strain, median % (IQR)*	-14 (-12 to -15)
Lateral s', median cm/s (IQR)*	6.7 (5.6-7.9)
Septal s', median cm/s (IQR)*	6.1 (5.1-7.2)
Average e', median cm/s (IQR)*	9.3 (8.1-10.9)
Mitral E velocity, median cm/s (IQR)*	89.7 (77.1-102.8)
Mitral deceleration time, median ms (IQR)*	212 (188-234)
Average E/e', median (IQR)*	9.4 (7.8-11.7)
Isovolumic relaxation time, median ms (IQR)	97 (89-108)
Pulmonary vein ratio, mean (SD)	0.7 (0.1)
Pulmonary vein deceleration time, median (IQR)	242 (223-258)
Left atrial volume indexed to BSA, median ml/m2 (IQR)	38 (32-49)
Left atrial ejection fraction, median % (IQR)	23 (15-33)
TAPSE mm, median (IQR)	18.7 (17.1-21.8)

* based on average of 3 index beats. 18 patients had insufficient image quality for a Simpson's biplane LVEF measurement and 21 patients had insufficient image quality for GLS.

Abbreviations: IQR= inter-quartile range; TAPSE= tricuspid annular plane systolic excursion

4.3.1 Within beat coefficient of variation

LVEF- The index beat approach had the smallest coefficient of variation (Confidence interval 95%) for LVEF of 23% (21-24), compared to 45% (42-48) for the 3 consecutive beats, 45% (43-48) for 5 consecutive beats and 48% (46-50) for 10 consecutive beats (**Figure 27** and **Table 17**). The difference between the coefficient of variation using the index beat and 3, 5 and 10 consecutive beats was found to be statistically significant, p=<0.001. For measuring on the index beat the mean RR2 (pre-preceding R to R interval) was 552 ms and the mean RR1 (preceding R to R interval) was 555 ms with a mean RR1/RR2 ratio of 1.00.

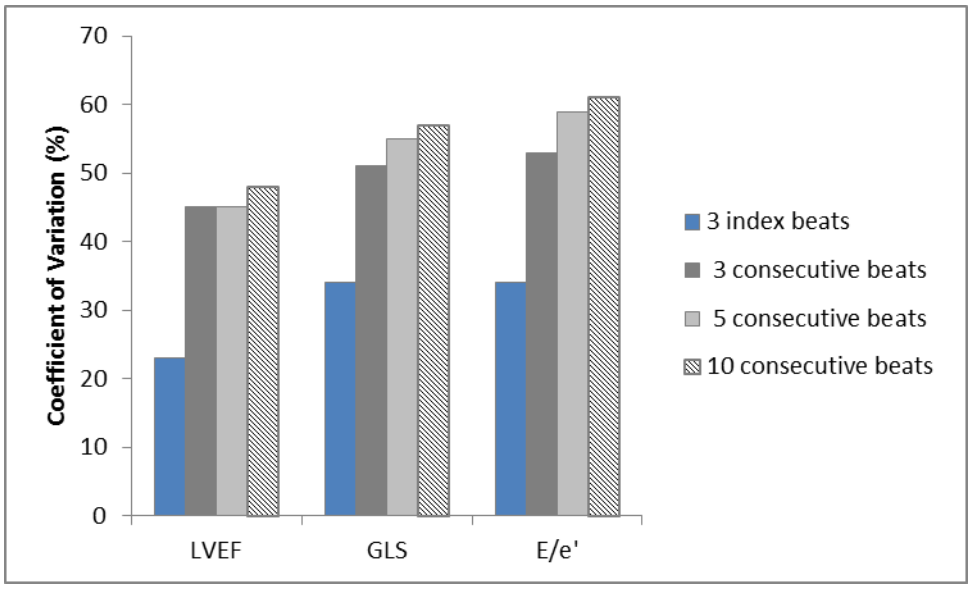
GLS: The index beat approach had the smallest coefficient of variation (Confidence interval 95%) of 34% (32-36) compared to 51% (42-59) for of 3 consecutive beats, 55% (48-61) for 5 consecutive and 57% (56-63) for 10 consecutive beats (see **Figure 27** and **Table 17**). The difference between the coefficient of variation using the index beat and 3, 5 and 10 consecutive beats was found to be statistically significant, <0.001. For measuring on the index beat the mean RR2 was 568 ms and the mean RR1 was 570 ms with a mean RR1/RR2 ratio of 1.00.

E/e': The index beat approach had the smallest coefficient of variation (Confidence interval 95%) of 34% (32-36), compared to 53% (49-56) for 3 consecutive beats, 59% (56-63) for 5 consecutive beats and 61% (58-64)for 10 consecutive beats (see **Figure 27** and **Table 17)**. The difference between the coefficient of variation using the index beat and 3, 5 and 10 consecutive beats was found to be statistically significant, <0.001. For measuring on the index beat the mean RR2 was 653 ms and the mean RR1 was 655 ms with a mean RR1/RR2 ratio of 1.00

Table 17. Coefficient of variation for within beat variability of the three index beats verses 3, 5 and 10 consecutive beats

	3 index beats	3 consecutive beats		5 consecutive beats		10 consecutive beats	
	CV (%) (95% Conf. Interval)	CV (%) (95% Conf. Interval)	Difference from three index beats z (p value)	CV (%) (95% Conf. Interval)	Difference from three index beats z (p value)	CV (%) (95% Conf. Interval)	Difference from three index beats z (p value)
LVEF	23 (21 to 24)	45 (42 to 48)	-9.59 (p<0.001)	45 (43 to 48)	-10.17 (p<0.001)	48 (46 to 50)	-10.28 (p<0.001)
GLS	34 (32 to 36)	51 (42 to 59)	-5.67 (p<0.001)	55 (48 to 61)	-8.41(p<0.001)	57 (52 to 61)	-9.30(p<0.001)
E/e’	34 (32 to 36)	53 (49 to 56)	-8.37 (p<0.001)	59 (56 to 63)	-10.25 (p<0.001)	61 (58 to 64)	-10.69 (p<0.001)

Figure 27. Within beat variability of three index beats, 3, 5 and consecutive beats. A bar chart displaying the coefficient of variation for within beat variability of LVEF Simpson's biplane, GLS and E/e' using three index beats, 3, 5 and 10 consecutive beats. Abbreviations: LVEF= Left ventricular ejection fraction; GLS= global longitudinal strain.



4.3.2 Intra and inter-operator reproducibility

Intra-operator reproducibility of a single index beat method verses average of 3, 5 and 10 beat method was tested in 50 patients using the parameters GLS and E/e'. Their median age was 79 years (IQR 73-85), heart rate 96 beats/min (IQR 90-107) and blood pressure 134/80 mmHg (IQR 123-146/ 75-86), see **Table 18**. For GLS the index beat method had the smallest bias and narrow limits of agreement, -0.5 (-3.6 to 2.6) compared to the conventional averaging of 3 beats -1.1 (-4.8 to 2.7), 5 beats -1.1 (-4.4 to 2.3) and 10 beats -1.0 (-4.0 to 2.0) (**Figure 28**). The index beat method also had the highest ICC with reasonable confidence intervals 0.82 (0.72 to 0.90), followed by the average of 10 beat method 0.80 (0.68 to 0.88), then average of 5 beats 0.76 (0.63 to 0.86) and average of 3 beat method 0.75 (0.61 to 0.85), see **Table 19**.

Similar findings were also seen for E/e', with the index beat method having the smallest bias and similar limits of agreement to the average of 10 beat method; -0.2 (-4.2 to 3.9) for the index beat method and -0.4 (-4.2 to 3.4) for the average of 10 beats. Whereas the intra-operator reproducibility of averaging 3 and 5 beats had a higher bias and wider limits of agreement; -0.7 (-6.2 to 4.8) and -0.6 (5.3 to 4.2) respectively (**Figure 28**). The index beat method had the highest ICC with narrow confidence intervals 0.91 (0.84 to 0.95), followed by the average of 10 beat method 0.88 (0.80 to 0.93), average of 5 beat method 0.80 (0.68 to 0.88) and average of 3 beat method 0.74 (0.60 to 0.85), see **Table 19**.

Table 18. Baseline demographics of patients included in the intra and inter-operator reproducibility study

Characteristic	All patients (n= 160)	Intra-operator reproducibility (n=50)	Inter-operator reproducibility (n=18)
Age, median years (IQR)	75 (69-82)	79 (73-85)	74 (66-84)
Women, n (%)	74 (46%)	25 (50%)	8 (44%)
Years in AF, mean years (SD)	3.8 (6)	3.2 (6)	4.3 (8)
EHRA score 3/4, n (%)	77 (48%)	22 (44%)	8 (44%)
Previous heart failure clinical diagnosis, n (%)	59 (37%)	13 (26%)	5 (28%)
Signs of heart failure at randomisation, n (%)	84 (53%)	27 (54%)	10 (56%)
NYHA class III/IV, n (%)	61 (38%)	21 (42%)	8 (44%)
Previous myocardial infarction, n (%)	13 (8%)	3 (6%)	2 (11%)
Previous stroke, n (%)	19 (12%)	5 (10%)	0 (0%)
Previous TIA, n (%)	15 (9%)	8 (16%)	0 (0%)
COPD, n (%)	29 (18%)	8 (16%)	3 (17%)
Diabetes mellitus, n (%)	38 (24%)	12 (24%)	5 (28%)
Previous rhythm control, n (%)	23 (14%)	7 (14%)	4 (22%)
Heart rate, median bpm (IQR)	96 (86-112)	96 (90-107)	99 (93-113)
Systolic BP, median mmHg (IQR)	134 (123-148)	134 (123-146)	132 (125-152)
Diastolic BP, median mmHg (IQR)	84 (76-93)	80 (75-86)	81 (76-86)
Body mass index, median kg/m^2 (IQR)	30 (26-34)	29 (27-33)	29 (26-34)
NTproBNP, median pg/mL (IQR)	1057 (744-1522)	1062 (738-1480)	1116 (761-1192)
Estimated GFR, median mL/min (IQR)	67 (55-77)	67 (55-73)	70 (52-83)
Anticoagulant medication, n (%)	135 (84%)	40 (80%)	14 (78%)
Antiplatelet medication, n (%)	9 (6%)	2 (4%)	1 (6%)
Antihypertensive medication, n (%)	116 (73%)	37 (74%)	14 (78%)
Inhalers for airways disease, n (%)	40 (25%)	7 (14%)	2 (11%)

Abbreviations: AF= atrial fibrillation; BP= blood pressure; COPD= chronic obstructive pulmonary disorder; EHRA= European Heart Rhythm Association; GFR= glomerular filtration rate; NTproBNP= N-terminal pro-B type natriuretic peptide; NYHA= New York Heart Failure Association functional classification; TIA= transient ischaemic attack

Figure 28. Bland and Altman plots to show GLS and E/e' intra-operator reproducibility in 50 patients. Bland and Altman plots displaying intra-operator reproducibility of GLS and E/e' measured using a single index beat (left), average of 5 beats (middle) and average of 10 beats (right) in 50 patients.

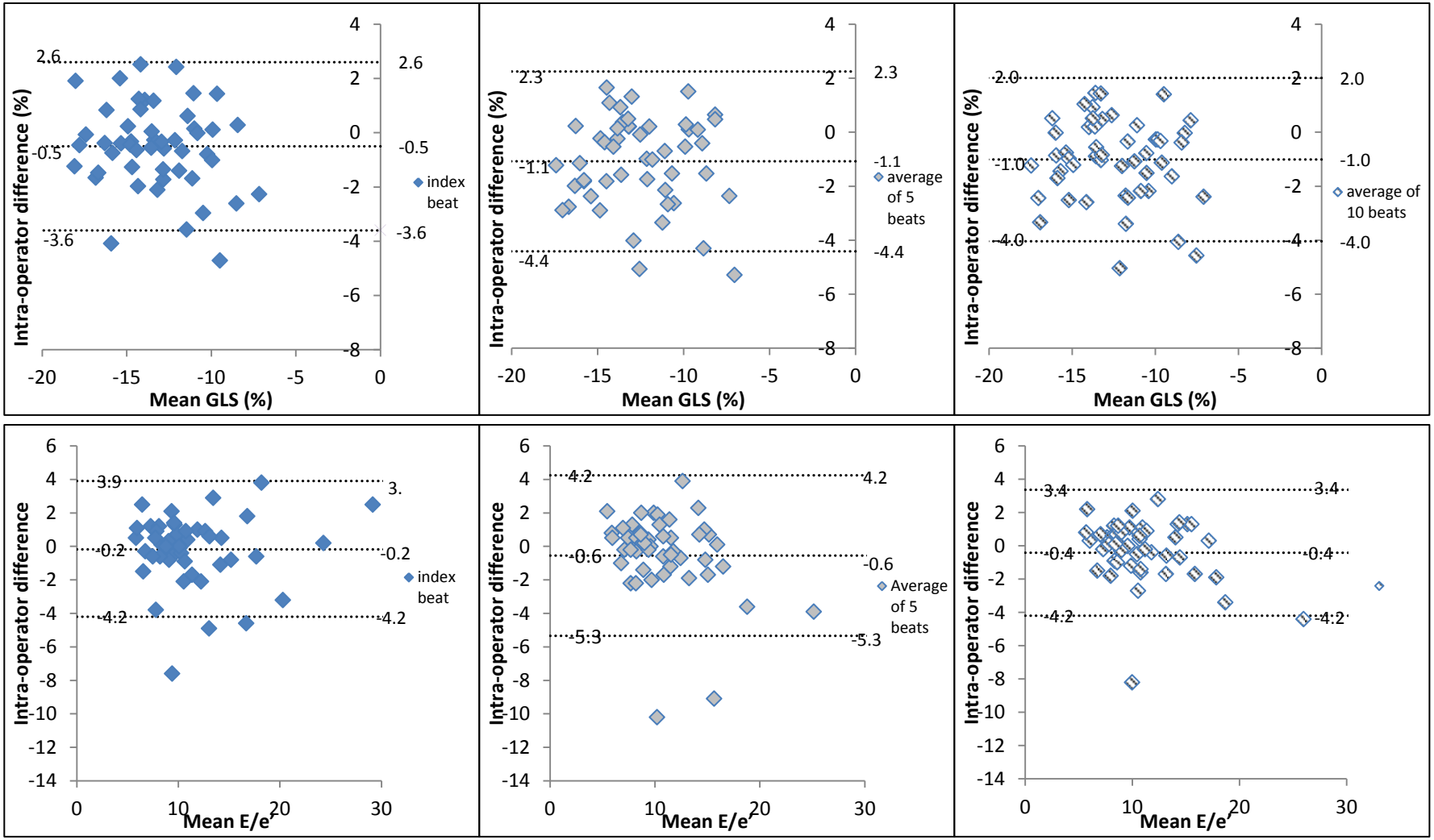


Table 19. Intra-operator reproducibility

	E/e' Intra-operator reproducibility		GLS Intra-operator reproducibility	
	Bias (limits of agreement)	ICC (95% Conf. Interval)	Bias (limits of agreement)	ICC (95% Conf. Interval)
Index Beat	-0.2 (-4.2 to 3.9)	0.91 (0.84 to 0.95)	-0.5 (-3.6 to 2.6)	0.82 (0.72 to 0.90)
Average of 3 beats	-0.7 (-6.2 to 4.8)	0.74 (0.60 to 0.85)	-1.1 (-4.8 to 2.7)	0.75 (0.61 to 0.85)
Average of 5 beats	-0.6 (5.3 to 4.2)	0.80 (0.68 to 0.88)	-1.1 (-4.4 to 2.2)	0.76 (0.63 to 0.86)
Average of 10 beats	-0.4 (-4.2 to 3.4)	0.88 (0.80 to 0.93)	-1.0 (-4.0 to 2.0)	0.80 (0.68 to 0.88)

Inter-operator reproducibility was tested in 18 randomly selected patients for GLS and E/e' Their median age was 74 years (IQR 66-84), heart rate was 99 beats/min (IQR 93-113) and blood pressure was 132/ 81 mmHg (IQR 125-152/76-86), see **Table 18**. For GLS the index beat had the smallest bias but the widest limits of agreement -0.3 (-5.5 to 5.0), compared to the average of 3 beats -0.8(-5.7 to 4.1), average of 5 beats -0.7 (-5.5 to 4.1) and average of 10 beats -0.7 (-5.3 to 3.9), see **Table 20** and **Figure 29**. The index beat method also had the lowest ICC 0.72 (0.45 to 0.88), compared to the average of 3 beats 0.74 (0.50 to 0.90), 5 beats 0.75 (0.50 to 0.90) and 10 beats 0.77 (0.54 to 0.91). However for E/e' the inter-operator reproducibility of E/e' was highest for the index beat with the smallest bias and narrowest limits of agreement -0.3 (-2.9 to 2.2), followed by the average of 10 beats with -0.9 (-6.1 to 4.2), then average of 5 beats with -1.1 (-6.5 to 4.2) and then average of 3 beats -1.1 (-5.4 to 3.2). The ICC was also highest for the index beat 0.94 (0.87 to 0.98), followed by the average of 3 beats ICC= 0.83 (0.64 to 0.93), the average of 10 beats ICC=0.93 (0.62 to 0.93) and average of 5 beats ICC= 0.78 (0.56 to 0.91), see **Table 20** and **Figure 29**.

Figure 29. Bland and Altman plots to show the inter-operator reproducibility of GLS and E/e' when using an index beat verses average of 5 and 10 beats

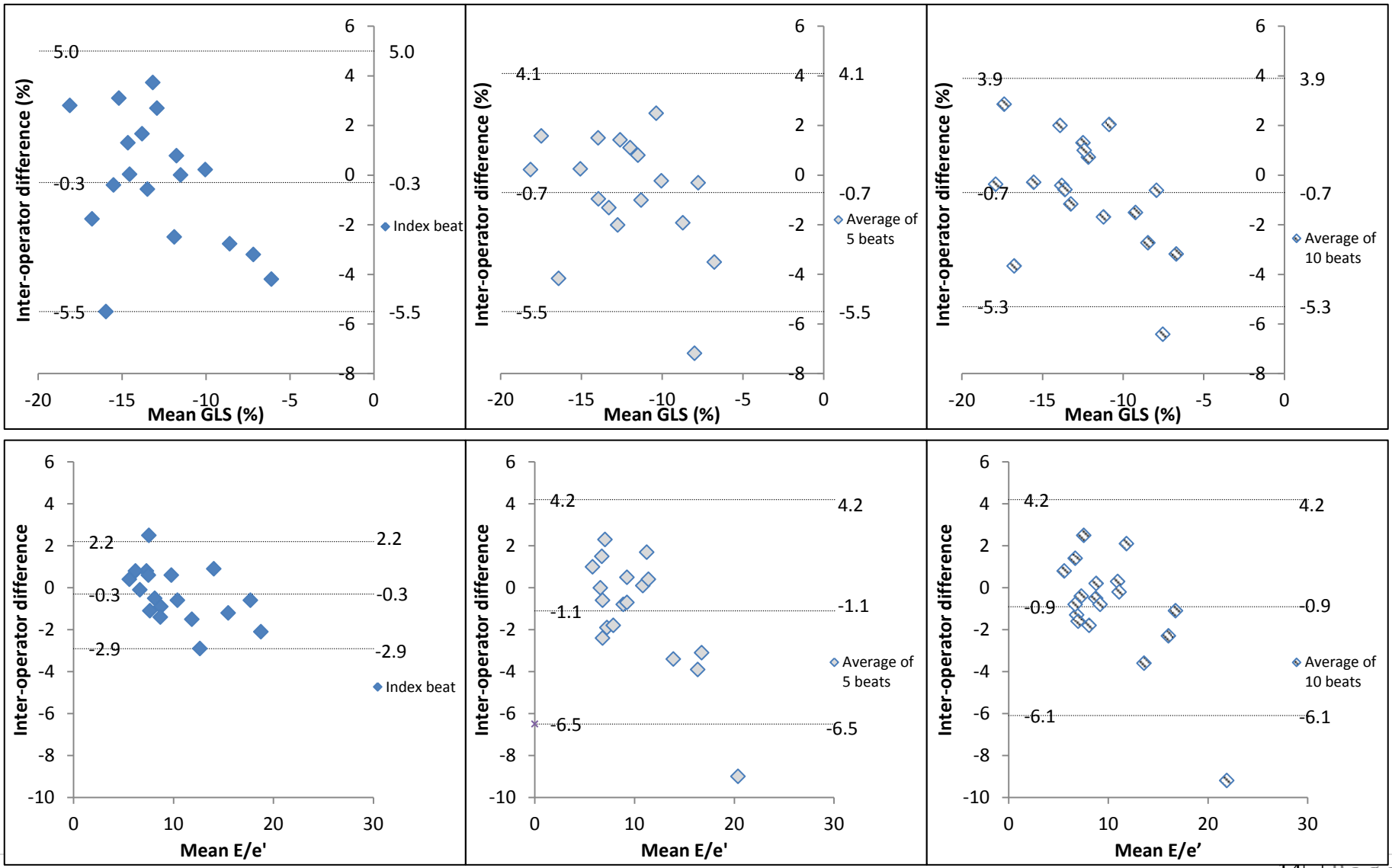


Table 20. Inter-operator reproducibility

	E/e' Inter-operator reproducibility		GLS Inter-operator reproducibility	
	Bias (limits of agreement)	ICC (95% Conf. Interval)	Bias (limits of agreement)	ICC (95% Conf. Interval)
Index Beat	-0.3 (-2.9 to 2.2)	0.94 (0.87 to 0.98)	-0.3 (-5.5 to 5.0)	0.72 (0.45 to 0.88)
Average of 3 beats	-1.1 (-5.4 to 3.2)	0.83 (0.64 to 0.93)	-0.8 (-5.7 to 4.1)	0.74 (0.50 to 0.90)
Average of 5 beats	-1.1 (-6.5 to 4.2)	0.78 (0.56 to 0.91)	-0.7 (-5.5 to 4.1)	0.75 (0.50 to 0.90)
Average of 10 beats	-0.9 (-6.1 to 4.2)	0.82 (0.62 to 0.93)	-0.7 (-5.3 to 3.9)	0.77 (0.54 to 0.91)

4.3.3 Efficiency of index beat method

The index beat method took the least amount of time to measure E/e' at 35.4 seconds (SD 4.8). This was 21% quicker than measuring E/e' using the average of 5 beats which took 44.7 seconds (SD 5.7; $p<0.001$) and 64% quicker than averaging 10 beats which took 98.1 seconds (SD 12.8; $p<0.001$); (**Table 21)**.

Table 21: Time taken to select and measure E/e' using an index beat verses averaging 5 and 10 consecutive beats

	Average time (SD) (ms)	**Mean E/e' (SD)**
Index beat	35.5 (4.8)	10.6 (4.1)
Average of 5 beats	44.7 (5.7)	10.5 (4.4)
Average of 10 beats	98.1 (12.8)	10.2 (4.3)

4.4 Discussion

In this study, the index beat method has been demonstrated to be more reproducible in patients with AF than conventional averaging of consecutive beats for systolic and diastolic parameters and also saves time. The within-beat coefficient of variability and intra/inter-observer reproducibility were favourable using this more physiological approach to imaging in patients who have a variable stroke volume and filling time. Using the index beat method routinely in clinical practice has the potential to improve workflow and productivity, enhance the reliability of echocardiography, and provide more confidence in the diagnosis and classification of heart failure in patients with AF.

Heart failure is common in patients with AF, and accurate assessment of systolic and diastolic left ventricular function is essential for patient management. Although current guidelines recommend averaging 5 to 10 consecutive beats(171, 172), this is based on consensus opinion and lacks reliable evidence.(177) Measuring consecutive beats is not only time-consuming and extends the time taken for echocardiography, but also the average value will vary according to what beats are selected, making reliability in clinical practice uncertain.(154, 178) AF is characterised by a loss of atrial contraction and so ventricular filling relies heavily on the length of the R to R interval, with variation in intervals leading to considerable challenges to achieve reproducible measurements.(179) In addition to cycle length, stroke volume is critically dependent on preload, and this is also variable in the setting of AF.(174) The real value of the index beat method, whereby cycles are chosen of similar length, may be to achieve a more physiologically appropriate measurement, be that of systolic or diastolic function. In this context, the end-diastolic volume should be similar and so (via the Frank-Starling mechanism) the contractility will also be similar, producing less variability between index beats for LVEF.(179-181) This will also apply to GLS, a useful parameter in detecting early myocardial dysfunction.(154, 182) E/e' a surrogate of filling pressure, is still reliant on

previous cycle lengths.(102, 183) The extremely high levels of variation using a 10 consecutive beats (CV 61% for E/e') highlight the limitations of current guideline-recommended practice.

Intra-operator reproducibility for both GLS and E/e' was shown to be highest when measuring on a single index beat or averaging 10 beats. Previous studies assessing strain rate have found a strong correlation between the index beat and averages of 10 and 15 beats with high levels of agreement.(132, 145) However it was found that measuring a single index beat was considerably quicker than measuring 10 consecutive beats, even for a technically straightforward measurement like E/e'. For more technically challenging measurements(184), it is probable that there would be an even greater advantage in time saved. It was also demonstrated that the index beat method has a high level of reproducibility between different operators, an important contribution to value within the clinical setting, enhancing the practicality of serial scans.

A major concern with nearly all previous studies as identified in **chapter 2** is the pre-selection of patients with "good echocardiography windows". This is the first study in which the index beat method has been interrogated in all patients, in this case healthcare referrals for rate control enrolled within a pragmatic randomised controlled trial. The trial-based setting allowed 'double-blinding' of the imaging process, with anonymised scans stored, analyses performed offline with a separate random code to the study identification number, measurements performed 6 months after acquisition, and no data available to the operators on patient details or clinical status. All patients were confirmed as being in AF at the time of echocardiography. Although randomised trials are usually selective in population, the RATE-

AF trial was designed to mimic routine practice as evidenced by the patient characteristics, including a median age of 75 years. The results are therefore relevant to the real world and suggest the index beat method should replace the recommended averaging of 5 to 10 consecutive beats in echocardiography guidelines. Further study is warranted to establish the association with long-term adverse clinical events. In the study, patients will undergo repeat echocardiography at 12 months, and then further follow-up using electronic healthcare outcomes.(163) Qualitative assessment is also desirable to establish how to effectively introduce the index beat approach in cardiology departments and the training required to aid clinical productivity.

The study was limited by non-simultaneous acquisition of Doppler and chamber images, and although this is currently standard practice globally, there are dual-Doppler probes available, which would be valuable in AF.(185) With pressure on echocardiography services increasing due to growing patient populations and wider indications, the index beat method could provide a reproducible method for patients in AF that also increases the efficiency of echocardiography.

4.5 Conclusion

The index beat approach, by selecting cardiac cycles which better represent overall systolic and diastolic function, has clear advantages for echocardiography in patients with AF. In a blinded analysis without preselection for image quality, I have shown that this method has better reproducibility and is quicker than conventional averaging of multiple consecutive heart beats. Further analysis is required to determine the optimum length of the preceding and pre-preceding R to R intervals chosen to measure the index beat on, to establish whether or not

there is a cut-off point for tachycardia and bradycardic heart rates that makes this method not applicable.

Although the index beat method has been shown to be more reproducible and time efficient, it remains unclear as to whether using an index beat is a reflection of the overall haemodynamic burden on the heart. It may be that the conventional method of averaging consecutive beats correlates better with the other biomarkers of heart function and the clinical status of the patient. The validity of the index beat method has never been compared with conventional averaging of consecutive beats. In the following chapter the validity of using the index beat method to measure LVEF Simpson's biplane, GLS and E/e' by correlating it with clinical outcomes, (NTproBNP and patient reported quality of life) is explored.

Chapter 5. Validity of systolic and diastolic parameters versus patient quality of life and NTproBNP

5.1 Introduction

Depending on type of AF 30-60% of patients are also diagnosed with some form of heart failure.(16) Therefore it is essential that cardiac dysfunction is promptly diagnosed so that correct treatment can be initiated to improve prognosis. The systematic review (**chapter 2**) has demonstrated a lack of information on the validity of systolic parameters in patients with AF. Although there have been more validity studies for diastolic parameters, (37) the effect of diastolic function on clinical status and neurohormonal biomarkers of heart failure is less clear. In **chapter 4** the index beat was the most reproducible method of obtaining systolic and diastolic measurements, however it has not been validated against clinical status of the patient or whether it correlates accurately with the heart failure biomarker NTproBNP. The aim of this study was to investigate the relationship between systolic and diastolic parameters using the average of three index beats and the average of 3, 5 and 10 consecutive beats with both patient symptoms and N-terminal pro-B-type natriuretic peptide (NTproBNP) as a biomarker of left ventricular dysfunction.

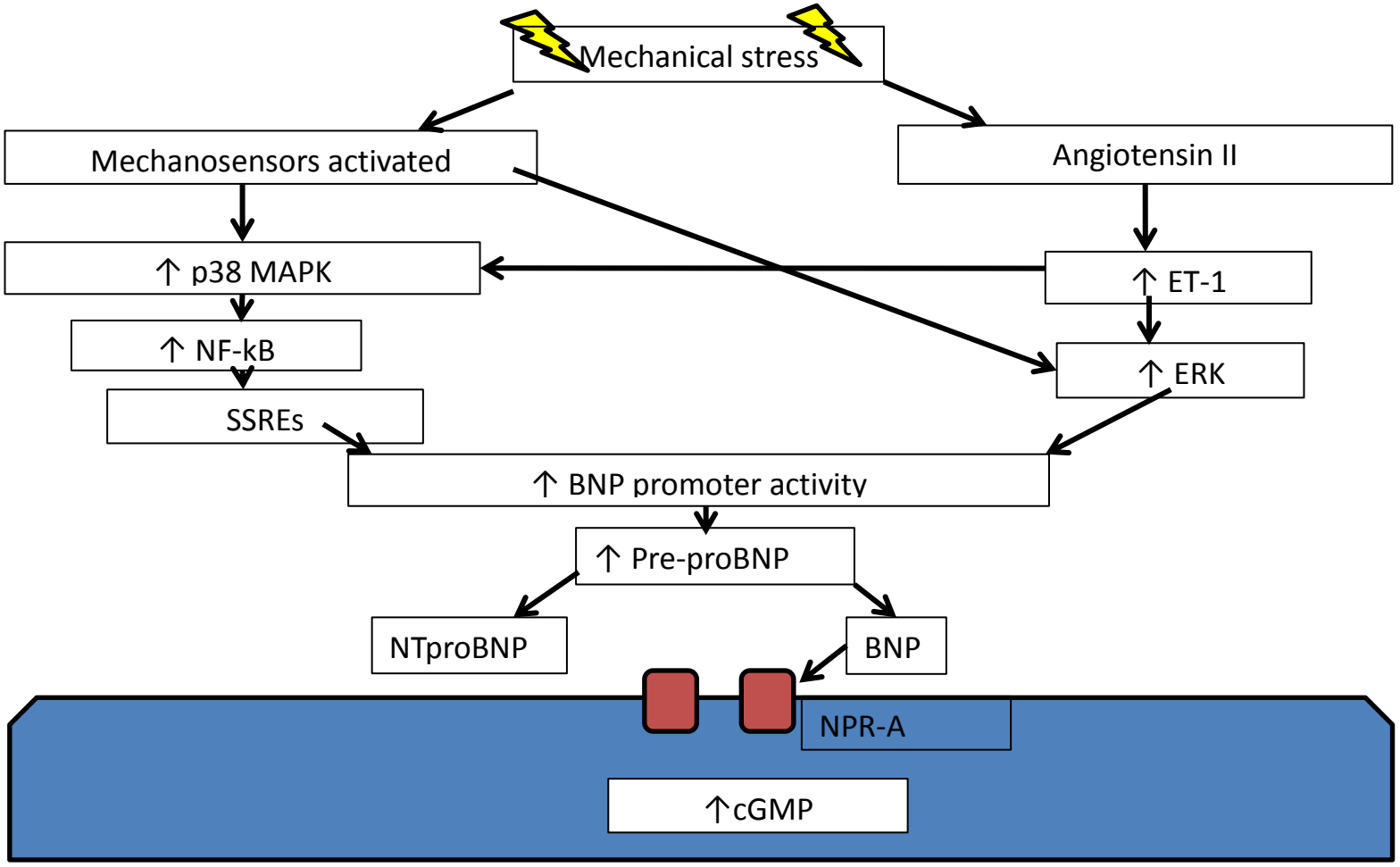
5.1.1 Background of NTproBNP

B-type natriuretic peptide (BNP) and NTproBNP are widely used as clinical indicators of cardiac dysfunction. An elevated level of NTproBNP indicates a poor prognosis, increasing the risk of death, cardiovascular death and hospitalisation.(186) BNP has clear utility for the detection of heart failure in sinus rhythm patients but the recommendations for patients in AF are unclear, for AF itself increases BNP levels independently of BNP status.(187)

BNP is a cardiac hormone released from both ventricular and atrial myocytes in response to myocardial wall stress.(186) The BNP gene is located on chromosome 1 and is synthesised under pathological conditions. NTproBNP and BNP are synthesised in both atrial and ventricular myocytes (188) in response to mechanical stress (high intra-cardiac pressure or

increase in ventricular volume), hypoxia and neurohormonal factors. Myocardial wall stress activates mechanosensors, which in turn trigger the activation of the mitogen-activated protein kinase (MAPK) pathway, resulting in the production of the signalling protein p38 MAPK. Mechanical stretch also results in the production of angiotensinogen II and endothelin-1 complexes, that also activate p38 MAPK via the extracellular signal regulated kinase (Figure 30). p38 MAPK activates nuclear factor kappa B (NF-kB), which binds to shear stress responsive elements, which stimulate the BNP-gene promoter resulting in the transcription of the 134 amino acid pre-proBNP. When the N-terminal of pre-proBNP is removed, it forms the 108 amino acid proBNP. The convertase enzymes furin or corin then cleave the proBNP to form the inactive 76 amino acid NTproBNP and the active 32 amino acid BNP.(189) These compounds are then released into the surrounding plasma and bind to the natriuretic peptide receptor A, which increases the production of cyclic Guanyl cyclase (cGMP). cGMP stimulates diuresis, vasodilation, inhibition of the RAAS and increases cardiac and vascular myocyte growth. Therefore, it acts to reduce intra-cardiac pressures within the heart (left ventricular end-diastolic pressure) and hence reduce cardiac wall stress.(190)

Figure 30. Pathway to show the synthesis of BNP and NTproBNP (adapted from Cao Z. et al, 2019(189)) Abbreviations: BNP= brain naturetic peptide; cGMP cyclic guanylyl cyclase= NPR-A= natriuretic peptide receptor A; NTproBNP= N-terminal pro-brain naturetic peptide; ET-1= endothelin-1; ERK= extracellular signal regulated kinase MAPK= mitogen-activated protein kinase; NF-kB= nuclear factor kappa B; p38= protein 38; SSRE= shear stress responsive elements



It is known that the level of NTproBNP is elevated in patients with AF and is predominantly released from the atrial myocytes,(187) however the data correlating NTproBNP with systolic and diastolic parameters using echocardiography, in patients in AF at the time of the scan are limited. A single study was identified in the systematic review (**chapter 2**) that validated systolic function in AF patients, by comparing LVEF with BNP and showed a weak correlation.(139) There have been no studies comparing GLS with BNP/NTproBNP in which the patient was in AF at the time of the scan.

5.1.2 Physical Component Score (PCS)

Both AF and heart failure have a significant adverse impact on patient's quality of life. However the exact relationship between symptoms and cardiac function and blood biomarkers such as NTproBNP remains largely unknown.(191) The ALPHA study investigated the relationship between AF and functional status using the New York Heart Association (NYHA) score, which is a combined evaluation of dyspnoea, fatigue and palpitations. Even after adjusting for age, gender, LVEF and aetiology of heart failure, the study found a greater likelihood of symptoms in a higher NYHA class in patients with AF compared to those with sinus rhythm; OR 2.5 (95% C.I. 2.08-3.00, $p < 0.001$).(192)

The questionnaire SF-36 is used globally to assess health-related quality of life. It is composed of eight different scales measuring: physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role and mental health. From these eights sections, a physical component score (PCS) and mental component score can be calculated.(193) The items from each component are scored on a scale and then averaged together; the higher score represents a superior level of health.(194)

5.1.3 Atrial Fibrillation Effect on Quality of Life (AFEQT) questionnaire

The AFEQT questionnaire was specifically developed to assess the effect of AF on quality of life and has reasonable validation compared to other questionnaires.(195) It is divided into six domains around patient perception of symptom burden, social ability, physical functioning, emotional status, AF-specific treatment concerns and satisfaction. Answers are scored on a scale of 1-7, which are transformed to a 0-100 scale. The higher the score, the better the quality of life in relation to AF.(196)

5.2 Method

All patients recruited to the RATE-AF trial underwent baseline echocardiography to assess systolic and diastolic left ventricular function. As described in **chapter 4** the parameters LVEF by Simpson's biplane, global longitudinal strain and the diastolic index E/e' were measured using the average of three index beats and the average of three, five and ten consecutive beats.

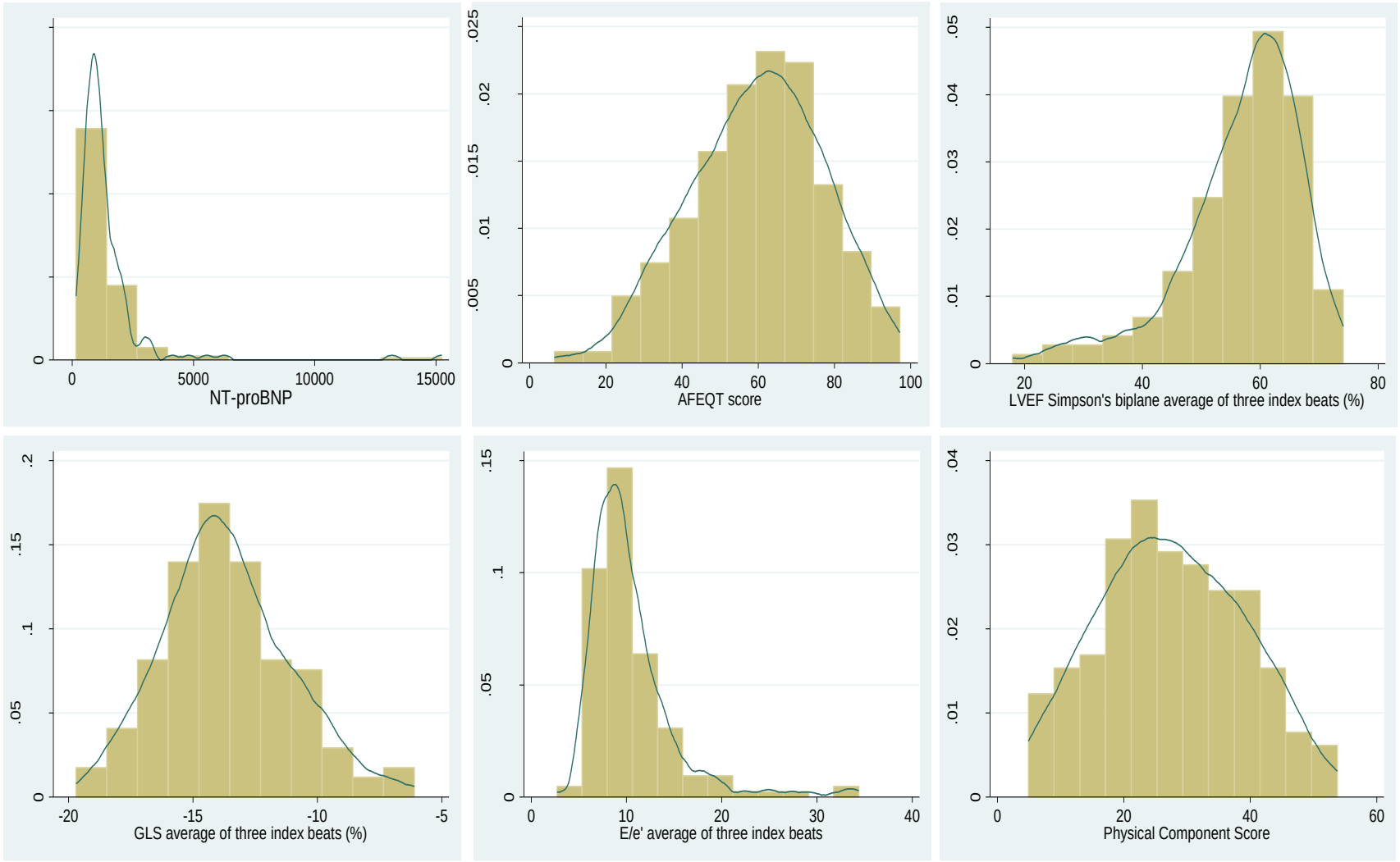
All patients had blood taken at baseline to measure NTproBNP level. NTproBNP was measured in the Queen Elizabeth Hospital's UKAS accredited clinical laboratory using the Abbott Alinity analyser following the manufacturer's standard operating procedure. To record patient reported quality of life, all patients answered the SF-36 quality of life questionnaire and AFEQT questionnaire at baseline. Questions in SF-36 related to physical functioning status were summed to form the physical component score (PCS) according to the method published by the SF-36 group.

5.2.1 Data synthesis and statistical analysis

Values of LVEF, GLS and E/e' derived from the average of three index beats, average of 3 , 5 and 10 consecutive beats were determined using previously described methods in **chapter 4**. Histograms with a kernel density line embedded were plotted to determine whether the

variables' data were normally distributed (**Figure 31**); NTproBNP, LVEF and E/e' were skewed so these parameters were transformed to the Log value of 2 (Log2).

Figure 31. K density plots of selected variables at baseline



Spearman's correlation coefficient was used to determine the association between the echocardiography values and NTproBNP, PCS and AFEQT score. To determine whether there was a significant difference in correlation coefficients with the independent variable, when using the average of three index beats, average of 3, 5 and 10 consecutive beats, the cross-correlation coefficient test was used (corcor). A 2-sided p-value of ≤ 0.05 was considered a significant difference in correlation coefficients.

Stepwise multiple linear regression was carried out for each dependent variable; for NTproBNP the co-variables age, gender, years in AF, heart rate, systolic blood pressure, weight, creatinine, history of myocardial infarction were used. For PCS and AFEQT score history of COPD/ emphysema and NTproBNP were also added to the model. These variables were chosen, as clinically they are known to have an effect on these outcomes. A p-value of 0.1 or less was used as a cut-off value to include independent variables into the multiple linear regression model. Variables that were retained in the step-wise model were used for multiple linear regression analysis with each echocardiography parameter. The Log2 of LVEF Simpson's biplane, GLS and Log2 of E/e' measured by the average of three index beats, average of 3, 5 and 10 consecutive beats were correlated using multiple linear regression with Log2 NTproBNP, PCS and AFEQT score. Beta coefficients with a p value ≤ 0.05 were considered statistically significant.

5.3 Results

160 patients underwent echocardiography with a median (IQR) NTproBNP of 1057 pg/ml (744-1522), PCS of 28 (19-36) and AFEQT score of 60 (48-71), see **Table 22**.

Table 22. Baseline patient demographics of variables used in the multiple linear regression models

Characteristic	n= 160
NTproBNP, median pg/mL (IQR)	1057 (744-1522)
PCS, median (IQR)	28 (19-36)
AFEQT score, median (IQR)	60 (48-71)
Heart rate, median bpm (IQR)	96 (86-112)
Systolic BP, median mmHg (IQR)	134 (123-148)
Age, median years (IQR)	75 (69-82)
Women, n (%)	74 (46.3%)
Years in AF, mean years (SD)	3.8 (6.2)
Previous myocardial infarction, n (%)	13 (8.1%)
COPD, n (%)	29 (18.1%)
Weight, median kg (IQR)	87 (70-101)
Creatinine median umol/l (IQR)	86 (73-101)
Left ventricular ejection fraction (average of three index beats), median % (IQR)	59 (52-64)
Left ventricular ejection fraction, (average of 3 beats) median % (IQR)	55 (50-60)
Left ventricular ejection fraction, (average of 5 beats) median % (IQR)	56 (50-60)
Left ventricular ejection fraction, (average of 10 beats) median % (IQR)	55 (49-59)
Global longitudinal strain, (average of three index beats) median % (IQR)	-13 (-11 to -15)
Global longitudinal strain, (average of 3 beats) median % (IQR)	-14 (-12 to -15)
Global longitudinal strain, (average of 5 beats) median % (IQR)	-13 (-11 to -15)
Global longitudinal strain, (average of 10 beats) median % (IQR)	-13 (-11 to -14)
Average E/e', (average of three index beats) median (IQR)	9.4 (7.8-11.7)
Average E/e', (average of 3 beats) median (IQR)	9.5 (7.7-11.8)
Average E/e', (average of 5 beats) median (IQR)	9.4 (7.7-12.0)
Average E/e', (average of 10 beats) median (IQR)	9.5 (8.0-12.3)

Abbreviations: AF= atrial fibrillation; AFEQT= Atrial Fibrillation Effect on Quality of Life; BP= blood pressure; COPD= chronic obstructive pulmonary disorder; IQR= inter-quartile range; kg= kilograms; NTproBNP= N-terminal pro-B-type naturetic peptide; PCS= physical component score; SD= standard deviation

5.3.1 The association between systolic and diastolic function on echocardiography with NTproBNP in AF patients measured using the index beat, average of 3, 5 and 10 averaged beats

LVEF Simpson's biplane was obtainable in 143 patients out of the baseline population of 160 patients; 17 patients were excluded due to insufficient image quality. Spearman's correlation showed a weak association between Log2 NTproBNP and Log2 LVEF measured by Simpson's biplane across all four measuring methods (average of three index beats, average of 3, 5 and 10 beats). There was no significant difference between the correlation coefficients, meaning that NTproBNP is weakly associated with LVEF regardless of which measuring method is used (**Table 23**).

Table 23. Spearman's rho to show the association between LVEF Simpson's biplane measured by the average of three index beats, average of 3, 5 and 10 beats with NTproBNP and the difference in correlation coefficient with NTproBNP between the average of three index beats and average of 3, 5 and 10 beats

LVEF Simpson's biplane measuring method	Spearman's rho (p value)	Difference in correlation from index beat method z (2-tailed p value)
Average of 3 index beats	-0.08 (p=0.32)	-
Average of 3 beats	-0.12 (p=0.17)	-0.34 (p=0.73)
Average of 5 beats	-0.12 (p=0.15)	-0.28 (p=0.78)
Average of 10 beats	-0.10 (p=0.25)	-0.20 (p=0.84)

Univariable linear regression analysis showed that for every unit increase in Log2 NTproBNP there was a reduction in the Log2 LVEF Simpson's biplane measured (**Table 24**), suggesting that a reduction in LVEF is associated with an increase in NTproBNP. However the r2 value from the univariable regression model was weak across all measuring methods (average of 3 index beats, average of 3, 5 and 10 consecutive beats) for quantifying LVEF, suggesting a weak association see **Table 24**.

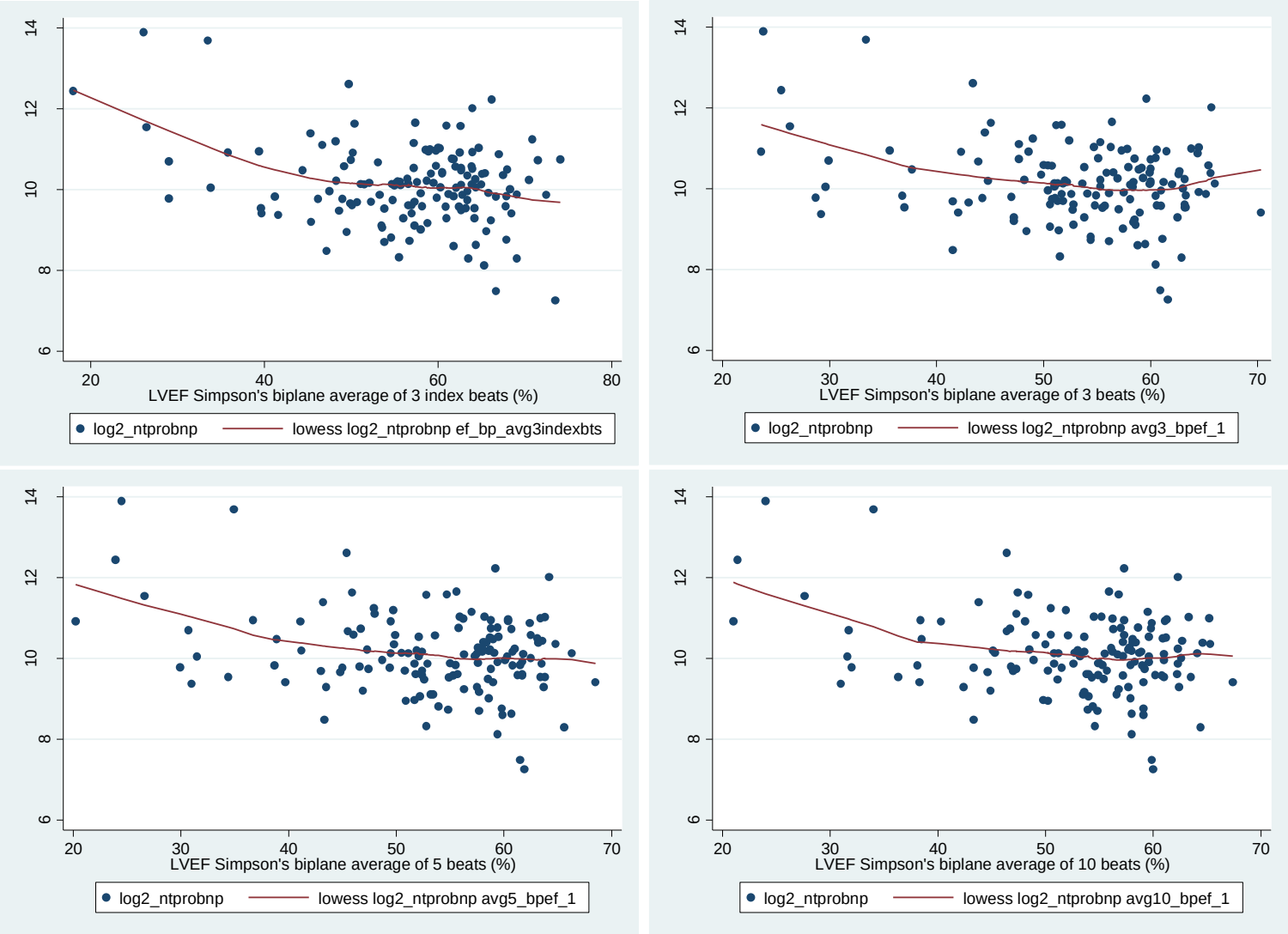
Multiple linear regression including the co-variables age, gender, years in AF, heart rate and creatinine was carried out. When adjusted for these co-variables a reduction in LVEF still predicted an increase in NTproBNP. An increase in NTproBNP was also significantly associated with an increase in age, creatinine level and female sex.

It was observed in **Figure 32** that data points of LVEF below 40%, the locally weighted smoothing line followed a negative correlation with increasing LVEF there is a reduction in NTproBNP. However above 40% the line flattens out and it was noted that the data points were widely clustered around the line, with some having a higher level of NTproBNP. Therefore suggesting that NTproBNP is less associated with LVEF in hearts with an LVEF above 40%.

Table 24. Univariable linear regression analysis and multiple linear regression analysis comparing Log2 NTproBNP with Log2 LVEF Simpson's biplane measured by the average of three index beats and average of 3, 5 and 10 beats (adjusted for age, years in AF, gender, heart rate and creatinine).

Measurement method of Log2 LVEF Simpson's biplane	Univariable linear regression		Multiple linear regression						
			(β coefficient)						
	β coefficient	R-squared	Log2 LVEF	Age (years) analysis	Years in AF (years)	Gender	Heart rate (bpm)	Creatinine (umol/l)	R-squared
Average of three index beats	-1.04 (p<0.001)	0.11 (p= <0.001)	-1.06 (p= <0.001)	0.04 (p=<0.001)	-0.02 (p=0.139)	0.36 (p=0.018)	0.01 (p=0.069)	0.02 (p=<0.001)	0.43 (p=<0.001)
Average of 3 beats	-1.01 (p<0.001)	0.10 (p=<0.001)	-1.08 (p=<0.001)	0.03 (p=<0.001)	-0.01 (p=0.552)	-0.46 (p=0.004)	0.00 (p=0.303)	0.02 (p=0.001)	0.41 (p=<0.001)
Average of 5 beats	-1.01 (p<0.001)	0.10 (p=<0.001)	-1.12 (p=<0.001)	0.03 (p=<0.001)	-0.01 (p=0.608)	-0.48 (p=0.003)	0.00 (p=0.345)	0.02 (p=<0.001)	0.42 (p=<0.001)
Average of 10 beats	-1.05 (p<0.001)	0.10 (p=>0.001)	-1.11 (p=<0.001)	0.03 (p=<0.001)	-0.01 (p=0.488)	-0.45 (p=0.004)	0.00 (p=0.355)	0.02 (p=<0.01)	0.42 (p=<0.001)

Figure 32. Scatter plots with a locally weighted smoothing line to show the association between LVEF Simpson's biplane measured by the average of three index beats, 3, 5 and 10 averaged beats with the Log2 NTproBNP



GLS was obtainable in 139 patients; 21 patients' images were excluded from the analysis due to insufficient image quality. Spearman's rho correlation showed a weak association between GLS and NTproBNP across all measuring methods. There was no significant difference between the correlation coefficients, meaning that NTproBNP is weakly associated with GLS regardless of which measuring method is used (**Table 25**).

Table 25. Spearman's rho to show the association between GLS measured by the average of three index beats, average of 3, 5 and 10 beats with NTproBNP and the difference in correlation coefficient with NTproBNP between the average of three index beats and average of 3, 5 and 10 beats

GLS measuring method	Spearman's rho (p value)	Difference in correlation from index beat method z (2-tailed p value)
Average of 3 index beats	0.06 (p=0.46)	-
Average of 3 beats	0.11 (p=0.21)	-0.04 (p=0.97)
Average of 5 beats	0.10 (p=0.22)	-0.31 (p=0.75)
Average of 10 beats	0.11 (p=0.21)	-0.03 (p=0.98)

Univariate analysis showed that for a unit increase in Log2 NTproBNP correlated with an increase in GLS and so reduction in contractility. However the r2 value was very weak, despite being statistically significant (**Table 26**).

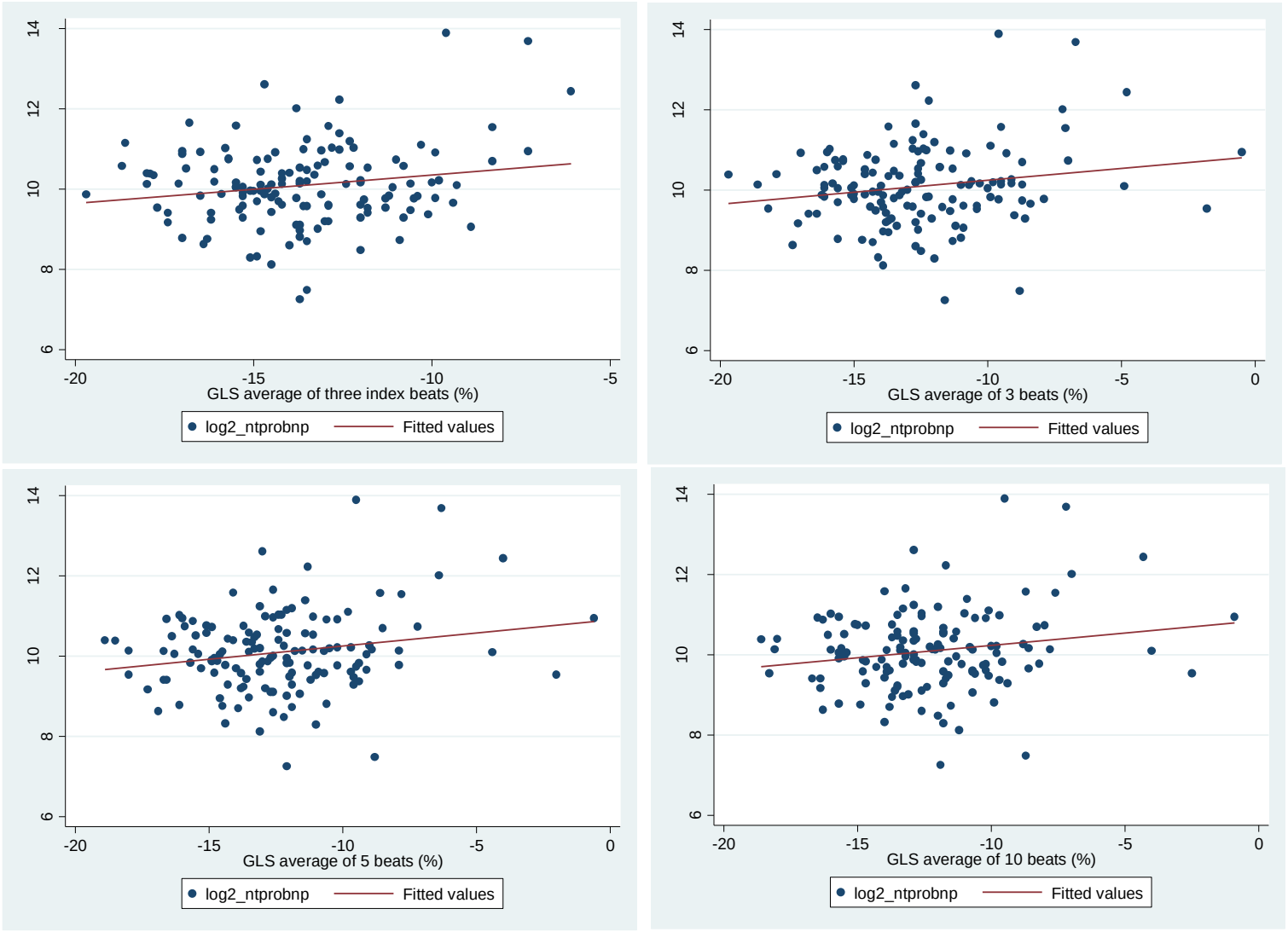
Multiple linear regression analysis showed a similar trend for GLS, with an increase in Log2 NTproBNP resulting in a significant increase in GLS. Age, gender and creatinine also had a significant beta coefficient with the Log2 of NTproBNP. A single unit increase in Log2 NTproBNP was associated with female gender, older age and increase in creatinine level (**Table 26**).

Figure 33 shows a weak association between GLS and NTproBNP. It was also noted that the majority of patients had a GLS below normal limits (-15.5% ±2.1).

Table 26. Univariable linear regression analysis and multiple linear regression analysis comparing Log2 NTproBNP with GLS measured by the average of three index beats and average of 3, 5 and 10 beats (adjusted for age, years in AF, gender, heart rate and creatinine).

Measurement method of GLS	Univariable linear regression		Multiple linear regression						
			(β coefficient)						
	β coefficient	R-squared	GLS (%)	Age (years)	Years in AF (years)	Gender	Heart rate (bpm)	Creatinine (umol/l)	R-squared
Average of three index beats	0.07 (p=0.033)	0.03 (p=0.033)	0.09 (p=0.004)	0.04 (p=<0.001)	-0.01 (p=0.344)	-0.39 (p=0.019)	0.01 (p=0.113)	0.02 (p=<0.001)	0.36 (p=<0.001)
Average of 3 beats	0.06 (p=0.031)	0.03 (p=0.031)	0.07 (p=0.006)	0.03 (p=<0.001)	-0.02 (p=0.23)	-0.38 (p=0.023)	0.01 (p=0.166)	0.02 (p=<0.001)	0.36 (p=<0.001)
Average of 5 beats	0.07 (p=0.020)	0.04 (p=0.020)	0.07 (p=0.006)	0.03 (p=<0.001)	-0.01 (p=0.253)	-0.37 (p=0.026)	0.01 (p=0.154)	0.02 (p=<0.001)	0.36 (p=<0.001)
Average of 10 beats	0.06 (p=0.034)	0.03 (p=0.034)	0.07 (p=0.007)	0.03 (p=<0.001)	-0.01 (p=0.255)	-0.38 (p=0.023)	0.01 (p=0.164)	0.02 (p=<0.001)	0.36 (p=<0.001)

Figure 33. Scatter plots with a line of best fit to show the association between GLS measured by the average of three index beats, 3, 5 and 10 averaged beats with the Log2 NTproBNP



E/e' was obtainable in all 160 patients. Spearman's correlation of E/e' and NTproBNP showed a moderate positively correlated association of statistical significance. There was no significant difference between the correlations derived from the average of three index beats and average of 3, 5 and 10 beats, meaning that NTproBNP is moderately associated with GLS regardless of which measuring method is used (**Table 27**).

Table 27. Spearman's rho to show the association between Log2 E/e' measured by the average of three index beats, average of 3, 5 and 10 beats with NTproBNP and the difference in correlation coefficient with NTproBNP between the average of three index beats and average of 3, 5 and 10 beats

E/e' measuring method	Spearman's rho (p value)	Difference in correlation from index beat method z (2-tailed p value)
Average of 3 index beats	0.40 (p=<0.001)	-
Average of 3 beats	0.41 (p=<0.001)	-1.08 (p=0.28)
Average of 5 beats	0.43 (p=<0.001)	-1.91 (p=0.06)
Average of 10 beats	0.43 (p=<0.001)	-1.02 (p=0.31)

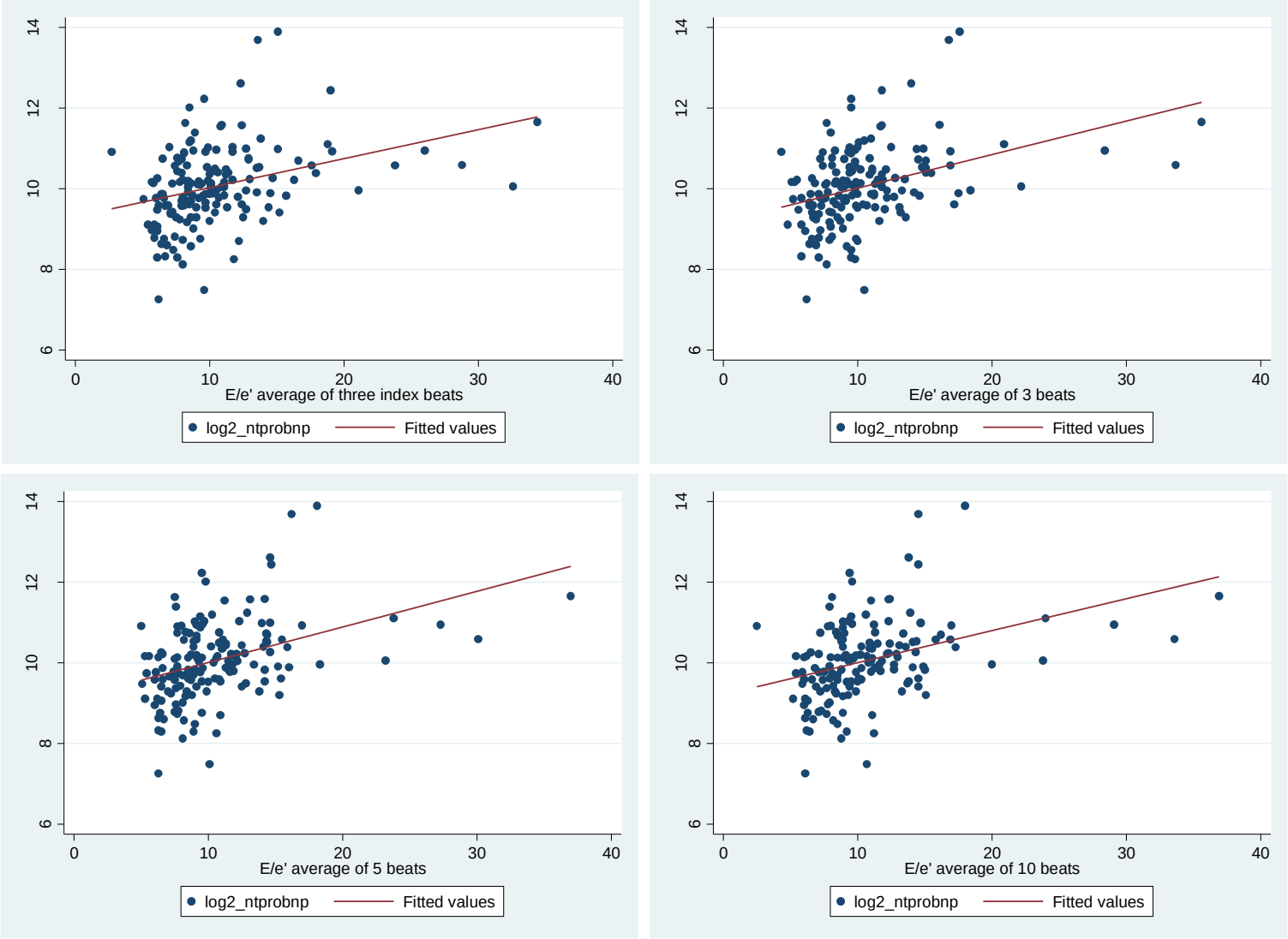
Univariate analysis showed that for every unit increase in Log2 NTproBNP, there was an increase in the Log2 E/e', suggesting that an increase in NTproBNP is associated with an increase in E/e'. Multiple linear regression analysis when adjusted for age, gender, years in AF, heart rate and creatinine showed again that with a unit increase in Log2 NTproBNP there was a significant increase in Log2 E/e'. An increase in Log2 NTproBNP was associated with a small but significant increase in age, heart rate and creatinine levels and also with female gender (**Table 28**).

Figure 34 shows a positive correlation between E/e' and Log2 NTproBNP; as E/e' increases Log2 NTproBNP increases.

Table 28. Univariable linear regression analysis and multiple linear regression analysis comparing Log2 NTproBNP with Log2 E/e' measured by the average of three index beats and average of 3, 5 and 10 beats (adjusted for age, years in AF, gender, heart rate and creatinine)

Measurement method of E/e'	Univariable linear regression		Multiple linear regression						
			(β coefficient)						
	β coefficient	R-squared	Log2 E/e'	Age (years)	Years in AF (years)	Gender	Heart rate (bpm)	Creatinine (umol/l)	R-squared
Average of three index beats	0.69 (p=<0.001)	0.13 (p=<0.001)	0.44 (p=0.001)	0.02 (p=0.005)	-0.02 (p=0.048)	-0.27 (p=0.064)	0.01 (p=0.014)	0.02 (p=<0.001)	0.38 (p=<0.001)
Average of 3 beats	0.79 (p=<0.0001)	0.16 (p=<0.001)	0.53 (p=<0.001)	0.02 (p=0.008)	-0.02 (p=0.059)	-0.29 (p=0.053)	0.01 (p=0.016)	0.02 (p=<0.001)	0.39 (p=<0.001)
Average of 5 beats	0.84 (p=<0.001)	0.18 (p=<0.001)	0.58 (p=<0.001)	0.02 (p=0.007)	-0.02 (p=0.046)	-0.27 (p=0.068)	0.01 (p=0.021)	0.02 (p=<0.001)	0.40 (p=<0.001)
Average of 10 beats	0.74 (p=<0.001)	0.15 (p=<0.001)	0.48 (p=<0.001)	0.02 (p=0.007)	-0.02 (p=0.046)	-0.26 (p=0.075)	0.01 (p=0.021)	0.02 (p=<0.001)	0.38 (p=<0.001)

Figure 34. Scatter plots with a line of best fit to show the association between E/e' measured by the average of three index beats, 3, 5 and 10 averaged beats with the Log2 NTproBNP



Information on baseline patient symptoms were collected using the SF-36 questionnaires (physical component score) and AFEQT questionnaire (AFEQT score). These parameters were compared with LVEF by Simpson's biplane, GLS and E/e' measured using the average of three index beats and average of 3, 5 and 10 consecutive beats.

5.3.2 The association between systolic and diastolic function on echocardiography with AFEQT score in AF patients measured using the index beat, average of 3, 5 and 10 averaged beats

Spearman's correlation coefficient showed a weak association between Log2 LVEF and AFEQT score suggesting LVEF and AFEQT are not associated. There was no significant difference in the correlations derived from the average of three index beats and average of 3, 5 and 10 beats, meaning that AFEQT score is weakly associated with LVEF regardless of which measuring method is used (**Table 29** and **Figure 35**).

Table 29. Spearman's rho to show the association between Log2 LVEF measured by the average of three index beats, average of 3, 5 and 10 beats with AFEQT score and the difference in correlation coefficient with AFEQT score between the average of three index beats and average of 3, 5 and 10 beats

LVEF measuring method	Spearman's rho (p value)	Difference in correlation from index beat method z (2-tailed p value)
Average of 3 index beats	-0.08 (p=0.34)	-
Average of 3 beats	-0.06 (p=0.48)	0.80 (p=0.42)
Average of 5 beats	-0.11 (p=0.18)	0.73 (p=0.47)
Average of 10 beats	-0.07 (p=0.44)	<-0.01 (p=1.00)

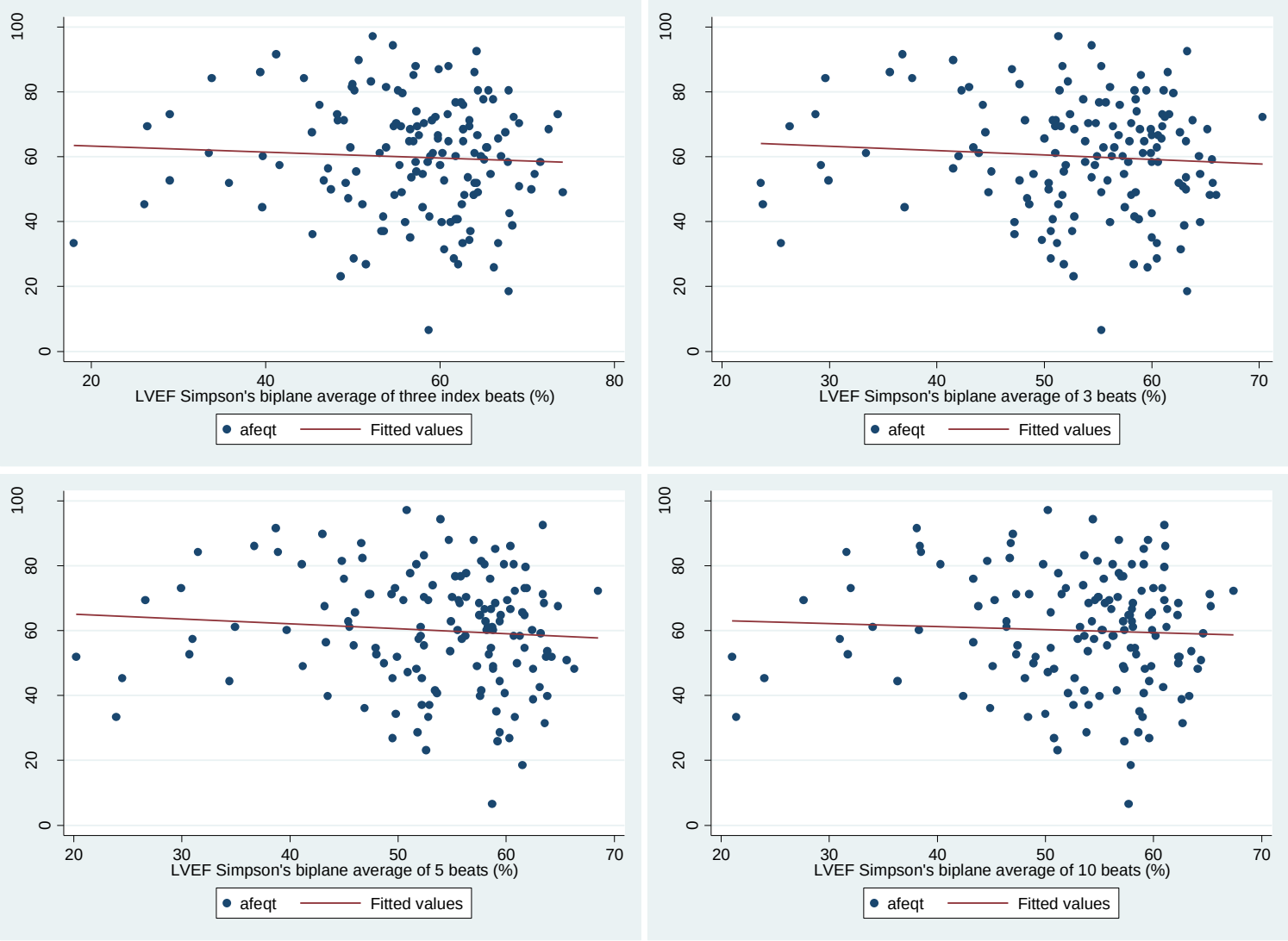
Stepwise multiple linear regression was initially performed with the parameters: history of COPD/emphysema, history of asthma, NTproBNP, age, years in AF, heart rate, systolic blood pressure, weight, gender, creatinine and history of myocardial infarction. The co-variables that were retained in the model (p values ≤0.10) were gender and creatinine.

Univariable regression of AFEQT score with the Log2 of LVEF showed that for every increase in a unit of Log2 LVEF there was a reduction in the AFEQT score (worsening symptoms), however this was statistically insignificant and the r2 values were very weak. Multiple linear regression for AFEQT score and Log2 LVEF (adjusted for gender and creatinine level) was again shown to have a statistically insignificant beta coefficient (**Table 30**). Therefore this data suggests that AFEQT score was not associated with LVEF measurement. However being of female gender was significantly associated with a lower AFEQT score. Therefore this is suggestive that AF has a greater impact on the quality of life of females compared to male patients. Also a lower creatinine level was associated with a higher AFEQT score, suggestive of AF having a greater impact on the quality of life in patients with impaired renal function (**Table 30**).

Table 30. Univariable linear regression analysis and multivariable linear regression analysis comparing AFEQT score with Log2 LVEF measured by the average of three index beats and average of 3, 5 and 10 beats (adjusted for gender and creatinine).

Measurement method of LVEF Simpson's biplane	Univariable linear regression		Multivariable linear regression			
			(β coefficient)			
	β coefficient	R-squared	Log2 LVEF	Gender	Creatinine (umol/l)	R-squared
Average of three index beats	-1.51 (p=0.752)	<0.01 (p=0.752)	-0.26 (p=0.956)	11.62 (p<0.001)	-0.12 (p=0.052)	0.10 (p=0.002)
Average of 3 beats	-3.39 (p=0.486)	<0.01 (p=0.486)	-0.63 (p=0.893)	11.87 (p<0.001)	-0.12 (p=0.058)	0.11 (p=0.002)
Average of 5 beats	-3.24 (p=0.503)	<0.01 (p=0.503)	-0.37 (p=0.936)	11.89 (p<0.001)	-0.12 (p=0.058)	0.11 (p=0.002)
Average of 10 beats	-1.56 (p=0.754)	<0.01 (p=0.754)	0.84 (p=0.860)	12.00 (p<0.001)	-0.12 (p=0.058)	0.11 (p=0.002)

Figure 35. Scatter plots with line of best fit to show the correlation between LVEF Simpson's biplane measured by the average of three index beats, 3, 5 and 10 averaged beats with AFEQT score



Spearman's correlation rho showed a weak correlation between GLS and AFEQT score which was not statistically significant across all measuring methods. There was no significant difference between the correlation derived from measuring GLS using the average of three index beats and average of 3, 5 and 10 beats, meaning that there is no association between GLS and AFEQT score regardless of which measuring method is used (**Table 31** and **F**igure **36**).

Table 31. Spearman's rho to show the association between GLS measured by the average of three index beats, average of 3, 5 and 10 beats with AFEQT score and the difference in correlation coefficient between the average of three index beats and average of 3, 5 and 10 beats

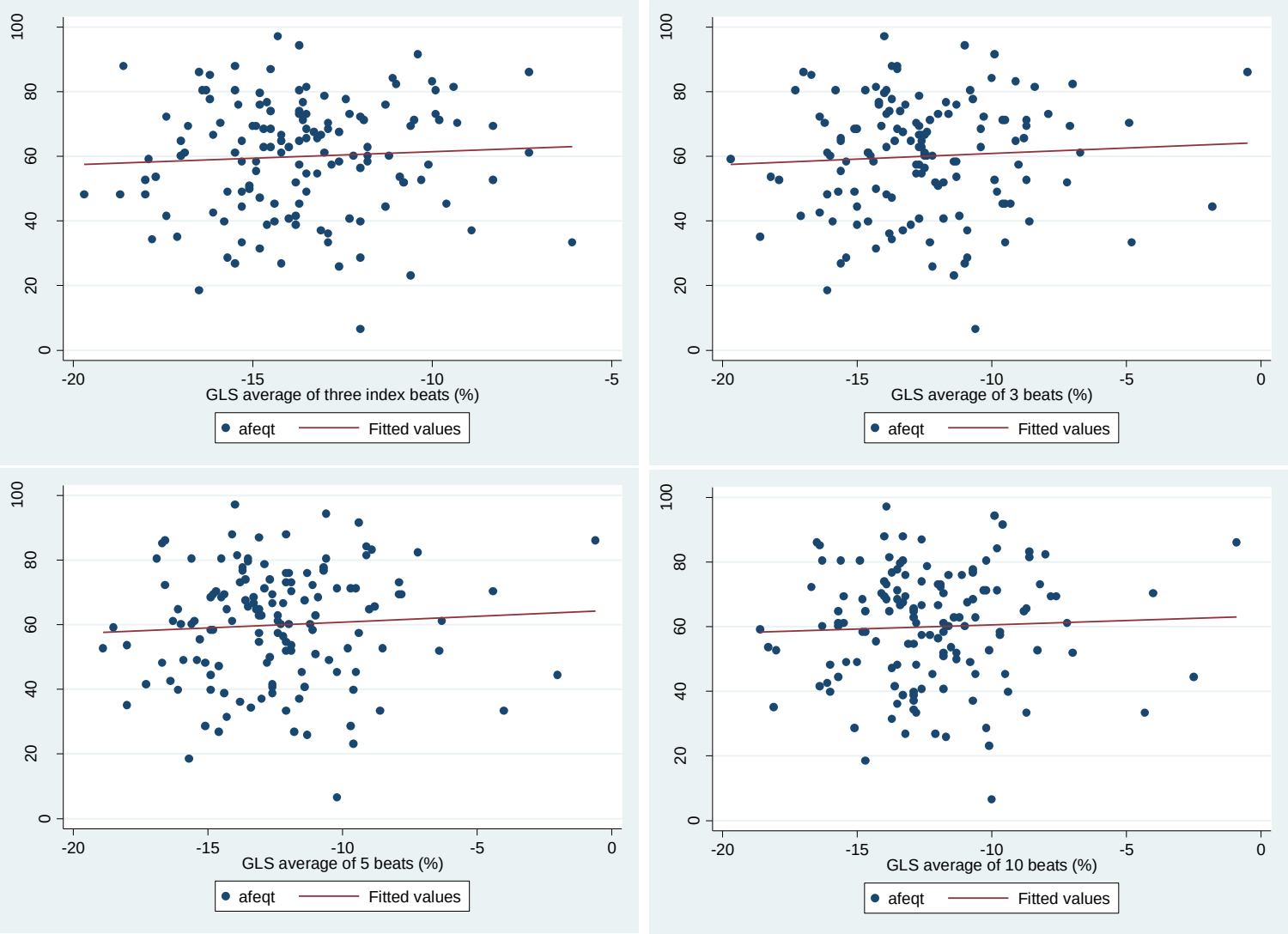
GLS measuring method	Spearman's rho (p value)	Difference in correlation from index beat method z (2-tailed p value)
Average of 3 index beats	0.07 (p=0.39)	-
Average of 3 beats	0.05 (p=0.54)	-0.04 (p=0.97)
Average of 5 beats	0.07 (p=0.40)	-0.07 (p=0.95)
Average of 10 beats	0.03 (p=0.72)	0.26 (p=0.79)

Univariate analysis comparing GLS with AFEQT showed a weak correlation, with every increase in a unit of AFEQT score associated with an increase in GLS (making it less negative) suggesting a reduction in contraction. However the beta coefficient for this observed increase was not statistically significant across all measuring methods of obtaining GLS (**Table 32**). Multiple linear regression analysis again demonstrated a small positive beta coefficient for GLS, suggesting that increasing AFEQT score is associated with an increase in GLS, however this was non-significant across all measuring methods. The only statistically significant beta coefficient from the model was gender suggesting that being male was associated with an increase in the AFEQT score (**Table 32**). This suggests again suggests that quality of life related to AF is more reduced in female patients.

Table 32. Univariable linear regression analysis and multivariable linear regression analysis comparing AFEQT score with GLS measured by the average of three index beats and average of 3, 5 and 10 beats (adjusted for gender and creatinine).

Measurement method of GLS	Univariable linear regression		Multivariable linear regression			
			(β coefficient)			
	β coefficient	R-squared	GLS	Gender	Creatinine (umol/l)	R-squared
Average of three index beats	0.40 (p=0.497)	<0.01 (p=0.497)	0.08 (p=0.889)	12.40 (p<0.001)	-0.12 (p=0.057)	0.11 (p=0.001)
Average of 3 beats	0.34 (p=0.482)	<0.01 (p=0.482)	0.16 (p=0.726)	12.37 (p<0.001)	-0.11 (p=0.061)	0.12 (p=0.001)
Average of 5 beats	0.36 (p=0.471)	<0.01 (p=0.471)	0.21 (p=0.652)	12.37 (p<0.001)	-0.11 (p=0.060)	0.12 (p=0.001)
Average of 10 beats	0.26 (p=0.607)	<0.01 (p=0.607)	0.06 (p=0.895)	12.43 (p<0.001)	0.12 (p=0.059)	0.11 (p=0.001)

Figure 36. Scatter plots with line of best fit to show the correlation between GLS measured by the average of three index beats, 3, 5 and 10 averaged beats with AFEQT score



Spearman's correlation coefficient showed a very weak association between Log2 E/e' and AFEQT score of no statistical significance. There was also no significant difference between the correlation derived from measuring E/e' using the average of three index beats and average of 3, 5 and 10 beats, meaning that there is no association between E/e' and AFEQT score regardless of which measuring method is used (**Table 33** and **Figure 37**)

Table 33. Spearman's rho to show the association between Log2 E/e' measured by the average of three index beats, average of 3, 5 and 10 beats with AFEQT score and the difference in correlation coefficient between the average of three index beats and average of 3, 5 and 10 beats

E/e' measuring method	Spearman's rho (p value)	Difference in correlation from index beat method z (2-tailed p value)
Average of 3 index beats	-0.02 (p=0.81)	-
Average of 3 beats	-0.02 (p=0.76)	-0.77 (p=0.44)
Average of 5 beats	-0.04 (p=0.58)	-0.26 (p=0.79)
Average of 10 beats	-0.01 (p=0.87)	-0.26 (p=0.79)

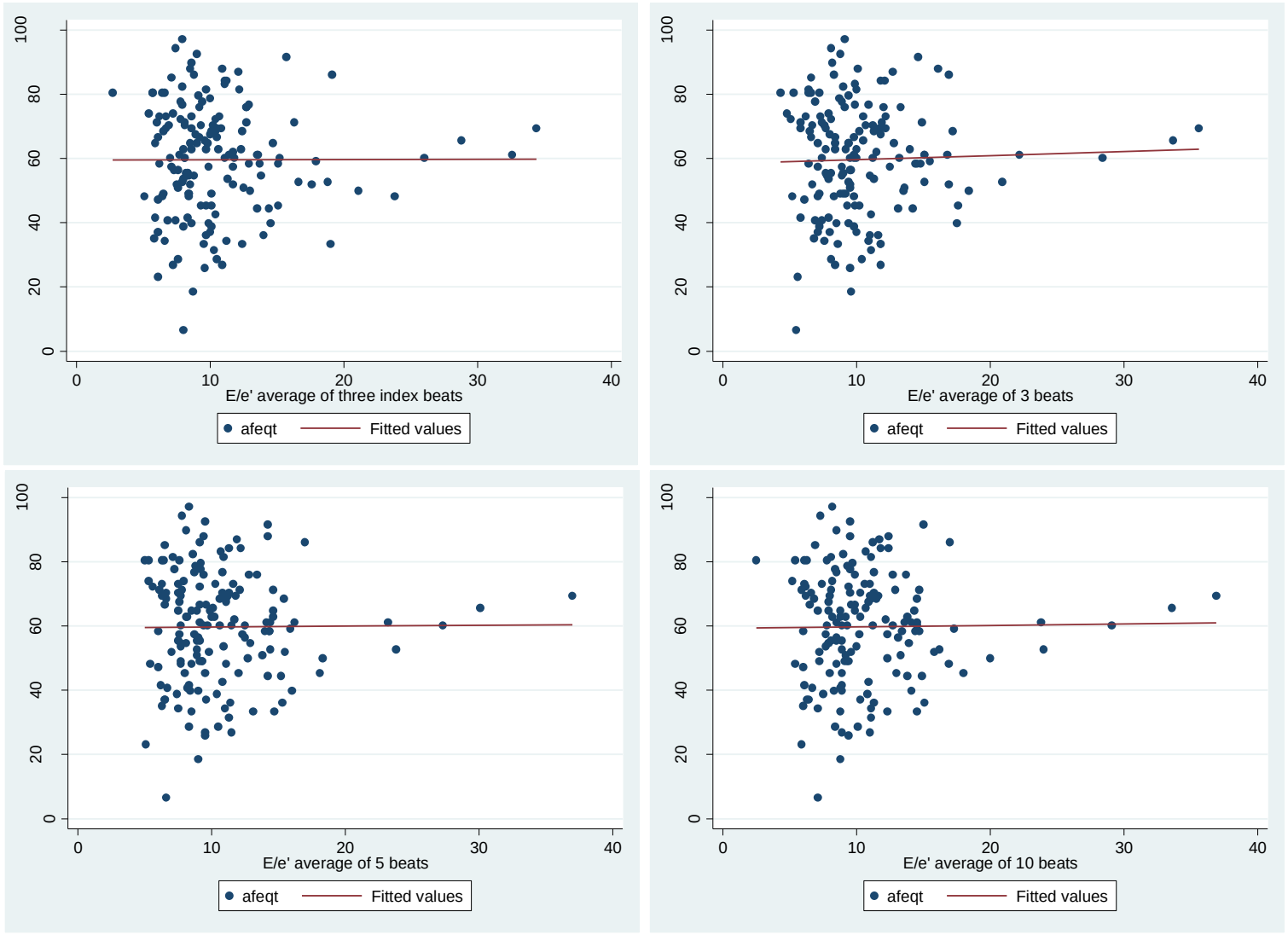
Univariate analysis of AFEQT score with Log2 E/e' showed a very weak correlation of no statistical significance. The beta coefficient demonstrated that an increase in AFEQT score is associated with a reduction in Log2 E/e' with the exception of parameters measured by the average of 3 beats in which it showed an increase in Log2 E/e'; despite these variations beta coefficient all were shown to be statistically insignificant (**Table 34**).

Multiple linear regression showed a non-significant association between an increase in AFEQT score and an increase in Log2 E/e'. As seen previously the only variable which was significantly associated with an increase in AFEQT score was gender; being male was associated with a higher AFEQT score (**Table 34**).

Table 34. Univariable linear regression analysis and multivariable linear regression analysis comparing AFEQT score with Log2 E/e' measured by the average of three index beats and average of 3, 5 and 10 beats (adjusted for gender and creatinine).

Measurement method of E/e'	Univariable linear regression		Multivariable linear regression			
			(β coefficient)			
	β coefficient	R-squared	Log2 E/e'	Gender	Creatinine (umol/l)	R-squared
Average of three index beats	-0.42 (p=0.871)	<0.01 (p=0.871)	1.63 (p=0.524)	11.42(p<0.001)	-0.10 (p=0.079)	0.10 (p=0.001)
Average of 3 beats	0.54 (p=0.843)	<0.01 (p=0.843)	2.41 (p=0.368)	11.64(p<0.001)	-0.11 (p=0.063)	0.10 (p=0.001)
Average of 5 beats	-0.15 (p=0.958)	<0.01 (p=0.958)	2.14 (p=0.435)	1.68 (p<0.001)	-0.11 (p=0.066)	0.10 (p=0.001)
Average of 10 beats	-0.21 (p=0.939)	<0.01 (p=0.939)	2.14 (p=0.414)	11.65(p<0.001)	-0.11 (p=0.065)	0.10 (p=0.001)

Figure 37. Scatter plots with line of best fit to show the correlation between E/e' measured by the average of three index beats, 3, 5 and 10 averaged beats with AFEQT score



5.3.3 The association between systolic and diastolic function on echocardiography with physical component score (PCS) in AF patients measured using the index beat, average of 3, 5 and 10 averaged beats

Spearman's correlation showed a weak statistically insignificant association between PCS and Log2 LVEF. There was no significant difference in the correlation between LVEF derived from the average of three index beats and LVEF derived from the average of 3, 5 and 10 beats, meaning that the association is weak regardless of what measuring method is used (**Table 35** and **Figure 38**).

Table 35. Spearman's rho to show the association between Log2 LVEF measured by the average of three index beats, average of 3, 5 and 10 beats with PCS and the difference in correlation coefficient between the average of three index beats and average of 3, 5 and 10 beats

LVEF measuring method	Spearman's rho (p value)	Difference in correlation from index beat method z (2-tailed p value)
Average of 3 index beats	-0.13 (p=0.14)	-
Average of 3 beats	-0.07 (p=0.39)	-0.31 (p=0.75)
Average of 5 beats	-0.12 (p=0.15)	0.02 (p=0.98)
Average of 10 beats	-0.11 (p=0.18)	-0.30 (p=0.76)

Stepwise linear regression was carried out including the physical component score (PCS) and the co-variables age, gender, years in AF, heart rate, systolic blood pressure, weight, creatinine, history of a myocardial infarction, NTproBNP and history of COPD/ emphysema. The variables age, gender, COPD/emphysema and weight were retained in the model (p=<0.1).

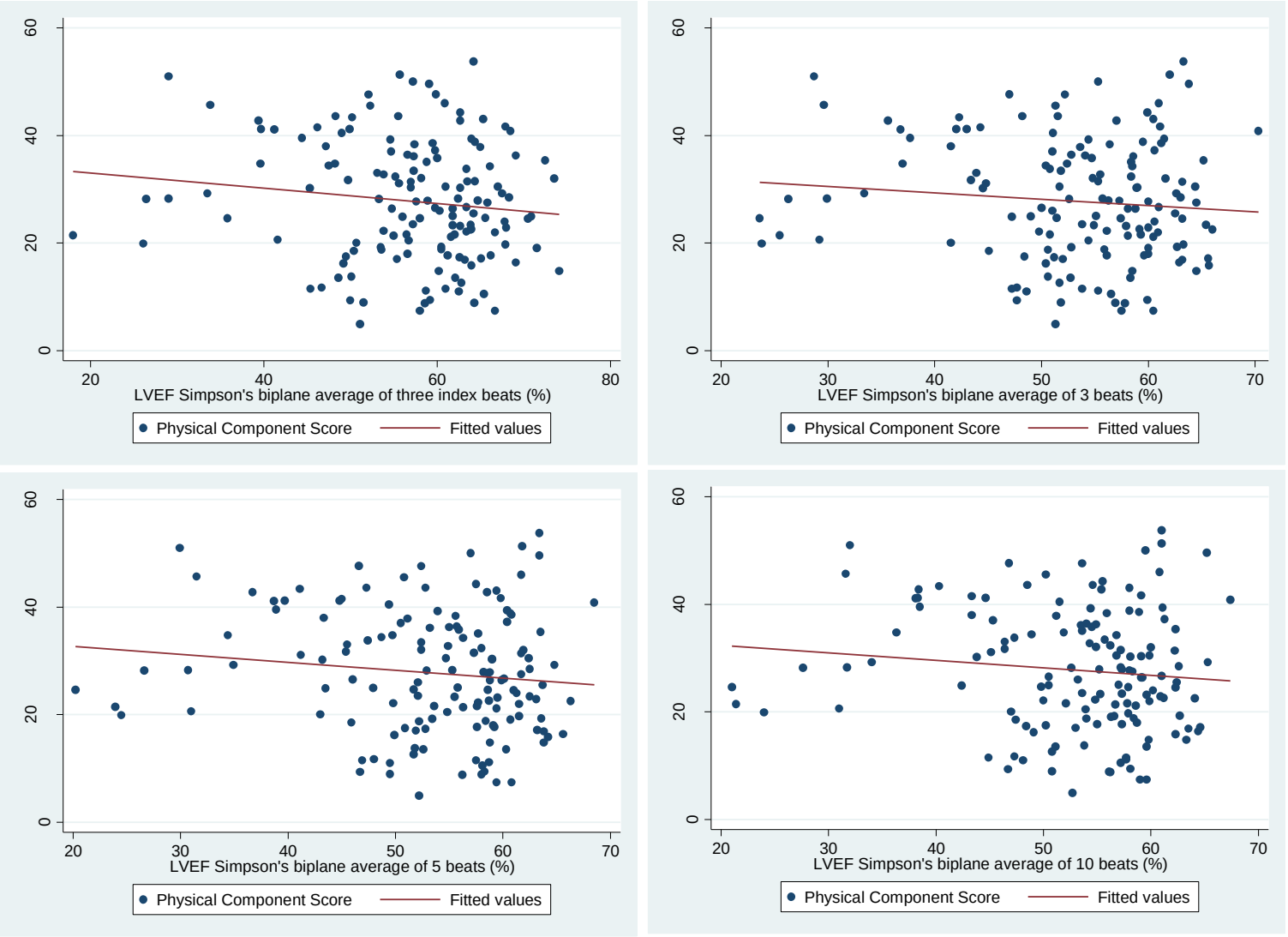
Univariate analysis suggested that for a unit increase in PCS there was a reduction in LVEF but this was shown to be statistically insignificant and the r2 was weak. Multiple linear regression showed that for a unit increase in PCS there is a reduction in LVEF Simpson's

biplane, however this was not statistically significant. Similarly to AFEQT the only significant beta coefficient was gender; being male was associated with a higher PCS (**Table 36**). Therefore suggesting that quality of life in relation to physical health status was better in male AF patients.

Table 36. Univariable linear regression analysis and multivariable linear regression analysis comparing PCS with Log2 LVEF measured by the average of three index beats and average of 3, 5 and 10 beats (adjusted for age, gender, COPD/emphysema and weight).

Measurement method of LVEF Simpson's biplane	Univariable linear regression		Multivariable linear regression					
			(β coefficient)					
	β coefficient	R-squared	Log2 LVEF	Age (years)	gender	COPD/ emphysema	Weight (kg)	R-squared
Average of three index beats	-4.09 (p=0.177)	0.01 (p=0.177)	-2.50 (p=0.396)	-0.19 (p=0.118)	6.43 (p=0.001)	-3.99 (p=0.103)	-0.06 (p=0.189)	0.12 (p=0.003)
Average of 3 beats	-3.71 (p=0.232)	0.01 (p=0.232)	-1.54 (p=0.612)	-0.20 (p=0.102)	6.40 (p=0.001)	-3.99 (p=0.108)	-0.06 (p=0.187)	0.12 (p=0.005)
Average of 5 beats	-4.19 (p=0.175)	0.01 (p=0.175)	-1.94 (p=0.522)	-0.20 (p=0.107)	6.36 (p=0.002)	-3.97 (p=0.110)	-0.06 (p=0.187)	0.12 (p=0.005)
Average of 10 beats	-3.79 (p=0.231)	0.01 (p=0.231)	-1.92 (p=0.533)	-0.20 (p=0.103)	6.41 (p=0.001)	-3.97 (p=0.110)	-0.06 (p=0.184)	0.12 (p=0.005)

Figure 38. Scatter plots with line of best fit to show the correlation between LVEF Simpson's biplane measured by the average of three index beats, 3, 5 and 10 averaged beats with Physical Component Score



Spearman's correlation coefficient showed a weak statistically insignificant association between GLS and PCS. There was no significant difference in the correlation between GLS derived from the average of three index beats and GLS derived from the average of 3, 5 and 10 beats, meaning that the association is weak regardless of what measuring method is used (**Table 37**).

Table 37. Spearman's rho to show the association between GLS measured by the average of three index beats, average of 3, 5 and 10 beats with PCS and the difference in correlation coefficient between the average of three index beats and average of 3, 5 and 10 beats

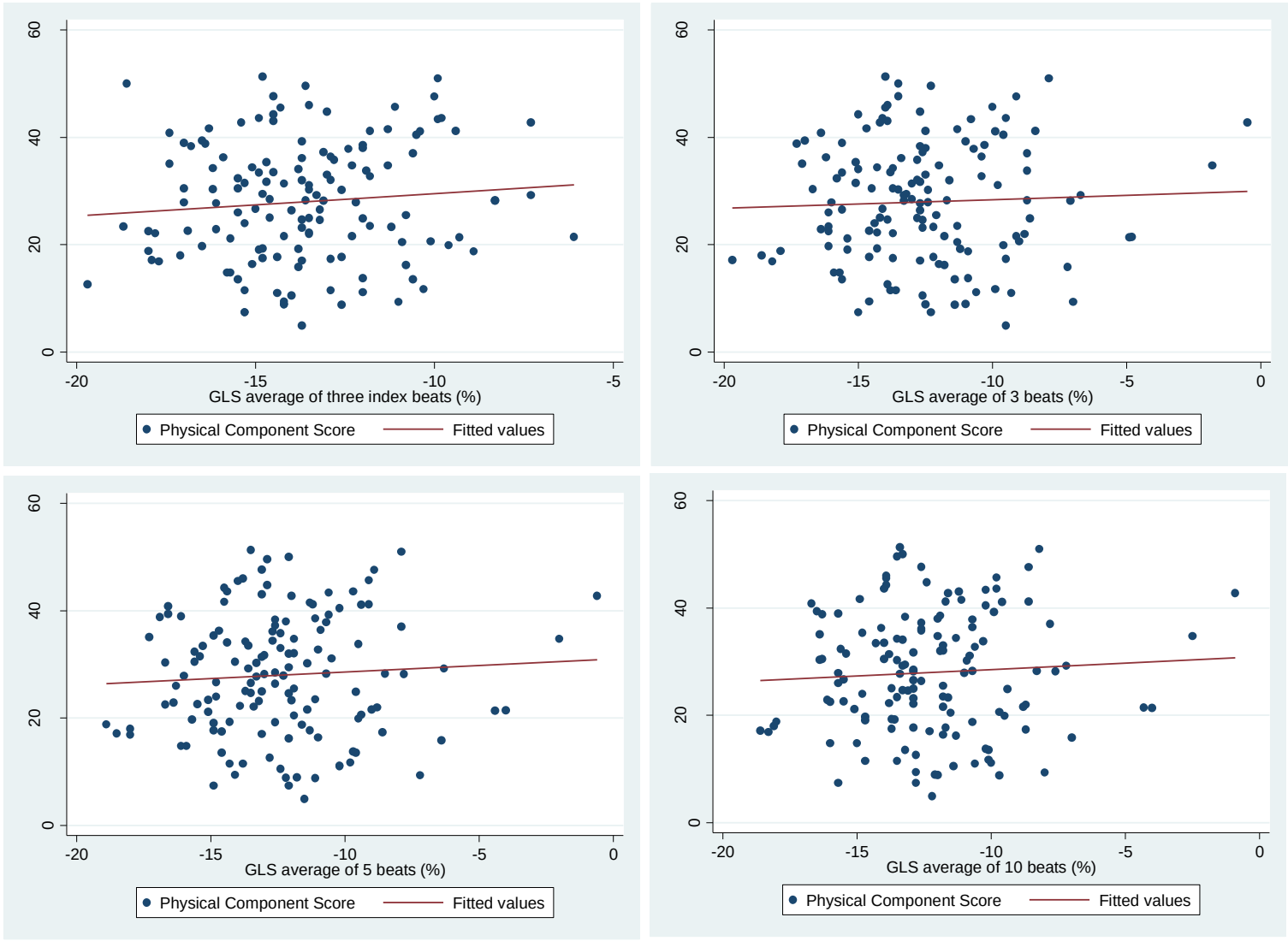
GLS measuring method	Spearman's rho (p value)	Difference in correlation from index beat method z (2-tailed p value)
Average of 3 index beats	0.09 (p=0.28)	-
Average of 3 beats	0.005 (p=0.96)	0.93 (p=0.35)
Average of 5 beats	0.04 (p=0.61)	0.53 (p=0.60)
Average of 10 beats	0.02 (p=0.82)	0.60 (p=0.55)

Univariate analysis of GLS and PCS demonstrated a weak association of no statistical significance. Multiple linear regression again showed a non-significant relationship between PCS and GLS. The co-variable age showed a significant beta coefficient suggesting that for a unit increase in PCS there is reduction in age, so younger people have a better physical health status. Weight was also shown to be significantly associated with PCS; with a reduction in weight associated with a higher physical health status. Finally similar to the AFEQT score, male gender was associated with a statistically significant increase in PCS (**Table 38**).

Table 38. Univariable linear regression analysis and multivariable linear regression analysis comparing PCS with GLS measured by the average of three index beats and average of 3, 5 and 10 beats (adjusted for age, gender, COPD/emphysema and weight).

Measurement method of GLS	Univariable linear regression		Multivariable linear regression					
			(β coefficient)					
	β coefficient	R-squared	GLS	Age (years)	gender	COPD/ emphysema	Weight (kg)	R-squared
Average of three index beats	0.42 (p=0.269)	0.01 (p=0.269)	0.11 (p=0.761)	-0.38 (p=0.003)	7.15 (p<0.001)	-3.19 (p=0.179)	-0.13 (p=0.010)	0.16 (p<0.001)
Average of 3 beats	0.16 (p=0.607)	<0.01 (p=0.607)	0.07 (p=0.809)	-0.38 (p=0.003)	7.20 (p<0.001)	-3.16 (p=0.184)	-0.13 (p=0.010)	0.16 (p<0.001)
Average of 5 beats	0.24 (p=0.441)	<0.01 (p=0.441)	0.18 (p=0.554)	-0.38 (p=0.03)	7.20 (p<0.001)	-3.15 (p=0.184)	-0.13 (p=0.009)	0.17 (p<0.001)
Average of 10 beats	0.24 (p=0.467)	<0.01 (p=0.467)	0.15 (p=0.638)	-0.38 (p=0.003)	7.19 (p<0.001)	-3.18 (p=0.180)	-0.13 (p=0.009)	0.16 (p<0.001)

Figure 39. Scatter plots with line of best fit to show the correlation between GLS measured by the average of three index beats, 3, 5 and 10 averaged beats with PCS



Spearman's correlation coefficient showed a very weak statistically insignificant association between Log2 E/e' and PCS. There was no significant difference in the correlation between E/e' derived from the average of three index beats and E/e' derived from the average of 3, 5 and 10 beats with PCS, meaning that the association is weak regardless of what measuring method is used (**Table 39**)

Table 39. Spearman's rho to show the association between Log2 E/e' measured by the average of three index beats, average of 3, 5 and 10 beats with PCS and the difference in correlation coefficient between the average of three index beats and average of 3, 5 and 10 beats

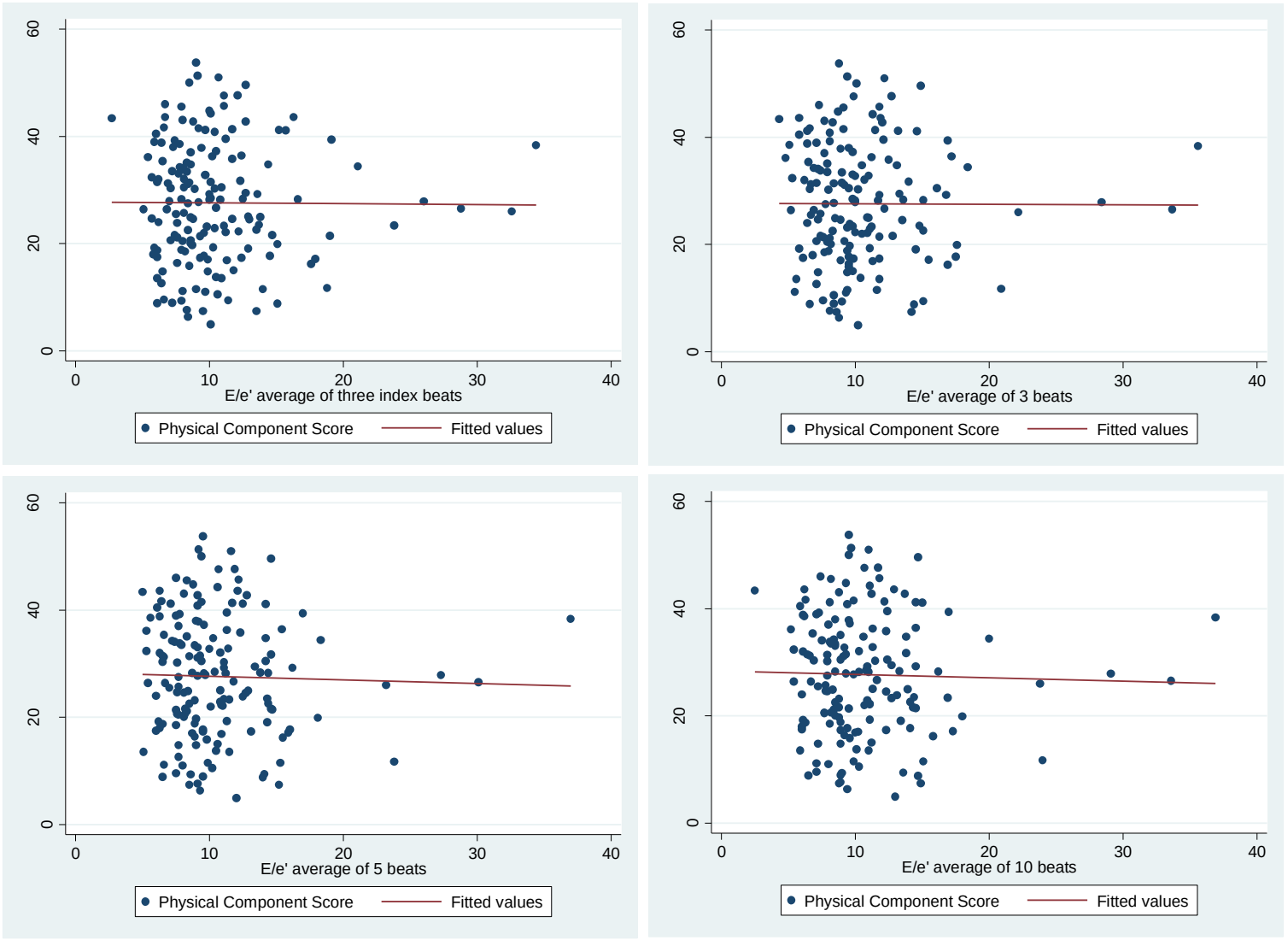
E/e' measuring method	Spearman's rho (p value)	Difference in correlation from index beat method z (2-tailed p value)
Average of 3 index beats	-0.02 (p=0.80)	-
Average of 3 beats	-0.02 (p=0.80)	-0.03 (p=0.97)
Average of 5 beats	-0.04 (p=0.61)	0.47 (p=0.64)
Average of 10 beats	-0.03 (p=0.67)	1.04 (p=0.30)

Univariate analysis of Log2 E/e' and PCS suggested that for a unit increase in PCS there is a reduction in Log2 E/e' however this was not significant and the r2 value was very weak. Multiple linear regression analysis again showed no significant association between Log2 E/e' and PCS. However from the model age was significantly associated with PCS, with a younger age associated with a higher physical health status. The presence of COPD/ emphysema was also associated with a reduction in physical health status. As seen before being of male gender and a lower weight was associated with a higher physical health status (**Table 40**).

Table 40. Univariable linear regression analysis and multivariable linear regression analysis comparing PCS with Log2 E/e' measured by the average of three index beats and average of 3, 5 and 10 beats (adjusted for age, gender, COPD/emphysema and weight).

Measurement method of E/e'	Univariable linear regression		Multivariable linear regression					
			(β coefficient)					
	β coefficient	R-squared	Log2 E/e'	Age (years)	gender	COPD/ emphysema	Weight (kg)	R-squared
Average of three index beats	-0.57 (p=0.738)	<0.01 (p=0.738)	1.80 (p=0.303)	-0.30 (p=0.018)	6.22 (p=0.001)	-4.78 (p=0.035)	-0.09 (p=0.041)	0.12 (p=0.002)
Average of 3 beats	-0.57 (p=0.751)	<0.01 (p=0.751)	1.28 (p=0.479)	-0.28 (p=0.026)	6.15 (p=0.001)	-4.63 (p=0.041)	-0.09 (p=0.043)	0.11 (p=0.002)
Average of 5 beats	-0.96 (p=0.597)	<0.01 (p=0.597)	1.35 (p=0.467)	-0.28 (p=0.026)	6.22 (p=0.001)	-4.70 (p=0.039)	-0.09 (p=0.041)	0.11 (p=0.002)
Average of 10 beats	-1.15 (p=0.508)	<0.01 (p=0.508)	1.35 (p=0.449)	-0.28 (p=0.025)	6.17 (p=0.001)	-4.82 (p=0.035)	-0.09 (p=0.031)	0.11 (p=0.002)

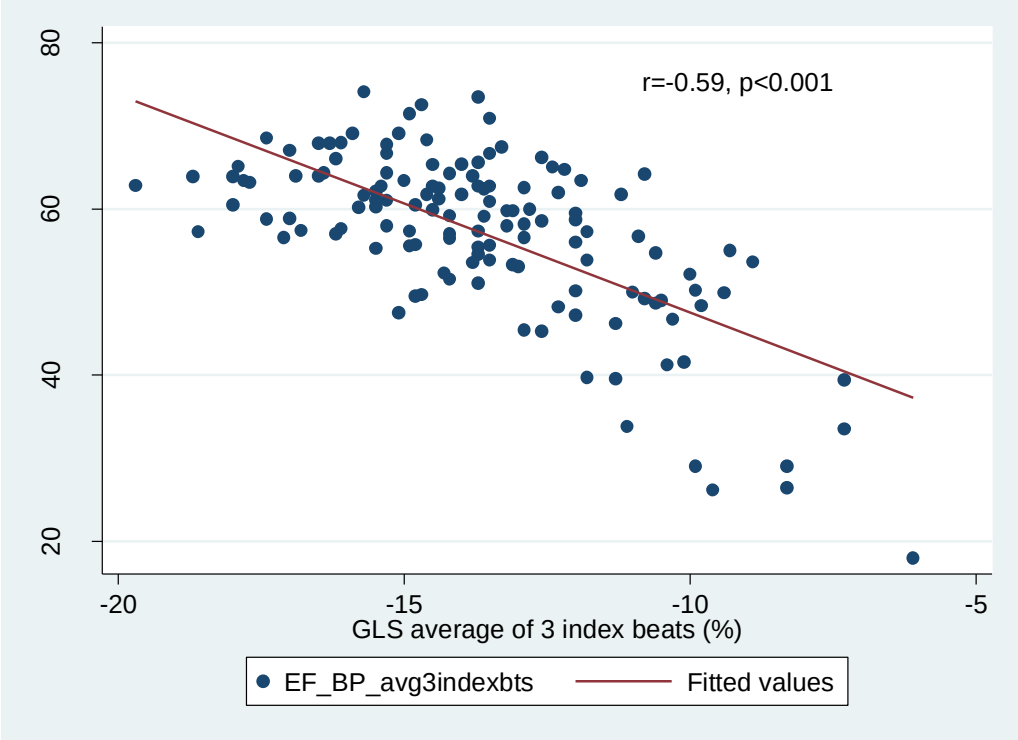
Figure 40. Scatter plots with line of best fit to show the correlation between E/e' measured by the average of three index beats, 3, 5 and 10 averaged beats with PCS



5.3.4 Comparisons between systolic and diastolic measurements

There was a negative moderate correlation between GLS and LVEF; as LVEF reduced GLS became less negative, r= -0.59, p<0.001. It was also noted that two thirds of the patients had a normal LVEF (≥55%) however out of these patients, 43% of them had a reduced GLS (below 15.5% ±2.1) (**Figure 41**).

Figure 41. Scatter plot with line of best fit to show correlation between GLS and LVEF Simpson's biplane measured by the average of three index beats with Spearman's correlation displayed



There was no significant correlation between LVEF and E/e', r=-0.14, p=0.103. However it was noted that there were some patients with a normal LVEF and a high E/e' (**Figure 42**). There was also no significant correlation between GLS and E/e', r= 0.07, p=0.416 (**Figure 43**).

Figure 42. Scatter plot with line of best fit to show correlation between LVEF Simpson's biplane and E/e' measured by the average of three index beats with Spearman's correlation displayed

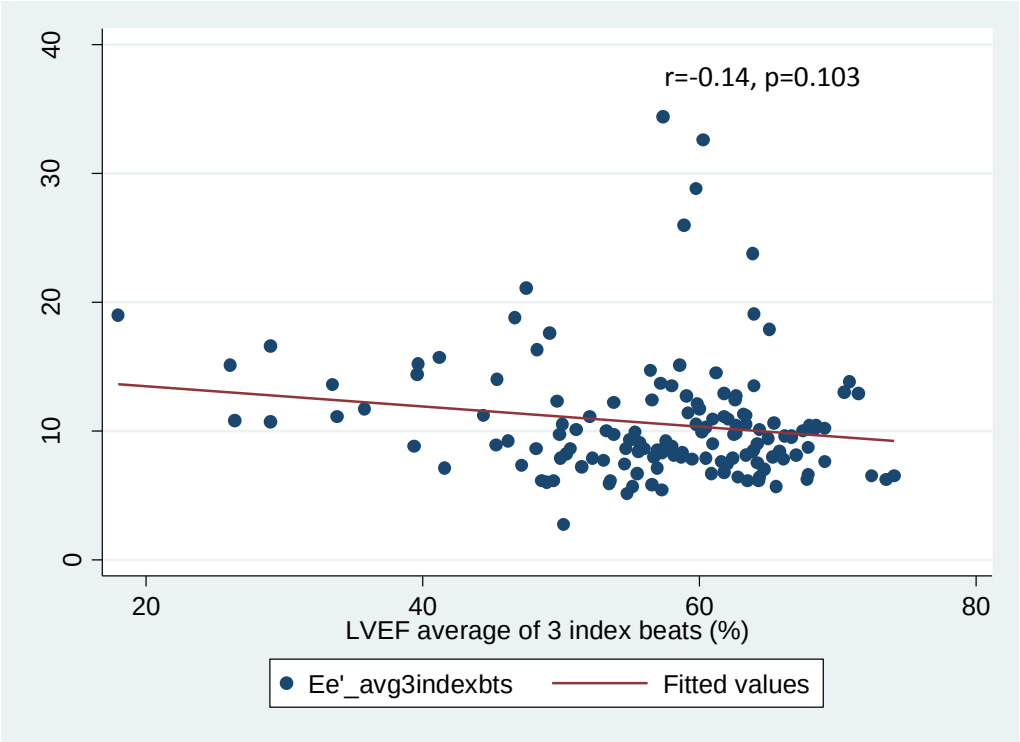
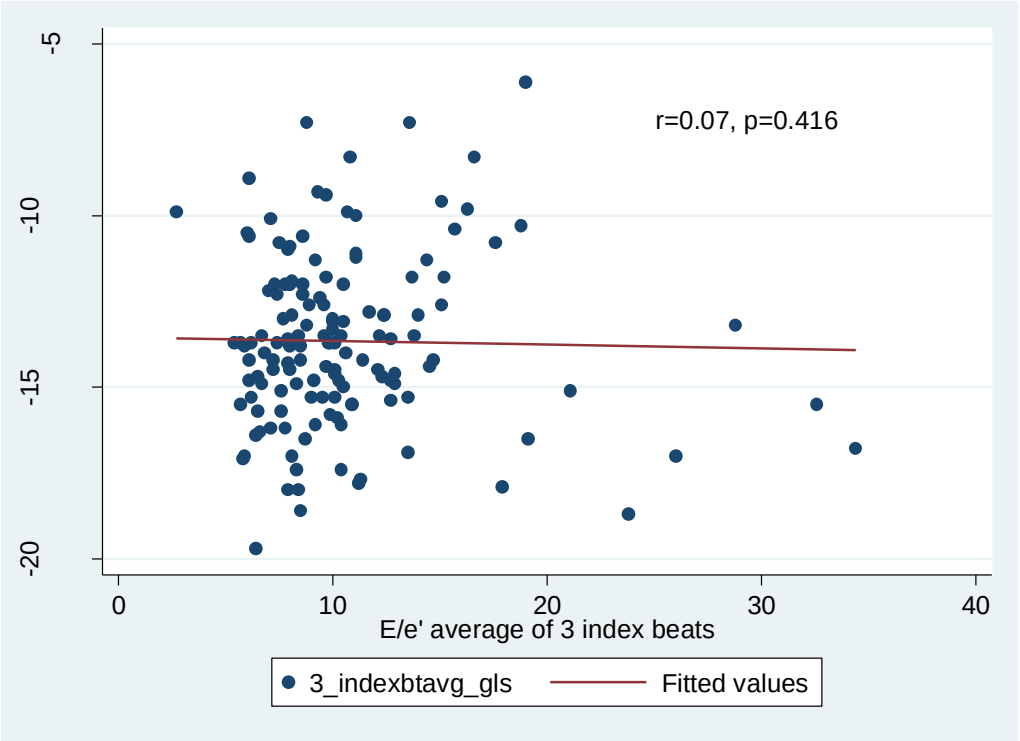


Figure 43. Scatter plot with line of best fit to show correlation between LVEF Simpson's biplane and E/e' measured by the average of three index beats with Spearman's correlation displayed



5.4 Discussion

This study on validity demonstrated that elevated NTproBNP was most strongly correlated with the diastolic parameter E/e' with a positive moderate in strength correlation . LVEF Simpson's biplane and GLS were both shown to be weakly associated with NTproBNP. LVEF, GLS and E/e' all correlated poorly with patient reported quality of life, as measured by the PCS and AFEQT score. There was also no significant difference in the correlations with predicted NTproBNP, PCS and AFEQT score when comparing correlations with echocardiographic measurements made using the average of three index beats and average of 3, 5 and 10 consecutive beats. This means that any measurement method can be used and there will be no difference in clinical outcome.

The data on the validity of systolic parameters in patients with AF are very limited. From **chapter 4** the index beat method was found to be more reproducible or equally reproducible to averaging 10 consecutive beats, but its validity in clinical practice remained uncertain. This study is the first time validity of the index beat method has been directly compared with a biomarker or symptom burden of patients with AF.

NTproBNP is released from cardiac myocytes in response to myocardial wall stress and increased ventricular filling pressures.(197) It is known that NTproBNP levels are raised in patients with AF compared to patients without AF.(198) In AF there are several pathological mechanisms that can contribute to raised NTproBNP levels, making direct correlations between specific systolic and diastolic measurements less clear. Studies have found that in the presence of AF atrial myocytes secrete BNP due to atrial remodelling and atrial stretch activating the BNP gene.(199) This is the first study in which the more stable BNP precursor (NTproBNP) has been compared with LVEF Simpson's biplane and GLS in patients in AF at the time of their echocardiogram. LVEF Simpson's biplane correlated weakly with

NTproBNP with a negative association; the lower the LVEF the higher the NTproBNP level. The more impaired the heart, the more stress the ventricular wall endures and it has been found that brain naturetic peptides are secreted proportional to the extent of stress the ventricular wall is under, in an effort to reduce the intra-ventricular pressure.(200) Radial contractility alone is not responsible for strain on the heart. This has been demonstrated before with Kim et al. who found that in a population of AF patients with preserved LVEF (LVEF >50%) there was no significant association with BNP levels (r= -0.251, p=0.065).(139) This demonstrates that strain on the heart is not associated with left ventricular dysfunction alone and may instead be associated more with diastolic dysfunction or may be a sign of early systolic dysfunction which can't be detected solely on ejection fraction.

Results from this study have shown that the association between the diastolic parameter E/e' and predicted NTproBNP is moderately correlated, with increasing E/e' predicting an increase in NTproBNP. The association between E/e' and raised NTproBNP levels have previously been observed in studies comparing E/e' with Log BNP which showed a very strong association in AF patients with preserved systolic function.(102) The mechanism for this is less clear but it is believed that it results from increased filling pressures, which may be due to dilated left atrium incurring greater volumes. NTproBNP may be directly released from the atria in response to raised left atrial pressures as well. The dilated left atrium may also contribute to a general increase in intra-cardiac volume, which can contribute to volume overload in the absence of systolic dysfunction.(139, 201) Therefore in this study patients despite having a preserved LVEF may have a raised NTproBNP level due to diastolic dysfunction and raised left atrial pressures causing volume overload, as a result of long-standing AF.

GLS was shown to be weakly associated with NTproBNP; with a less negative strain (reduced longitudinal function of the ventricle) predicting an increase in NTproBNP. This is in contrast to studies in patients with sinus rhythm, which has found that GLS has a strong correlation with NTproBNP, which is stronger than the association observed with LVEF.(197) In this study despite having a weaker strength of correlation the points were distributed evenly along the line of best fit, suggesting that NTproBNP is linearly proportional to the reduction in GLS. The normal GLS value for a Philips machine in a patient population of 60 years and over in sinus rhythm is -16.7% (± 2.1)(49); it was observed that the mean GLS from this population of permanent AF patients was -13.7% which is reduced. This has previously been demonstrated that GLS was significantly reduced in AF patients compared to patients in sinus rhythm matched for age, sex, heart rate, LVEF and LV mass.(202) There was also a proportion of patients who despite having a normal LVEF had reduced GLS and a raised NTproBNP. This suggests that AF patients may have a normal ejection fraction but the heart may still be under strain, causing raised levels of NTproBNP as a result of myocardial wall stress. GLS measures the function of the longitudinal muscle fibres, which are found in the subendocardial layer of the LV wall. The subendocardial layer is susceptible to damage caused by haemodynamic overload resulting in raised ventricular filling pressures, which often can occur with AF. Therefore GLS may be useful in detecting early systolic dysfunction caused by the haemodynamic problems of AF alone, which may precede overt LV systolic dysfunction.(202) It has also been found that reduced GLS is a predictor of the development of AF, so it is possible that reduced GLS was present in these patients before the onset of AF.(203) GLS was shown to not be associated with E/e', suggesting that reduction in GLS is unlikely to be due to diastolic dysfunction; this has been observed in patients with sinus rhythm before in which E/'e was not affected by GLS. (204)

Despite GLS being weakly associated with NTproBNP in patients with AF other studies have identified GLS as a strong predictor of mortality risk. Therefore it should not be excluded as a useful predictor of clinical outcome.(115, 136, 137)

Across all echocardiographic parameters the correlation with NTproBNP when measured by the index beat and average of consecutive beats did not significantly differ. This suggests that although the index beat method is more reproducible (**chapter 4**) there was no difference in clinical validity when compared to conventional averaging of consecutive beats. Therefore this means that the index beat method can confidently be used to measure systolic and diastolic parameters without compromising the correlation with clinical outcome.

No systolic and diastolic parameters were found to predict either PCS or AFEQT score. It would be expected clinically that patients with worsening parameters of systolic and diastolic dysfunction would have a greater symptom burden of dyspnoea, fatigue and reduced exercise tolerance.(205) However this data suggests that echocardiographic parameters do not correlate with symptoms in AF patients or it may be that the quality of life scoring system used does not accurately delineate symptoms related to cardiac function from other conditions. It may be that symptoms limiting physical activity are related to other conditions such as arthritis, lung disease and general frailty in this patient population. It is also known that 25-30% of patients with AF do not experience any symptoms at all. Previous studies comparing LVEF with physical functioning score from the SF-36 questionnaire in patients with sinus rhythm, have found that significant associations were only detected in patients with severely reduced ejection fraction.(205, 206) There has only been one study previously comparing LVEF with PCS from the SF-36 questionnaire; Dorian *et al* found that LVEF poorly correlated with PCS and was unrelated to quality of life and NYHA class.(207) In this study only 11 patients out of the 143 in which LVEF Simpson's biplane could be measured had an LVEF <40% which may account for the lack of association detected. As with all

results from patient self-reported quality of life questionnaires, it is all subjective and although a patient may clinically have similar symptoms, their perception on their severity may be significantly different.(208)

However, gender did significantly predict symptoms, with women having more symptoms related to physical activity. This has been observed before in a study looking at difference in patient symptoms assessed by the AFEQT score between genders in the AF population, in which it was found that women with AF have more symptoms of dyspnoea, palpitations and fatigue and a lower quality of life.(209) Female gender and increased age is also associated with reduced PCS in patients with cardiovascular disease.(210)

In comparison to validity studies in patients with sinus rhythm NTproBNP and quality of life scores in patients with AF do not correlate as strongly. Different clinical outcomes such as the more traditionally used cardiovascular events, hospitalisation and mortality may serve as a better clinical correlate.

The limitations of the results from this chapter are that this is baseline data only and from a relatively small sample size. Also the quality of life questionnaires did not adjust for non-cardiovascular conditions such as arthritis and respiratory problems, which may account for the lack of association seen when correlating with parameters of systolic and diastolic function. Measurement error is also inherent in a single time point QoL measure.

5.5 Conclusion

There was no significant difference in the validity of using the average of three index beats with averaging consecutive beats when compared with NTproBNP and quality of life measures. E/e' was the strongest predictor of NTproBNP levels, suggesting diastolic dysfunction contributes significantly to myocardial wall stress. The systolic parameters LVEF and GLS were shown to have a weak correlation with NTproBNP, particularly in those

patients with a preserved ejection fraction, where in some patients NTproBNP levels were elevated despite an LVEF within normal range. Therefore in AF patients this suggests that the level of NTproBNP cannot be used to predict the degree of systolic dysfunction.

Echocardiographic parameters of systolic and diastolic function, have been found to not be associated with quality of life in AF patients, using the SF-36 PCS and AFEQT score. Further studies comparing echocardiographic parameters with alternative measures of patient functional status are required, to establish whether echocardiographic parameters are associated with patient symptoms.

In the following chapter the findings from this thesis are brought together and future directions of where further research is required are discussed.

Chapter 6. General Discussion and future work

AF is the most prevalent cardiac arrhythmia in the population and as the patient population gets older, it is predicted to further increase in prevalence. One of the key problems with AF is the development of heart failure; from recent registries, it is now believed that up to 50% of patients with AF have some form of heart failure.(16, 22) Therefore it is essential that we can accurately determine left ventricular systolic and diastolic function, so that the type of heart failure can be correctly categorised and managed appropriately. For this to be achieved measurements used to evaluate systolic and diastolic function must be reproducible and clinically valid. However, the assessment of systolic and diastolic function in patients with AF is challenging due to the variable length in cardiac cycles (R to R intervals) and loss of atrial contraction. This means that achieving reproducible results is difficult. Current guidelines suggest based on consensus opinion; averaging 5 beats for systolic function and averaging 5 to 10 beats for diastolic function.(171) Recent studies have shown that these recommendations are not optimum.(177) Furthermore, there is uncertainty as to whether the parameters validated in patients with sinus rhythm, have the same validity for patients in atrial fibrillation.

Therefore the aim of this thesis was to investigate the optimal method to achieve reproducible measurements by comparing the validity and reproducibility of the index beat method with conventional averaging of consecutive beats. The validity of systolic and diastolic parameters in relation to clinical biomarkers of heart failure (NTproBNP) and patient symptoms was also assessed.

6.1 Summary of findings and Future directions

6.1.1 Systematic review of imaging methods to assess systolic function in AF patients

Before beginning the systematic review (**chapter 2**) it was known that there were very few studies assessing the validity of systolic function in echocardiography for AF patients, but the validity of other imaging modalities was unknown.(37) The systematic review showed that across imaging techniques, echocardiography had the most studies on validity in AF with very few studies for CMR and nuclear imaging and no studies at all for cardiac CT. From the echocardiography studies on clinical outcomes, GLS was identified as being a better predictor of cardiovascular mortality and events, compared to measurements of LVEF and was shown to correlate well with invasively derived dP/dt (a measurement of contractile function). However the more widely used parameter of systolic function LVEF, has not been externally validated, raising concerns as to whether the LVEF cut-off values for AF patients are the same as those validated in patients with sinus rhythm. Previous reproducibility studies suggested that measurements of systolic function were highly reproducible and the index beat method was as good as using the average of all beats taken (10 to 13). However, these conclusions were drawn from studies in which the patient population had been highly selected for good quality acoustic windows, meaning that these findings may differ in the general AF population. Also the use of the index beat in measuring systolic parameters had not been externally validated. The data for CMR and nuclear was very small, with no studies comparing systolic measures with clinical outcomes in AF patients. There have also been no inter-imaging modality studies in this group of patients, so measurements of systolic function cannot be reliably inter-changed between modalities.

Future Directions

The systematic review has revealed a significant lack of validity studies of systolic measurements using cardiac imaging in AF patients, with no studies comparing systolic measurements between modalities. This presents a need for prospective cross-sectional studies comparing measurements of systolic function between imaging modalities. For example the measurement of LVEF needs to be derived from echocardiography, nuclear SPECT and MUGA, CMR volumes and cardiac CT and then compared to confirm whether or not the measurement can be used interchangeably between modalities to guide patient management. This will ensure that results are correctly interpreted and any serial monitoring of ventricular systolic function using different imaging modalities will accurately detect any change in systolic function.

It was also shown that the LVEF measurement by echocardiography has not been externally validated in AF patients. Therefore given that this measurement is often used to guide clinical management of patients,(3) external validity studies are urgently needed. The challenge in this study would be identifying a gold-standard value for systolic function. In patients with sinus rhythm the invasive angiography parameter dP/dt is considered the gold-standard method of determining contractility.(143) Prospective studies are needed in AF patients to simultaneously compare echocardiographic systolic parameters measured by the index beat and averaging of consecutive beats with invasively derived dP/dt, to determine which systolic parameters correlate best with contractility. To do this I would propose obtaining dP/dt traces using a left ventricle catheter, while simultaneously obtaining echocardiography traces of lateral and septal TDIs and 30 beat loops of the apical 4, 3 and 2 chamber view to measure GLS, s' and LVEF post-procedure. Right heart catheterisation will similarly be used to correlate E/e' using TDI with pulmonary capillary wedge pressure. Around 1200 patients undergo either left heart catheterization or percutaneous coronary intervention at the Queen

Elizabeth Hospital per year of which 10% are in AF. These patients awaiting left heat catheterization would be approached to take part in the study.

6.1.2 A simple method to improve the reliability of echocardiography in patients with atrial fibrillation

The first aim was to explore the reproducibility of the index beat method against conventional averaging of consecutive beats (**chapter 4**). The study showed that the index beat method had a significantly lower within beat variability compared to averaging 3, 5 and 10 consecutive beats across LVEF Simpson's biplane, GLS and E/e'. Intra and inter operator studies showed that a single index beat method was more reproducible than averaging 3 and 5 consecutive beats and was either as reproducible or more reproducible than averaging 10 consecutive beats. This finding reflects what has previously been reported in the literature with the index beat method correlating strongly with an average of 10 beats or more.(101, 132, 154) Furthermore the index beat method was also found to be significantly more time efficient than conventional averaging of 5 and 10 beats. Therefore not only is the index beat more reproducible it will also save the echocardiographer time in obtaining measurements, increasing the efficiency of echocardiography departments.

Finally in **chapter 5** the index beat method's validity was compared with the average of 3, 5 and 10 beats by correlating them with NTproBNP and patient reported quality of life in the form of the AFEQT sore and physical component score (PCS) derived from the SF-36 questionnaire. There was no difference in the associations between the index beat method and conventional methods and so not only is the index beat method more reproducible and more time efficient, it does not compromise clinical validity.

Future directions

The index beat method was shown to be more reproducible and more time efficient without compromising clinical validity when compared to conventional averaging of 3, 5 and 10 consecutive beats. However, this is not the first time the index beat method has been mentioned in the literature as a reproducible alternative to averaging of 5 and 10 beats.(37) It remains unclear as to why this method has not been introduced into routine clinical practice or mentioned as an alternative in clinical guidelines. This may be due to a lack of knowledge about the index beat method or uncertainty of its validity in clinical practice. This means going forward initially this method would be introduced into the cardiology department at the Queen Elizabeth hospital Birmingham, starting with in depth training on how to perform the index beat method. To follow this, the index beat method would be introduced into clinical practice and a pilot study would be developed to assess the feasibility of the index beat method, ultimately expanding the study to other centres. Feasibility outcomes could be duration of the echocardiogram study and/or analysis and qualitative assessment, of whether the index beat method improves the clinical management of patients. The feasibility outcomes could then be compared with other matched centres still using the conventional averaging of consecutive beats. To measure on an index beat, does require more attention from the echocardiographer, than simply measuring a random number of consecutive beats. If from the study this proves a challenge, selection of the index beat could be facilitated with artificial intelligence; by accurately tracking the R to R intervals on the ECG, automated recognition of the index beat could be enabled. This would help echocardiographers in using the index beat method in clinical practise and minimize operator error of incorrectly selecting an index beat. In order for this to be successful, collaboration with industry (such as Philips and General Electric healthcare) would be required to introduce this on to the echocardiogram machines used in clinical practice.

6.1.3 Validity of systolic and diastolic parameters vs patient symptoms and NTproBNP

A problem highlighted from the systematic review was an uncertainty of how echocardiographic parameters affected clinical outcome. In **chapter 5** LVEF Simpson's biplane, GLS and E/e' were correlated with NTproBNP and the patient symptoms (PCS and AFEQT score). The value E/e' has been shown to correlate most strongly with NTproBNP, suggesting that diastolic dysfunction contributes significantly to myocardial wall stress, despite a lot of patients having a normal ejection fraction. Also noted from the validity studies was a reduced GLS despite having an LVEF within normal limits. Data from the systematic review has shown that GLS is a better predictor of cardiovascular events than LVEF(135), however in this study it was shown to be weakly associated with NTproBNP.

It was found that all three parameters of systolic and diastolic function were not associated with patient symptoms (measured by AFEQT score and PCS). This may have been due to echocardiographic measures being a poor predictor of patient symptoms or an issue with the questionnaires used to assess patient symptoms.

Future Directions

To further validate the index beat against conventional averaging of beats, a superior method to patient reported quality of life needs to be used to assess its association with clinical outcome. Measurements of systolic and diastolic function using the index beat method verses average of 5 or 10 beats, need to be correlated with information such as the composite of cardiovascular death, heart failure hospitalisation and other major cardiac events. This would require a greater population of patients to achieve a sufficient power and so collaboration with other echocardiography centres might be needed in order to collate echocardiogram studies.

To better understand how echocardiographic measurements are associated with patient symptoms, more robust methods of assessing functional status need to be considered. The

parameter peak oxygen consumption (VO2 max), which can be derived from cardiopulmonary exercise-testing can be used to evaluate the capacity of the cardiorespiratory system in patients.(211) In comparison to quality of life scores, this may provide a more accurate assessment of patient symptoms related to the cardiovascular system. Echocardiographic parameters of systolic and diastolic function should be correlated with VO2 max, to determine which parameters are more associated with a decline in functional status in the AF population. For systolic parameters this has never been carried out for patients in AF at the time of their echocardiogram.

This thesis has concentrated on the effects of left ventricular systolic and diastolic dysfunction on myocardial stress and patient symptoms. However the contribution of the right heart and pulmonary vascular resistance on symptoms has not been assessed. Previous studies have shown that the co-existence of pulmonary hypertension and AF reduces the functional capacity and increases heart failure symptoms in patients more than in those without AF.(212) It would be useful to determine from this RATE-AF population, the association of right ventricular function and pulmonary hypertension with symptoms and NTproBNP, and how this is related to the patients with preserved and impaired systolic function. It may reveal that it is the degree of right ventricular dysfunction and pulmonary hypertension that manifests symptoms rather than degree of left ventricular systolic and diastolic function.

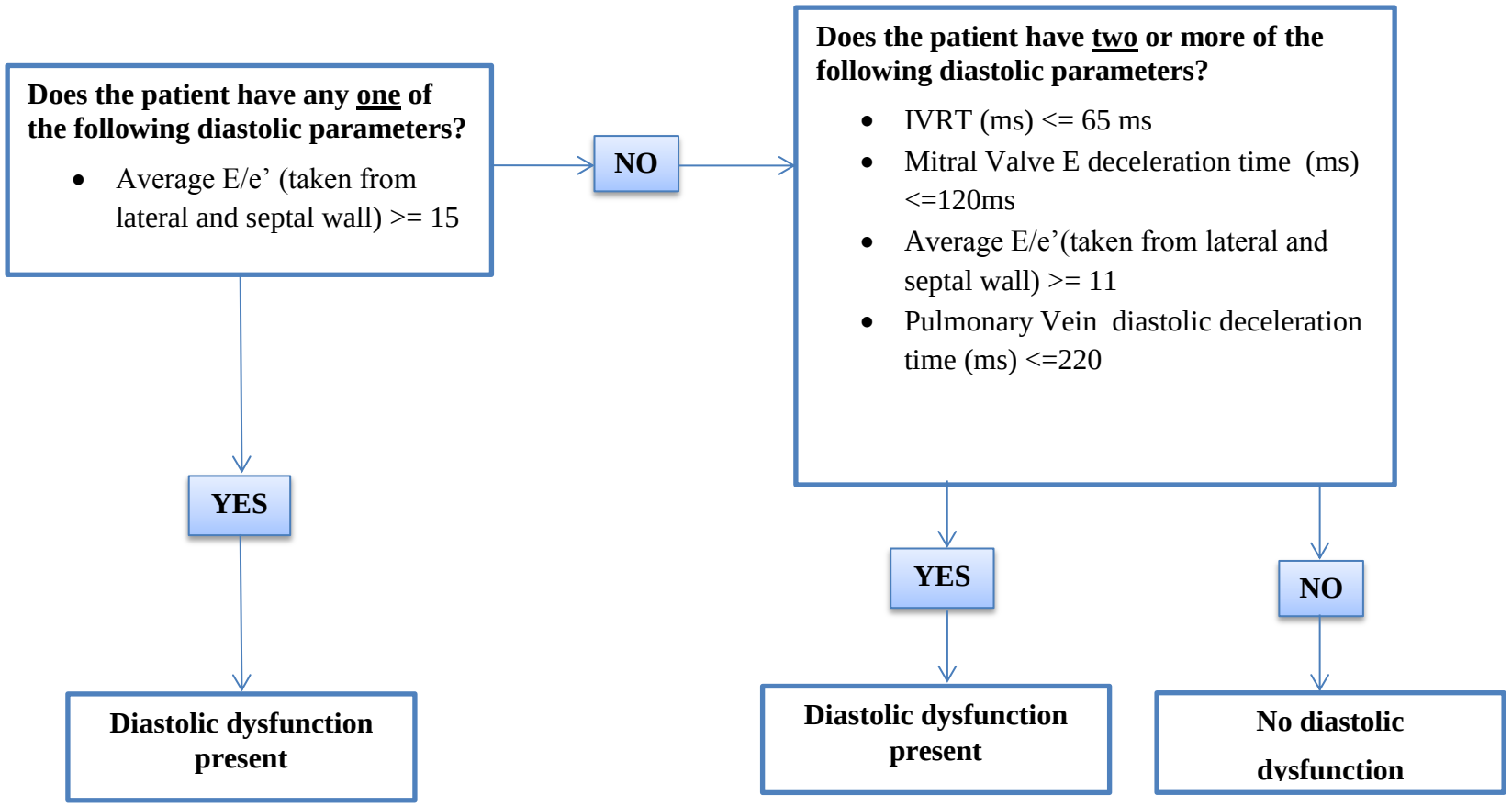
In addition to this the left atrial size and function has not been assessed in this thesis. The left atrium acts as a reservoir for blood returning from the pulmonary circulation, a conduit to transport blood into the left ventricle and a pump to propel blood into the LV contributing to cardiac output.(213) In patients with AF the LA remodels resulting in dilatation and reduction in contractile function. Studies have shown that a reduction in left atrial function measured by an abnormal strain could be related to heart failure and the onset of symptoms.(214, 215) Therefore attention should be paid to how left atrial function correlates

with NTproBNP, patient symptoms and functional status. Studies have shown that a reduction in LA ejection fraction and increase in LA volume has been associated with an increase in the risk of mortality.(216) Measurements of left atrial ejection fraction, volume and strain in patients with permanent AF should be correlated with clinical measures in future studies.

A greater number of studies have validated diastolic function parameters against pulmonary capillary wedge pressure,(37) and this study has also proven E/e' to be more strongly associated with myocardial wall stress, compared to LVEF and GLS. However there remains uncertainty in clinical practice on how to accurately assess diastolic function in patients with AF at the time of their echocardiogram. It is common to find the statement "unable to assess diastology due to patient in AF" on echocardiogram reports, despite parameters such as E/e' and pulmonary diastolic deceleration time been shown to correlate highly with pulmonary capillary wedge pressure. Prospective studies correlating pulmonary capillary wedge pressures with parameters of diastolic function need to be carried out in order to create an official guideline (similar to the ASE's diastolic dysfunction algorithm(36)) for the diagnosis of diastolic dysfunction in AF patients. This study has clearly highlighted the impact of diastolic dysfunction causing stress on the heart in AF patients. Therefore, it is important that this be stated in echocardiogram reports, as diastolic dysfunction may play a critical role in AF patients' development and worsening of heart failure.

As part of the RATE-AF trial the diastolic composite was designed for the outcome of diastolic function, which was based on current data in the literature(37) (see **Figure 44**. As a starting point to formulate an algorithm for the assessment of diastolic dysfunction in patients with AF, the composite could be validated against pulmonary capillary wedge pressures in those patients in AF undergoing right heart catheter assessment.

Figure 44. Diastolic function composite based on available data for validity of diastolic parameters in AF patients



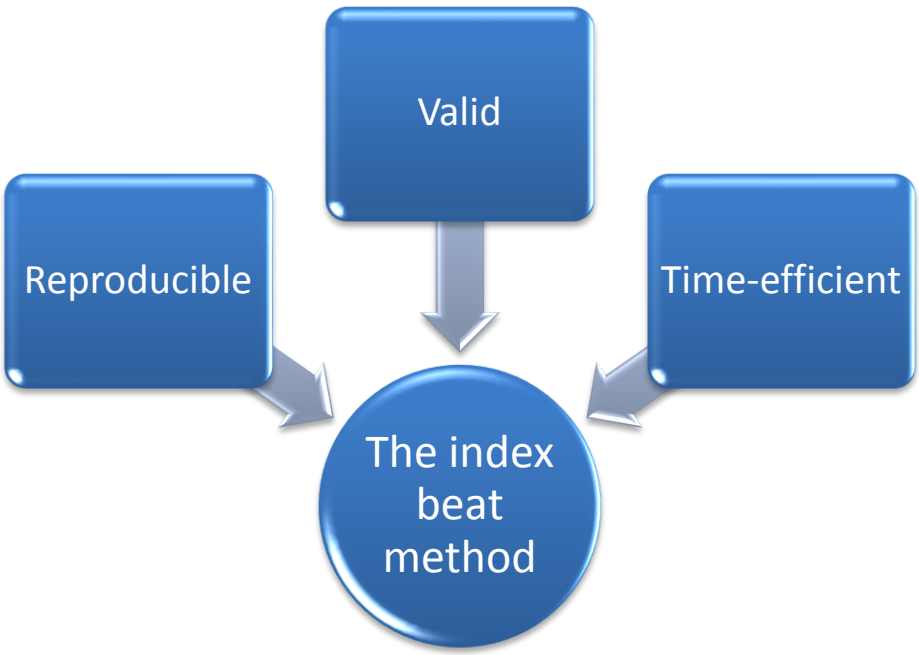
6.2 Conclusion

The use of the index beat method has been proven to be more reproducible and time efficient than conventional averaging of consecutive beats, without compromising validity when correlating with natriuretic peptides and patient-reported quality of life scores (

Figure 45). Further studies are needed to validate the index beat method with more robust clinical parameters such as exercise tolerance and long-term clinical outcomes.

Accurate echocardiography studies to determine systolic and diastolic function in AF patients will lead to early diagnosis of heart failure and so correct management of these patients. If AF patients are optimally managed for their heart failure, this will ultimately lead to an improvement in patient's quality of life, fewer hospital admissions and could improve the long-term prognosis of AF patients.

Figure 45. Summary figure to show the outcome of testing the reproducibility, validity and efficiency of the index beat method



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Appendices

1. Link to RATE-AF protocol version 2.0
2. Patient information leaflet
3. Consent form
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5. Randomisation form
6. Baseline CRF
7. SF-36 questionnaire
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Appendix 1: Link to the RATE-AF protocol

Please follow the link below for the latest version (version 2.0) of the RATE-AF protocol:

https://www.birmingham.ac.uk/Documents/college-mds/trials/bctu/RATE-AF/RATE-AF-Protocol-v2.0-23Jan2018-clean.pdf

Appendix 2: Content of patient information leaflet for RATE-AF trial

The RATE-AF Study

PATIENT INFORMATION LEAFLET

We would like to invite you to take part in our research study

Before you decide, we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions (this should take about ten minutes). You can talk to others about the study if you wish. Please ask us if there is anything that is not clear.

What is the purpose of the study?

Atrial fibrillation is a common condition where the heart rhythm is irregular. It usually requires medication to control heart rate, but we currently don't know which medication is

better for patients. The aim of this study is to find out which, of two treatments (digoxin or bisoprolol), improves quality of life and the function of your heart.

Why have I been invited? Can I say no?

You have been invited as you have atrial fibrillation and need medication to help to control of your heart rate. Your doctors will be starting treatment and we would like your consent to randomly assign you to one of these two medications (digoxin or bisoprolol) as your initial therapy.

It is up to you to decide whether to join the study or not. If you decide not to take part, your standard of care will not be affected and you will receive medications to control heart rate as part of your clinical care. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason.

Are there any benefits to taking part?

You will be seen more regularly than normal because you are taking part in a study and you will have access to the study team. However, there will also be questionnaires, tests and visits to the hospital that might be an inconvenience. Although there may be no direct benefit to you, we hope this study will benefit all future patients with atrial fibrillation.

What will happen to me if I take part?

Sometimes we don't know which way of treating patients is best. To find out, we need to compare different treatments by putting patients into groups with each receiving a different treatment.

Before any study procedures take place, you will be asked to sign a consent form to enter the study. This will stay on record in your study file, be noted in your medical records and available for review by the study monitors, with a copy made for you to keep.

A computer will decide at random (like tossing a coin) which treatment you will have. Half of the people taking part will be prescribed digoxin and the other half will be prescribed bisoprolol.

Once the treatment is assigned, you and your doctors will know which treatment you are given. We will avoid giving patients the other drug unless absolutely needed. Additional treatments can still be given according to your needs.

At the beginning of the study, we will assess your quality of life (using questionnaires) and your heart function (using an ultrasound scan). We will reassess your quality of life at 6 months and 12 months after starting treatment, and look again at your heart function at 12 months. During the study, we will also take blood samples (approximately 20 mL which is equivalent to four teaspoons), monitor your heart rate and check your physical fitness with a walking test.

How many visits are there and how long will it take?

The initial visit will last a couple of hours, so that we can go through this information leaflet in detail and accurately record all of your details. Once you start the treatment, we will arrange one or two short visits in the first month (usually around 30 minutes each) to see whether you need a higher dose of the medication or any additional treatments, in order to get your heart rate to less than 100 beats per minute. At 6 months the visit will take about an hour, and at 12 months about two hours. All visits will be scheduled at the Queen Elizabeth Hospital in Birmingham.

Expenses and payments

Although you won't be paid to take part in the study, we are able to cover all your expenses to attend the study visits. In most cases, we are happy to book a taxi for you to attend and go home afterwards, as well as support any costs for food and drink.

How will I receive the medications?

For the first few months, we will supply your medication from our pharmacy. Once you are stable on your treatment, you can receive prescriptions from your GP in the normal way. All patients in this study are over the age of 60 and receive free NHS prescriptions.

You should take the study medication regularly as directed and continue all other regular medication, including blood thinning tablets.

Are the medications and tests safe?

The two treatments we are using (digoxin and bisoprolol) are safe and have been used for many years as part of the normal treatment for atrial fibrillation. As with any drug, there are potential side effects, but serious complications are very rare. The most common side effects from digoxin include stomach upset, dizziness, blurred vision and headache, and for bisoprolol include tiredness, headache, dizziness, and breathlessness. Some patients with atrial fibrillation need pacemakers to support their heart rhythm. We will carefully monitor your heart rate and any side effects, and take action where needed. This may include changing a treatment or withdrawing you from the study. There will be an independent safety committee that will oversee the trial.

All the tests you will receive are safe and part of normal clinical care for patients with atrial fibrillation. The ultrasound scans (echocardiogram) are similar to what mothers receive in pregnancy (but assess the heart instead). The walking tests take about 6 minutes, are very

relaxed and patients can stop when they need to. Monitoring of heart rate uses a small device attached to the chest, which records for 24 hours.

What happens when the research study stops?

After the study finishes, your care will continue either with your cardiologist or GP. The treatments you started on may continue, or you may change to other treatments if these prove to be better.

What if new information becomes available?

Sometimes we get new information about the treatment being studied. If this happens, your research doctor will tell you and discuss whether you should continue in the study. If the study is stopped for any other reason, we will tell you and arrange your continuing care.

What will happen if I don't want to carry on?

You can withdraw from the study at any time without giving a reason. However, we would like to keep in contact with you to let us know your progress. Information collected until your withdrawal may still be used. Any stored blood or tissue samples that can still be identified as yours will be destroyed if you wish.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions (see contact details on the last page). If you remain unhappy and wish to complain formally, you can do this by contacting the Patient Advice and Liaison Services (PALS) at the Queen Elizabeth Hospital on 0121 371 3280 or PALS@uhb.nhs.uk.

In the event that something does go wrong and you are harmed during the research due to someone's negligence, then you may have grounds for legal action and compensation against the sponsor (the University of Birmingham) but you may have to pay your legal costs. The normal NHS complaints mechanisms will still be available to you, if appropriate.

Will my details be kept confidential?

All information which is collected about you, including from your medical records, will be kept strictly confidential, and any stored information about you will have your name and address removed so that you cannot be recognised. We will take all reasonable steps available in order to protect your privacy.

Personal and research data will be stored for up to 25 years. Any future use of this data will follow the same principles as discussed above, and only shared within the research team. Outside of this team (including in any articles we publish about the research), all data will refer to groups of patients, anonymised to protect privacy.

Involvement of your family doctor

Your GP will need to be kept informed of your participation in the study. By consenting to take part, you agree to us sharing your progress in the study with your GP, as needed for your clinical care.

What will happen to any samples I give?

Blood samples will be used to develop new tests that may help doctors choose the right treatment for patients in the future. We will store the blood you give, at the University of Birmingham Human Biomaterials Resource Centre and possibly in Research Laboratories overseas, within Europe. Samples will only be labelled with a code to ensure your privacy. Samples will be stored for four years and then securely destroyed.

Will any genetic tests be done?

If you agree, after receiving your blood samples we will isolate the genetic material (DNA). In the future, we hope that genetic factors can help doctors to use appropriate medications for each individual patient that avoids side effects. Storing this DNA will help us to see differences in group of patients (not individuals) who benefit or don't benefit from the treatments. Your personal details will always remain confidential; we will never disclose any individual details and all future research will undergo ethical review.

Are there any additional ways I can help?

We will be asking ten patients to help look at the quality of life questionnaires in detail to see if they are a good way to capture information that helps to look after patients with atrial fibrillation. Three half-day sessions will be planned over the 12-month period and any volunteers will receive financial compensation for their time.

We are also planning future studies in patients with atrial fibrillation. You can give consent for us to contact you about future research (you can specify whether and how you wish to be contacted).

What will happen to the results of the research?

The results of the quality of life questionnaires, the heart scans and some of your blood tests will <u>not</u> be used to direct your clinical care during the study. These will remain concealed to the study doctors to keep an unbiased assessment of the two treatments. However, if any troubling symptoms come to light during the study visits, the research nurses will alert the study doctors and take appropriate action.

At the end of the study, we plan to publish the study findings in a medical journal. You will not be identified in any publication. Following this, we will send out a summary of the findings to you.

Who is organising and funding the research?

The study is sponsored by the University of Birmingham and is being funded by the National Institute for Health Research (part of the Department of Health). No member of the research team is being paid for including you in this study.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the East Midlands - Derby Research Ethics Committee.

Who else is taking part?

We aim to include 160 patients with atrial fibrillation in this study. The results will help us to plan a future large study to demonstrate whether these treatments can help to reduce admissions to hospital.

Key points about this research:

Patients with atrial fibrillation usually need medications to control heart rate

We currently don't know which medication is the best to improve quality of life and heart function

This study will randomly assign patients to initial treatment with two common drugs and test them over 12 months

The study mirrors normal clinical care for this condition and will involve questionnaires, blood tests, a walking test and heart ultrasound scans

Our aim is to improve the care of patients with atrial fibrillation and help doctors choose the right medication for the right person

Thank you for taking the time to read this information leaflet and for considering taking part in this research project.

If you have any questions, please contact the study research team on:

Phone: 07867 551 957

Email: Karina.Bunting@uhb.nhs.uk

Appendix 3: Consent form

CONFIDENTIAL WHEN COMPLETE <TO BE PRINTED ON LOCAL TRUST HEADED PAPER>

RATE-AF Trial
Participant Consent Form

Participant Trial Number: ☐☐☐☐ **Please initial each box to confirm consent ↓**

1. I confirm that I have read and understood the Participant Information Sheet dated: ☐☐/☐☐/☐☐☐☐ **version** ☐.☐ for the above trial. I have had the opportunity to think about the information, ask questions and have had these answered to my satisfaction. ☐

2. I understand that my participation in this trial is voluntary and that I am free to withdraw at any time, without giving a reason and without my medical care or legal rights being affected. I understand that data collected up to my time of withdrawal may be used. ☐

3. I understand that sections of my medical notes or information related directly to my participation in this trial may be looked at by responsible individuals from the sponsor, regulatory authorities and research personnel where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

4. I understand that my doctor will provide a copy of this consent form and personal information about my progress, in confidence, to the central organisers at Birmingham Clinical Trials Unit (BCTU) for use in the RATE-AF Trial. ☐

5. I understand that my General Practitioner will be informed of my participation in this research ☐

6. I understand that the trial researchers may contact me by telephone, text or email and that my relevant contact details may be passed to the BCTU to assist with this. ☐

7. I understand that my data, collected as part of this research, will be stored securely for up to 25 years and that during this time it may be looked at again by research personnel in relation to the RATE-AF Trial. ☐

8. I agree to participate in the RATE-AF Trial ☐

In order to participate in the RATE-AF trial you <u>MUST</u> consent to points 1-8 above and initial the corresponding boxes.

Name of participant	Date	Signature
		Witness Signature *(if applicable)*
Name of person receiving consent	Date	Signature

Original to be filed in the Investigator's Site File; 1 copy for patient; 1 copy to be kept with patient's hospital record; 1 copy to be sent to BCTU

Appendix 4: Optional Consent form

University Hospitals Birmingham NHS
NHS Foundation Trust

CONFIDENTIAL WHEN COMPLETE

RATE-AF Trial
Participant Optional Consent Form

Participant Trial Number: ☐☐☐☐ **Please initial each box to confirm consent ↓**

1. I agree that a sample of my blood donated by me may be stored for future genetic (DNA) tests to help understand effects of the study treatment and genetic factors that might contribute to atrial fibrillation. This sample will be for medical research only and my results will be kept confidential. Any study using this material would require Research Ethics Committee approval. I understand that these samples may be analysed in research laboratories outside of this hospital, in the UK and oversees, within Europe. ☐

2. I agree that a sample of my blood donated by me may be stored for future biochemical tests to help understand effects of the study treatment and biochemical factors that might contribute to atrial fibrillation. This sample will be for medical research only and my results will be kept confidential. Any study using this material would require Research Ethics Committee approval. I understand that these samples may be analysed in research laboratories outside of this hospital, in the UK and oversees, within Europe. ☐

3. I understand that the information held and maintained by NHS Digital and other central UK bodies may be used to help contact me or provide information about my health status in the future. I understand that my name, postcode and date of birth will be shared with these central bodies. ☐

4. I am happy to be contacted by the Research Team to participate in a focus group to discuss my experience of participating in the trial. ☐

5. I am happy to be contacted in the future about relevant studies. ☐

6. I agree to participate in the **sub-study of physical activity and heart rate monitoring** in the RATE-AF trial after reading the additional participant information leaflet (v1.0 23-Jan-2018). I understand my participation is voluntary and I can withdraw at any time. I also understand that the research data collected as part of this physical activity sub-study will be kept confidential and may be used in future research unrelated to the RATE-AF trial. ☐

7. I agree to participate in **the sub-study of nerve activity and heart rate in the RATE-AF trial** after reading the additional participant information leaflet (v1.0 23-Jan-2018). I understand my participation is voluntary and I can withdraw at any time. I also understand that the research data collected as part of this nerve activity sub-study will be kept confidential and may be used in future research unrelated to the RATE-AF trial. ☐

Points 1-7 above are OPTIONAL for participation in RATE-AF; please initial these boxes only if you agree to them.

Name of participant	Date	Signature
		Witness Signature *(if applicable)*
Name of person receiving consent	Date	Signature

Original to be filed in the Investigator's Site File; 1 copy for patient; 1 copy to be kept with patient's hospital record; 1 copy to be sent to BCTU

Appendix 5: Randomisation form

EudraCT No.: 2015-005043-13 CONFIDENTIAL WHEN COMPLETE

RATE-AF Randomisation Form

PLEASE COMPLETE BEFORE RANDOMISATION

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SITE DETAILS				
Name of person completing this form:				
Referring site:	UHB ☐	SWBH ☐	HEFT ☐	GP ☐ (*please specify*) .....

PATIENT IDENTIFICATION DETAILS	
Date of birth:	D D / M M M / Y Y Y Y
Hospital number:	☐☐☐☐☐☐☐
NHS number:	☐☐☐☐☐☐☐☐☐☐
Gender:	Male ☐ Female ☐

ELIGIBILITY CHECKLIST
If any of the shaded boxes are ticked, the patient is **NOT** eligible to be randomised into the RATE-AF trial

	No	Yes
Is the patient aged 60 years or over?	■	☐
Does the patient have permanent AF, characterised (at time of randomisation) as a physician decision for rate-control with no current plans for cardioversion, anti-arrhythmic medication, or ablation therapy?	■	☐
Does the patient have symptoms of breathlessness (New York Heart Association Class II or more)?	■	☐
Is the patient able to provide written, informed consent?	■	☐
Does the patient have an established indication for beta-blocker therapy, e.g. myocardial infarction in the last 6 months?	☐	■
Does the patient have known contraindications for therapy with beta-blockers or digoxin, e.g. a history of severe bronchospasm that would preclude use of beta-blockers, or known intolerance to these medications?	☐	■
Does the patient have a baseline heart rate <60 bpm?	☐	■
Does the patient have a history of second or third-degree heart block?	☐	■
Does the patient have supraventricular arrhythmias associated with accessory conducting pathways (e.g. Wolff-Parkinson-White syndrome) or a history of ventricular tachycardia or ventricular fibrillation?	☐	■
Is the patient awaiting pacemaker implantation (including cardiac resynchronisation therapy), have a pacemaker-dependent rhythm or a history of atrioventricular node ablation?	☐	■
Is there a history of decompensated heart failure (evidenced by need for intravenous inotropes, vasodilators or diuretics) within 14 days prior to randomisation?	☐	■
Does the patient have a current diagnosis of obstructive hypertrophic cardiomyopathy, myocarditis or constrictive pericarditis?	☐	■
Has the patient undergone heart transplantation, or is on a waiting list for heart transplantation?	☐	■
Is the patient receiving renal replacement therapy (haemodialysis or peritoneal dialysis)?	☐	■
Is there a history of major surgery, including thoracic or cardiac surgery, within 3 months of randomisation?	☐	■

ELIGIBILITY CHECKLIST

If any of the shaded boxes are ticked, the patient is **NOT** eligible to be randomised into the RATE-AF trial

	No	Yes
Does the patient have severe, concomitant non-cardiovascular disease (including malignancy) that is expected to reduce life expectancy?	☐	☒

Eligibility criteria confirmed by (name):
This **must** be confirmed by a **medically qualified doctor** who has signed the delegation log .....

MODIFIED EHRA SCORE

Modified EHRA score: 1 ☐ 2a ☐ 2b ☐ 3 ☐ 4 ☐

Guidance on selecting modified EHRA score:

1:	*None; AF does not cause any symptoms*
2a:	*Mild; normal daily activity not affected; patient not troubled by symptoms*
2b:	*Moderate; normal daily activity not affected; patient troubled by symptoms*
3:	*Severe; normal daily activity affected by symptoms relating to AF*
4:	*Disabling; normal daily activity discontinued*

CONSENT DETAILS

Has the patient given informed consent to participate in the study? (if no, this patient cannot be randomised) No ☒ Yes ☐

Version of informed consent form used: ☐.☐

Date of patient consent: ☐☐/☐☐/☐☐☐☐

Optional consents

Has the patient given permission for their blood samples to be stored for future genetic tests?	No ☐ Yes ☐
Has the patient consented for their blood samples to be stored for future biochemical tests?	No ☐ Yes ☐
Has the patient given permission for their data on central NHS databases to be included in the analysis data set?	No ☐ Yes ☐
Has the patient given permission to be contacted by the Research Team regarding participation in a focus group	No ☐ Yes ☐
Has the patient given permission for them to be contacted about further studies?	No ☐ Yes ☐
Has the patient agreed to participate in the sub-study of physical activity and heart rate monitoring?	No ☐ Yes ☐
Has the patient agreed to participate in the sub-study of nerve activity and heart rate?	No ☐ Yes ☐

RANDOMISATION TO TREATMENT ALLOCATION

Online randomisation: www.trials.bham.ac.uk/rate-af **(24hrs)**
Log on to the RATE-AF database and follow the instructions on screen
OR
Telephone randomisation: 0800 953 0274 **(UK toll free), 9am to 5pm Mon-Fri.**

RANDOMISED TREATMENT ALLOCATION **(please tick one):**
Digoxin ☐ OR **Bisoprolol** ☐

RATE-AF Trial Number: ☐☐☐☐

Date of randomisation: ☐☐/☐☐☐/☐☐☐☐

Randomisation Form completed by:
You **must** have signed the trial signature and delegation log

Date: ☐☐/☐☐☐/☐☐☐☐ **Signature:** .....

Please return this completed form to the RATE-AF Trial Office, University of Birmingham Clinical Trials Unit, College of Medical & Dental Sciences, Public Health Building, University of Birmingham, Edgbaston, Birmingham, B15 2TT

Appendix 6: Baseline CRF

EudraCT No.: 2015-005043-13 CONFIDENTIAL WHEN COMPLETE

RATE-AF Baseline CRF

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IDENTIFYING DETAILS

Patient initials: ☐☐☐	Trial Number: ☐☐☐☐
Gender: Male ☐ Female ☐	Patient self-declared ethnicity code: ☐☐ (Please refer to coded list, **Note 1** at the end of this document)
Date of visit: D D / M M M / Y Y Y Y	

QUALITY OF LIFE QUESTIONNAIRES

Has the patient completed the following?	SF-36	No ☐ Yes ☐
	EQ5D-5L	No ☐ Yes ☐
	AF-EQT	No ☐ Yes ☐

BLOOD TESTS

Clinical samples (all bloods to be taken non-fasted)

Test		Test	
Sodium:	☐☐☐ mmol/L	Albumin:	☐☐ g/L
Potassium:	☐☐.☐ mmol/L	Calcium:	☐.☐☐ mmol/L
Urea:	☐☐.☐ mmol/L	Phosphate:	☐.☐☐ mmol/L
Creatinine:	☐☐☐ micromol/L	Magnesium	☐.☐☐ mmol/L
eGFR	☐☐☐ mL/min/ 1.73m²	Hb:	☐☐☐ g/L
		HCT:	☐.☐☐ L/L
INR:	☐☐.☐	NT-proBNP:	☐☐☐☐ ng/L

CONCOMITANT MEDICATIONS

Please indicate whether the patient is on any of the following medication:

Anticoagulant medication: No ☐ Yes ☐

If known, please indicate which medication(s) the patient is on from the list below:

Warfarin ☐	Acenocoumarol ☐	Phenindione ☐	Dabigatran ☐	Edoxaban ☐	Rivaroxaban ☐	Apixaban ☐

Antiplatelet medication: No ☐ Yes ☐

If known, please indicate which medication(s) the patient is on from the list below (choose as many as required):

Aspirin ☐	Dipyridamole ☐	Prasugrel ☐	Clopidogrel ☐	Ticagrelor ☐

Trial Number: ☐☐☐☐ Date of Visit: ☐☐/☐☐☐/☐☐☐☐

Antihypertensive medication: No ☐ Yes ☐				
If known, please indicate which medication(s) the patient is on from the list below (choose as many as required):				
ACEi ☐	ARB ☐	Thiazide/loop diuretics ☐	CCBs ☐	Alpha-blockers ☐
Aldosterone antagonists ☐	Others ☐ *Please specify:*			
Inhalers for airway disease: No ☐ Yes ☐				

MEDICAL HISTORY

Please provide details about the patients past medical history:

Atrial Fibrillation

What year was the patient diagnosed with atrial fibrillation? ☐☐☐☐

Modified EHRA score: 1 ☐ 2a ☐ 2b ☐ 3 ☐ 4 ☐

Guidance on selecting modified EHRA score:

1:	*None; AF does not cause any symptoms*
2a:	*Mild; normal daily activity not affected; patient not troubled by symptoms*
2b:	*Moderate; normal daily activity not affected; patient troubled by symptoms*
3:	*Severe; normal daily activity affected by symptoms relating to AF*
4:	*Disabling; normal daily activity discontinued*

Heart Failure

Has the patient been diagnosed with heart failure? No ☐ Yes ☐

Please complete the following:

NYHA Functional Classification: I ☐ II ☐ III ☐ IV ☐

Guidance on selecting NYHA Functional Classification:

I	*No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnoea.*
II	*Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation or dyspnoea.*
III	*Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation or dyspnoea.*
IV	*Unable to carry out any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.*

Vascular System

Has the patient had a myocardial infarction (MI)? No ☐ Yes ☐

Date of most recent MI: ☐☐/☐☐☐☐ Date unknown: ☐

Has the patient had any of the following? Coronary angioplasty or stents ☐ Coronary artery bypass surgery ☐ Heart valve replacement ☐

Has the patient had a stroke? No ☐ Yes ☐

Date of most recent stroke: ☐☐/☐☐☐☐ Date unknown: ☐

Has the patient had a transient ischaemic attack (TIA)? No ☐ Yes ☐

Date of most recent TIA: ☐☐/☐☐☐☐ Date unknown: ☐

Trial Number: ☐☐☐☐ Date of Visit: D D / M M M / Y Y Y Y

Smoking Status	Never smoked ☐ Ex-smoker ☐ Current smoker ☐	
Alcohol	Does the patient have more than 8 drinks per week containing alcohol?	No ☐ Yes ☐
Respiratory System	Does the patient have asthma?	No ☐ Yes ☐
	Does the patient have COPD/ emphysema?	No ☐ Yes ☐
Gastrointestinal System	Does the patient have liver disease?	No ☐ Yes ☐
Endocrine System	Has the patient been diagnosed with: Type I diabetes ☐ Type II diabetes ☐ If yes to either, how is the patient's diabetes controlled? Insulin ☐ Oral medication ☐ Diet ☐ Has the patient had complications relating to their diabetes? No ☐ Yes ☐ *If yes, please specify below:* Retinopathy ☐ Nephropathy ☐ Neuropathy ☐ Vascular ☐	
	Has the patient received treatment for thyroid disease? No ☐ Yes ☐ *If yes, please specify below:* Hypothyroid (underactive thyroid) ☐ Hyperthyroid (overactive thyroid) ☐	
Bleeding	Has the patient had any major bleeds? No ☐ Yes ☐ *If yes, please specify where below:* Intracranial ☐ Gastrointestinal ☐ Other ☐ *please specify:*	
	Date of most recent bleed: M M M / Y Y Y Y	Date unknown: ☐

Please provide details of any unplanned hospital admissions and procedures relating to AF and/ or heart failure:				
Has the patient had any unplanned admissions for AF or heart failure in the last 12 months? No ☐ Yes ☐				
Has the patient taken previously anti arrhythmic drugs? No ☐ Yes ☐				
Amiodarone ☐	Dronedarone ☐	Flecainide ☐	Profafenone ☐	Sotalol ☐
Others ☐ *please specify:*				
Has the patient previously undergone any cardioversions? No ☐ Yes ☐ If yes, how many? ☐				
Has the patient previously undergone AF ablation? No ☐ Yes ☐ If yes, how many? ☐				

Trial Number: ☐☐☐☐ Date of Visit: ☐☐/☐☐☐/☐☐☐☐

Does the patient have a pacemaker? No ☐ Yes ☐

If yes, please complete the following section:

When was the pacemaker fitted? ☐☐☐/☐☐☐☐

Type of pacemaker: Single chamber ☐ Dual chamber ☐ ICD ☐

Reason for implantation: Bradycardia ☐ AF (e.g. with tachy-brady syndrome) ☐ Heart failure ☐ Syncope ☐

Please provide details of any medications that the patient has previously taken to normalise their heart rate:

Has the patient previously taken any of the following medication to normalise their heart rate? No ☐ Yes ☐

If yes, please specify which medications and the date that the last dose was taken below:

	No	Yes	When was the last dose taken? (MMM/YYYY) If date not known, please tick 'unknown'
Digoxin	☐	☐	☐☐☐/☐☐☐☐ Unknown ☐
Verapamil	☐	☐	☐☐☐/☐☐☐☐ Unknown ☐
Diltiazem	☐	☐	☐☐☐/☐☐☐☐ Unknown ☐
Beta blocker	☐	☐	☐☐☐/☐☐☐☐ Unknown ☐

BASELINE PROCEDURES AND ASSESSMENTS

12-lead ECG:

Heart rate ☐☐☐ bpm | QRS duration ☐☐☐ ms | QT interval ☐☐☐ ms

Echocardiogram:

Estimated ejection fraction: < 40% ☐ 40-49% ☐ ≥ 50% ☐

Office blood pressure and heart rate. To be taken whilst patient is at rest, in a seated position:

BP 1: ☐☐☐/☐☐☐ mmHg | BP 2: ☐☐☐/☐☐☐ mmHg

Radial artery heart rate: ☐☐☐ bpm | Apex beat heart rate: ☐☐☐ bpm

Calculate heart rate from at least 30 second measurement

Trial Number: ☐☐☐☐ Date of Visit: ☐☐/☐☐☐/☐☐☐☐

Physical examination:	
Does the patient have any signs of heart failure?	No ☐ Yes ☐
If yes, please indicate which ones below:	
Lung crepitations consistent with heart failure	No ☐ Yes ☐
Peripheral oedema	No ☐ Yes ☐
Raised jugular vein pressure	No ☐ Yes ☐
Abnormal heart sounds	No ☐ Yes ☐
Please specify:	

Anthropometric measurements:		
Height: *to nearest cm* ☐☐☐ cm	Weight: *to nearest kg* ☐☐☐ kg	Waist circumference: *taken above the hip bones in expiration, to nearest cm* ☐☐☐ cm

Please provide details of the patients recent (within the last 7 days) physical activity:	
During the last 7 days, how much time did the patient spend sitting on a week day?	☐☐☐☐ minutes per weekday
During the last 7 days, on how many days did the patient walk for at least 10 minutes at a time?	☐ days per week
What is the total amount of time the patient spent walking over the last 7 days?	☐☐☐☐ minutes per week
During the last 7 days, on many days did the patient undertake moderate physical activities?	☐ days per week
How much time in total has the patient spent over the last 7 days doing moderate physical activities?	☐☐☐☐ minutes per week
During the last 7 days, on how many days did the patient undertake vigorous physical activities?	☐ days per week
How much time in total has the patient spent over the last 7 days doing vigorous physical activities?	☐☐☐☐ minutes per week

Guidance on completing physical activity fields:

Sitting	*Ask the patient to think about the time they spent sitting on week days during the last 7 days. Include time spent at work, at home, while doing course work, and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television.*
Walking	*Ask the patient to think about the time they spent walking in the last 7 days. This includes at work and at home, walking to travel from place to place, and any other walking that they might have done solely for recreation, sport, exercise, or leisure.*
Moderate physical activities	*Ask the patient to think about the time they spent undertaking activities which take moderate physical effort over the last 7 days. Moderate physical activities are those that made them breathe somewhat harder than normal and may have included carrying light loads, bicycling at a regular pace, or doubles tennis. Do not include walking. Again, ask that the patient thinks about only those physical activities that they did for at least 10 minutes at a time.*
Vigorous physical activities	*Ask the patient to think about all the vigorous activities which take hard physical effort that they did in the last 7 days. Vigorous activities are those that made them breathe much harder than normal and may include heavy lifting, digging, aerobics, or fast bicycling. Ask that the patient thinks about only those physical activities that they did for at least 10 minutes at a time.*

Trial Number: ☐☐☐☐ Date of Visit: D D / M M M / Y Y Y Y

Six-minute walk test:	
Did the patient undergo the six-minute walk test? No ☐ Yes ☐	
Total time spent undertaking the test: ☐ : ☐☐ min/s	Total distance covered: ☐☐☐ m, to nearest m
Was the test stopped prematurely? No ☐ Yes ☐	
If yes, please specify the reason the procedure was stopped (choose one option):	Breathlessness ☐ Fatigue ☐ Claudication ☐ Chest pain ☐ Other pain e.g. joint ☐ Other (please specify) ☐ .....
Peak heart rate: ☐☐☐ bpm	

Mini mental state examination (please refer to RATE-AF Worksheet). Record only the total test score on this CRF:
MMSE total test score: ☐☐ /30

Baseline CRF completed by:
You **must** have signed the trial signature and delegation log

Name: ..... **(please print)**

Date: D D / M M M / Y Y Y Y **Signature:** .....

Note 1: Ethnicity codes based on 2011 Census	
31	White - English / Welsh / Scottish / Northern Irish / British
32	White - Irish
33	White - Gypsy or Irish Traveller
34	White - Any Other White background
35	Mixed / Multiple ethnic group - White and Black Caribbean
36	Mixed / Multiple ethnic group - White and Black African
37	Mixed / Multiple ethnic group - White and Asian
38	Mixed / Multiple ethnic group - Any Other Mixed / multiple ethnic background
39	Asian / Asian British – Indian
40	Asian / Asian British – Pakistani
41	Asian / Asian British – Bangladeshi
42	Asian / Asian British – Chinese
43	Asian / Asian British - Any other Asian background
44	Black / African / Caribbean / Black British – African
45	Black / African / Caribbean / Black British – Caribbean
46	Black / African / Caribbean / Black British – Any other Black / African / Caribbean background
47	Other ethnic group – Arab
48	Other ethnic group – Any other ethnic group
98	Any other
99	Not known/not provided

Appendix 7: SF-36 quality of life questionnaire

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Thank you for completing this survey!

For each of the following questions, please tick the one box that best describes your answer.

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **Compared to one year ago, how would you rate your health in general now?**

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a mile	☐ 1	☐ 2	☐ 3
h Walking several hundred yards	☐ 1	☐ 2	☐ 3
i Walking one hundred yards	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

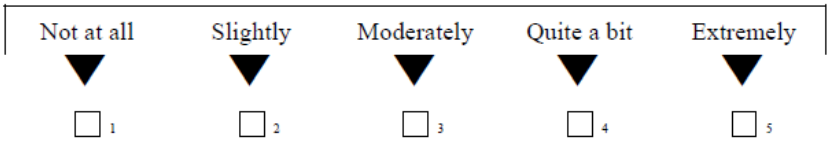
4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

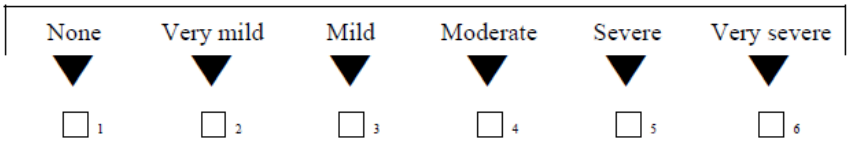
5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

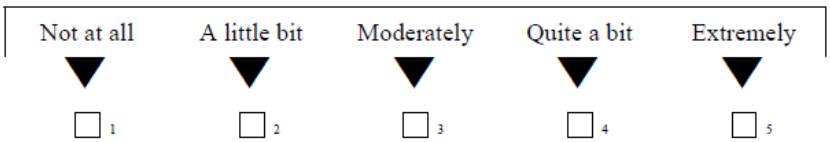
6. **During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?**



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



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



9. **These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. 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 <u>past 4 weeks</u>…**

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

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

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get ill more easily than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

Appendix 8: EQ-5D-5L questionnaire

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

We would like to know how good or bad your health is TODAY.

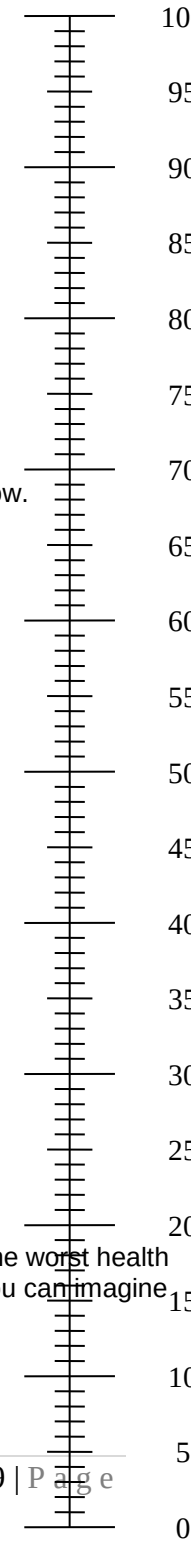
This scale is numbered from 0 to 100.

100 means the best health you can imagine.
0 means the worst health you can imagine.

Mark an X on the scale to indicate how your health is TODAY.

YOUR HEALTH TODAY = ☐

Now, please write the number you marked on the scale in the box below.



Appendix 9: AFEQT questionnaire

Atrial Fibrillation Effect on QualiTy-of-life (AFEQT) Questionnaire

Section 1. Occurrence of atrial fibrillation Name or ID:_____

Are you currently in atrial fibrillation? ☐ Yes ☐ No

If No, when was the last time you were aware of having had an episode of atrial fibrillation? (Please check one answer which best describes your situation)

__earlier today
__within the past week
__within the past month
__1 month to 1 year ago
__ more than 1 year ago
__I was never aware of having atrial fibrillation

Section 2. The following questions refer to how atrial fibrillation affects your quality of life.

On a scale of 1 to 7, over the past 4 weeks, as a result of your atrial fibrillation, how much were you bothered by:
(Please circle one number which best describes your situation)

	Not at all bothered Or I did not have this symptom	Hardly bothered	A little bothered	Moderately bothered	Quite a bit bothered	Very bothered	Extremely bothered
1. Palpitations: Heart fluttering, skipping or racing	1	2	3	4	5	6	7
2. Irregular heart beat	1	2	3	4	5	6	7
3. A pause in heart activity	1	2	3	4	5	6	7
4. Lightheadedness or dizziness	1	2	3	4	5	6	7

On a scale of 1 to 7, over the past 4 weeks, have you been limited by your atrial fibrillation in your:
(Please circle one number which best describes your situation)

	Not at all limited	Hardly limited	A little limited	Moderately limited	Quite a bit limited	Very limited	Extremely limited
5. Ability to have recreational pastimes, sports, and hobbies	1	2	3	4	5	6	7
6. Ability to have a relationship and do things with friends and family	1	2	3	4	5	6	7

On a scale of 1 to 7, over the past 4 weeks, as a result of your atrial fibrillation, how much difficulty have you had in:
(Please circle one number which best describes your situation)

	No difficulty at all	Hardly any difficulty	A little difficulty	Moderate difficulty	Quite a bit of difficulty	A lot of difficulty	Extreme difficulty
7. Doing any activity because you felt tired, fatigued, or low on energy	1	2	3	4	5	6	7
8. Doing physical activity because of shortness of breath	1	2	3	4	5	6	7
9. Exercising	1	2	3	4	5	6	7
10. Walking briskly	1	2	3	4	5	6	7
11. Walking briskly uphill or carrying groceries or other items, up a flight of stairs without stopping	1	2	3	4	5	6	7
12. Doing vigorous activities such as lifting or moving heavy furniture, running, or participating in strenuous sports like tennis or racquetball	1	2	3	4	5	6	7

Atrial Fibrillation Effect on QualiTy-of-life (AFEQT) Questionnaire

On a scale of 1 to 7, over the past 4 weeks as a result of your atrial fibrillation, how much did the feelings below bother you? (Please circle one number which best describes your situation)

	Not at all Bothered	Hardly bothered	A little bothered	Moderately bothered	Quite a bit bothered	Very bothered	Extremely bothered
13. Feeling worried or anxious that your atrial fibrillation can start anytime	1	2	3	4	5	6	7
14. Feeling worried that atrial fibrillation may worsen other medical conditions in the long run	1	2	3	4	5	6	7

On a scale of 1 to 7, over the past 4 weeks, as a result of your atrial fibrillation treatment, how much were you bothered by: (Please circle one number which best describes your situation)

	Not at all bothered	Hardly bothered	A little bothered	Moderately bothered	Quite a bit bothered	Very bothered	Extremely bothered
15. Worrying about the treatment side effects from medications	1	2	3	4	5	6	7
16. Worrying about complications or side effects from procedures like catheter ablation, surgery, or pacemakers therapy	1	2	3	4	5	6	7
17. Worrying about side effects of blood thinners such as nosebleeds, bleeding gums when brushing teeth, heavy bleeding from cuts, or bruising.	1	2	3	4	5	6	7
18. Worrying or feeling anxious that your treatment interferes with your daily activities	1	2	3	4	5	6	7

On a scale of 1 to 7, overall, how satisfied are you **at the present time** with:
(Please circle one number which best describes your situation)

	Extremely satisfied	Very satisfied	Somewhat satisfied	Mixed with satisfied and dissatisfied	Somewhat dissatisfied	Very dissatisfied	Extremely dissatisfied
19. How well your current treatment controls your atrial fibrillation?	1	2	3	4	5	6	7
20. The extent to which treatment has relieved your symptoms of atrial fibrillation?	1	2	3	4	5	6	7

Name or ID:_____

Appendix 10. Mini mental health state questionnaire

EudraCT No.: 2015-005043-13 CONFIDENTIAL WHEN COMPLETE

RATE-AF
SMMSE Worksheet

UNIVERSITY OF BIRMINGHAM | BCTU

IDENTIFYING DETAILS	
Patient initials: ☐☐☐	Trial Number: ☐☐☐☐
Date of visit: ☐☐/☐☐☐/☐☐☐☐	

TIMEPOINTS		
Please indicate below, which visit this CRF relates to:		
Baseline ☐	6 months ☐	12 months ☐

! When complete, this form should be filed in the site file and should not be sent to BCTU !

STANDARDIZED MINI-MENTAL STATE EXAMINATION (SMMSE)

Say to the patient: I am going to ask you some questions and give you some problems to solve. Please try to answer as best you can.
Further guidance on scoring this test can be found in the SMMSE work guide

QUESTION	TIME ALLOWED	SCORE
What year is this? *Accept exact answer only*	*10 seconds*	☐ /1
Which season is this? *During the last week of the old season or first week of a new season, accept either*	*10 seconds*	☐ /1
What month is this? *On the first day of a new month or the last day of the previous month, accept either*	*10 seconds*	☐ /1
What is today's date? *Accept previous or next date*	*10 seconds*	☐ /1
What day of the week is this? *Accept exact answer only*	*10 seconds*	☐ /1
What country are we in? *Accept exact answer only*	*10 seconds*	☐ /1
What county are we in? *Accept exact answer only*	*10 seconds*	☐ /1
What city/town are we in? *Accept exact answer only*	*10 seconds*	☐ /1
What is the name of this building? *Accept exact name of institution only*	*10 seconds*	☐ /1
What floor are we on? *Accept exact answer only*	*10 seconds*	☐ /1
SAY: **I am going to name three objects. When I am finished, I want you to repeat them. Remember what they are because I am going to ask you to name them again in a few minutes.** SAY the following words slowly at 1-second intervals - **ball/ car/ man**	*20 seconds*	Scored below
SAY: Spell the word **WORLD** *(you may help the person to spell the word correctly).* **Now spell it backwards** *If the person cannot spell world even with assistance, score zero. Refer to accompanying guide for scoring instructions.*	*30 seconds*	☐ /5
Now what where the three objects I asked you to remember? *Score one point for each correct answer regardless of order*	*10 seconds*	☐ /3

RATE-AF MMSE Worksheet Page 1 of 4 Version 1.0, 11 October 2016

Trial Number: ☐☐☐☐ Date of Visit: ☐☐/☐☐/☐☐☐☐

SHOW **wristwatch**. ASK: **What is this called?** *Score one point for correct response; accept 'wristwatch' or 'watch'; do not accept 'clock' or 'time', etc.*	*10 seconds*	☐ /1
SHOW **pencil**. ASK: **What is this called?** *Score one point for correct response; accept 'pencil' only; score zero for pen.*	*10 seconds*	☐ /1
SAY: **I would like you to repeat this phrase after me: No ifs, ands or buts** *Score one point for a correct repetition. Must be exact, e.g. no ifs or buts, score zero.*	*10 seconds*	☐ /1
SAY: **Read the words on the page and then do what it says**. Then hand the person the sheet with '**CLOSE YOUR EYES**' on it. *If the subject reads and does not close their eyes, repeat up to three times. Score only if subject closes eyes.*	*10 seconds*	☐ /1
HAND **the person a pencil and paper**. SAY: **Write any complete sentence on that piece of paper**. *Note: The sentence must make sense. Ignore spelling errors*	*30 seconds*	☐ /1
PLACE **design, eraser and pencil in front of the person**. SAY: **Copy this design please.** *Allow multiple tries. Wait until person is finished and hands it back. Score only for correctly copied diagram with a 4-sided figure between two 5-sided figures.*	*1 minute*	☐ /1
ASK **the person if they are right or left-handed.** Take a piece of paper and hold it up in front of the person. SAY: **Take this paper in your right/left hand (whichever is non-dominant), fold the paper in half once with both hands and put the paper down on the floor.** *Score 1 point for each instruction executed correctly:* • *Takes paper correctly in hand* • *Folds it in half* • *Puts it on the floor*	*30 seconds*	☐ /3
TOTAL TEST SCORE		☐☐ /30

! When complete, please record total test score on the relevant CRF (baseline or follow-up) !

CLOSE YOUR EYES

Trial Number: ☐☐☐☐ Date of Visit: ☐☐/☐☐☐/☐☐☐☐

Please write any sentence:

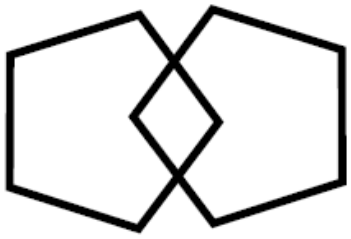
.....

.....

.....

.....

Please copy the drawing:



Appendix 11. Up-titration CRF

EudraCT No.: 2015-005043-13 CONFIDENTIAL WHEN COMPLETE

RATE-AF
Up-titration Visit Worksheet

UNIVERSITY OF BIRMINGHAM | BCTU

IDENTIFYING DETAILS	
Patient initials: ☐☐☐	Trial Number: ☐☐☐☐
Date of visit: ☐☐/☐☐☐/☐☐☐☐	

TIMEPOINTS			
Please indicate below, which visit this worksheet relates to:			
1st ☐	2nd ☐	3rd ☐	4th ☐
Is this the patient's last up-titration visit? No ☐ Yes ☐		*If yes, please organise the 24 hour tape*	

QUALITY OF LIFE QUESTIONNAIRES		
Has the patient completed the following?	SF-36	No ☐ Yes ☐
	EQ5D-5L	No ☐ Yes ☐
	AF-EQT	No ☐ Yes ☐

MEDICAL HISTORY	
Please provide details about the patients recent medical history:	
Atrial Fibrillation	Modified EHRA score: 1 ☐ 2a ☐ 2b ☐ 3 ☐ 4 ☐
	Guidance on selecting modified EHRA score: **1:** *None; AF does not cause any symptoms* **2a:** *Mild; normal daily activity not affected; patient not troubled by symptoms* **2b:** *Moderate; normal daily activity not affected; patient troubled by symptoms* **3:** *Severe; normal daily activity affected by symptoms relating to AF* **4:** *Disabling; normal daily activity discontinued*
Heart Failure	Has the patient been diagnosed with heart failure? No ☐ Yes ☐ *If yes, please complete the following:* NYHA Functional Classification: I ☐ II ☐ III ☐ IV ☐
	Guidance on selecting NYHA Functional Classification: **I** *No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnoea.* **II** *Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation or dyspnoea.* **III** *Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation or dyspnoea.* **IV** *Unable to carry out any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.*

RATE-AF Up-titration Worksheet Page 1 of 5 Version 2.0, 18 January 2018

Trial Number: ☐☐☐☐ Date of Visit: D D / M M M / Y Y Y Y

Please provide details of any oral medications that the patient is currently taking to normalise their heart rate:						
Oral medication				Current dose & frequency		
Type	Agent/ Brand	No	Yes	Dose	Units	Frequency
Digoxin		☐	☐			
β-blocker		☐	☐			
Diltiazem		☐	☐			
Verapamil		☐	☐			
Amiodarone		☐	☐			
Others (*please specify*)		☐	☐			
		☐	☐			

FOLLOW-UP PROCEDURES AND ASSESSMENTS

12-lead ECG:

Heart rate ☐☐☐ bpm	QRS duration ☐☐☐ m/s	QT interval ☐☐☐ m/s

Office blood pressure and heart rate. To be taken whilst patient is at rest, in a seated position:	
BP 1: ☐☐☐/☐☐☐ mmHg	BP 2: ☐☐☐/☐☐☐ mmHg
Radial artery heart rate: ☐☐☐ bpm	Apical heart rate: ☐☐☐ bpm

Physical examination:	
Does the patient have any signs of heart failure?	No ☐ Yes ☐
If yes, please indicate which ones below:	
Lung crepitations consistent with heart failure	No ☐ Yes ☐
Peripheral oedema	No ☐ Yes ☐
Raised jugular vein pressure	No ☐ Yes ☐
Abnormal heart sounds	No ☐ Yes ☐
Please specify:	

Anthropometric measurements:	
Weight: ☐☐☐ kg, to nearest kg	

Trial Number: ☐☐☐☐ Date of Visit: ☐☐/☐☐/☐☐☐☐

Please provide details of the patients recent (within the last 7 days) physical activity:	
During the last 7 days, how much time did the patient spend sitting on a week day?	☐☐☐☐ minutes per weekday
During the last 7 days, on how many days did the patient walk for at least 10 minutes at a time?	☐ days per week
What is the total amount of time the patient spent walking over the last 7 days?	☐☐☐☐ minutes per week
During the last 7 days, on many days did the patient undertake moderate physical activities?	☐ days per week
How much time in total has the patient spent over the last 7 days doing moderate physical activities?	☐☐☐☐ minutes per week
During the last 7 days, on how many days did the patient undertake vigorous physical activities?	☐ days per week
How much time in total has the patient spent over the last 7 days doing vigorous physical activities?	☐☐☐☐ minutes per week

Guidance on completing physical activity fields:

Sitting	*Ask the patient to think about the time they spent sitting on week days during the last 7 days. Include time spent at work, at home, while doing course work, and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television.*
Walking	*Ask the patient to think about the time they spent walking in the last 7 days. This includes at work and at home, walking to travel from place to place, and any other walking that they might have done solely for recreation, sport, exercise, or leisure.*
Moderate physical activities	*Ask the patient to think about the time they spent undertaking activities which take moderate physical effort over the last 7 days. Moderate physical activities are those that made them breathe somewhat harder than normal and may have included carrying light loads, bicycling at a regular pace, or doubles tennis. Do not include walking. Again, ask that the patient thinks about only those physical activities that they did for at least 10 minutes at a time.*
Vigorous physical activities	*Ask the patient to think about all the vigorous activities which take hard physical effort that they did in the last 7 days. Vigorous activities are those that made them breathe much harder than normal and may include heavy lifting, digging, aerobics, or fast bicycling. Ask that the patient thinks about only those physical activities that they did for at least 10 minutes at a time.*

TREATMENT COMPLIANCE

Has the patient been compliant with drugs used to control heart their rate? *Assessed by asking the participant how much of their medication they've taken*	All ☐	Some ☐	None ☐	
If some, how compliant has the patient been? *Assessed by asking the participant*	> 75 % ☐	> 50 – 75 % ☐	> 25 – 50 % ☐	≤ 25 % ☐

Trial Number: ☐☐☐☐ Date of Visit: ☐☐/☐☐☐/☐☐☐☐

ADVERSE EVENTS

Please record patient reported adverse events:

Since the last visit, has the participant been unwell or experienced any side-effects or other adverse events? No ☐ Yes ☐

If 'yes', please complete below:
If a previously recorded AE has resolved or changed since the last visit, please update the AE records.

Did the event include any of the following?

	No	Yes		No	Yes
Gastrointestinal upset	☐	☐	Dizziness	☐	☐
Blurred vision	☐	☐	Headache	☐	☐
Rash	☐	☐	Lethargy	☐	☐
Peripheral oedema	☐	☐	Upper respiratory tract symptoms	☐	☐
Symptomatic bradycardia	☐	☐	Symptomatic hypotension	☐	☐

Other (*please specify*) .....

.....

.....

.....

Has the patient stopped taking trial medication because of **adverse event(s)?** No ☐ Yes ☐

If yes, has the medication been stopped? Temporarily ☐ Permanently ☐

If medication has been stopped **permanently**, what date was the last dose of medication taken? ☐☐/☐☐☐/☐☐☐☐

If medication has been stopped temporarily, please provide dates:
Date stopped: ☐☐/☐☐☐/☐☐☐☐
Date restarted: ☐☐/☐☐☐/☐☐☐☐

If the patient has stopped taking medication for **any reason other than adverse events,** please provide details below, including the date medication was stopped:

.....

Date stopped: ☐☐/☐☐☐/☐☐☐☐

Trial Number: ☐☐☐☐ Date of Visit: ☐☐/☐☐/☐☐☐☐

Serious adverse events:

SAE: Any adverse event, reaction or unexpected adverse reaction, respectively that: Results in death; is life threatening; requires hospitalisation or prolongation of existing hospitalisation; results in persistent or significant disability or incapacity; consists of a congenital anomaly.

Since the last visit, has the participant experienced any serious adverse events? No ☐ Yes ☐

If 'yes', please complete an SAE form

TREATMENT PLAN

Please record the patient's treatment plan (select applicable):

Stay on current rate control therapy	☐
Increase current rate control therapy	☐
Reduce current rate control therapy	☐
If on β-blocker switch to alternative agent	☐

Additional therapy? ☐ *If yes, please complete the following section:*

Agent: ..... Dose: ..... Units: ..... Frequency: .....

Stop randomised treatment? ☐ *If yes, please complete the following section:*

Agent: ..... Dose: ..... Units: ..... Frequency: .....

Up-titration worksheet completed by:
You **must** have signed the trial signature and delegation log

Name: .....
(please print)

Date: ☐☐/☐☐☐/☐☐☐☐ **Signature:** .....

Appendix 12: Serious adverse event reporting form

EudraCT: 2015-005043-13 CONFIDENTIAL WHEN COMPLETE

RATE-AF
SAE Form Part 1

UNIVERSITY OF BIRMINGHAM | BCTU

! Please fax the completed form (and any relevant reports) to the RATE-AF Trial Office on 0121 415 9135 or 0121 415 9136 within 24 hours of being made aware of the SAE. !

IDENTIFYING DETAILS	
Trial No.: ☐☐☐☐	Participant initials: ☐☐☐
Date of birth: ☐☐ / ☐☐☐ / ☐☐☐☐	

REPORT DETAILS		
Is this report?	Initial ☐ Follow-up ☐	
If this is a follow-up report, has the relatedness changed as a result of new information?	No ☐	Yes ☐
If follow-up, give the SAE ref. number: (ref. no. will be provided by BCTU)	☐☐ / ☐☐☐☐	

TRIAL INTERVENTION CAUSALITY ASSESSMENT

The assessment of causality **must** be confirmed by a physician so delegated and recorded on the Delegation Log:

Causality Assessment *(tick only one)*

1) Unrelated to trial intervention	☐	Unrelated
2) Unlikely to be related to trial intervention	☐	
3) Possibly related to trial intervention	☐	Related
4) Probably related to trial intervention	☐	
5) Definitely related to trial intervention	☐	

If boxes 3-5 in the 'Causality Assessment' have been ticked, please give reasons why you consider the event to be related to the intervention:

.....

.....

.....

.....

REASON FOR REPORTING SAE

Please refer to Section 10 in the current protocol.

Seriousness of event (please provide a response to each question)	No	Yes	Details
Death	☐	☐	If Yes, date of death: DD/MMM/YYYY
Life threatening event	☐	☐	
In-patient hospitalisation or prolongation of existing hospitalisation	☐	☐	If Yes, **Initial** ☐ **Prolonged** ☐ If **Yes**, number of days spent in hospital as result of the SAE (or number of days estimated prolongation): ☐☐☐
Persistent or significant disability/incapacity; or consists of a congenital anomaly or birth defect	☐	☐	
Other pertinent medical reason for reporting?	☐	☐	If **Yes**, please specify: .....

DETAILS OF EVENT

Date of onset:	DD/MMM/YYYY
Date it became serious	DD/MMM/YYYY
Date resolved:	DD/MMM/YYYY

Brief description of event/ diagnosis e.g. relevant investigations, treatment:

.....

.....

.....

.....

.....

In the investigators opinion, is this a cardiovascular-related event? *As judged by a medically qualified doctor* *If yes, please complete a Cardiovascular Event Form*	No ☐ Yes ☐ Not assessable ☐
CTCAE category Please refer to coded list at the end of this form	☐☐

RANDOMISED TREATMENT ALLOCATION

Please indicate which trial treatment the patient was randomised to:

Investigational Medicinal Products	Tick if yes	Start date (dd/mmm/yyyy)	Stop date (dd/mmm/yyyy)	Tick if continuing	Dose	Unit	Freq.
Digoxin	☐	DD/MMM/YYYY	DD/MMM/YYYY	☐			
Bisoprolol	☐	DD/MMM/YYYY	DD/MMM/YYYY	☐			

Has the patient taken any other drugs which may interact with the intervention or influence the SAE? No ☐ Yes ☐

CONCOMITANT MEDICATION

Please provide details of other medication the patient was taking/ given immediately prior to the event:

- A list of concomitant medications taken within the 7 days prior to the event will be requested at a later date and should be documented on the Concomitant Medication Continuation Sheet

Drug Name (generic name)	Indication	Start date (dd/mmm/yyyy)	Stop date (dd/mmm/yyyy)	Tick if continuing	Dose	Unit	Freq.	Route*
		DD/MMM/YYYY	DD/MMM/YYYY	☐				
		DD/MMM/YYYY	DD/MMM/YYYY	☐				
		DD/MMM/YYYY	DD/MMM/YYYY	☐				
		DD/MMM/YYYY	DD/MMM/YYYY	☐				
		DD/MMM/YYYY	DD/MMM/YYYY	☐				
		DD/MMM/YYYY	DD/MMM/YYYY	☐				
		DD/MMM/YYYY	DD/MMM/YYYY	☐				
		DD/MMM/YYYY	DD/MMM/YYYY	☐				
		DD/MMM/YYYY	DD/MMM/YYYY	☐				
		DD/MMM/YYYY	DD/MMM/YYYY	☐				
		DD/MMM/YYYY	DD/MMM/YYYY	☐				
		DD/MMM/YYYY	DD/MMM/YYYY	☐				
		DD/MMM/YYYY	DD/MMM/YYYY	☐				
		DD/MMM/YYYY	DD/MMM/YYYY	☐				
		DD/MMM/YYYY	DD/MMM/YYYY	☐				
		DD/MMM/YYYY	DD/MMM/YYYY	☐				

**Select from the following for medication route: Buccal (buc), Inhaled (INH), Intramuscular (IM), Intravenous (IV), Nasal (NAS), Oral (PO), Rectal (PR), By ear (AU), Topical (top), Subcutaneous (SQ), Sublingual (SL), Transdermal (TD), Unknown (UKN)*

RELEVANT MEDICAL HISTORY

Please list any underlying comorbidities or lab tests or investigations that are relevant. Where investigations or lab tests are appended please ensure patient identifiable details are replaced with the trial number. If none, please indicate 'nil relevant':

.....

.....

.....

.....

.....

DETAILS OF PERSON REPORTING

Signature of Person Reporting: **(you must have signed the site delegation log)**	Name of Person Reporting: ..... Position: .....
Tel:	Email: .....
Fax:	Date: ☐☐/☐☐☐/☐☐☐☐
Signature of Principal Investigator: (if not reported by PI)	

Please fax the completed form (and any relevant reports) to the RATE-AF Trial Office on **0121 415 9135** or **0121 415 9136** within **24 hours** of being made aware of the SAE.

Coded Reference Lists

Common Terminology Criteria for Adverse Events (CTCAE Coded List)

Code	Category	Code	Category
1	Allergy/Immunology	15	Infection
2	Auditory/Ear	16	Lymphatics
3	Blood/Bone Marrow	17	Metabolic/Laboratory
4	Cardiac Arrhythmia	18	Musculoskeletal/Soft Tissue
5	Cardiac General	19	Neurology
6	Coagulation	20	Ocular/Visual
7	Constitutional Symptoms	21	Pain
8	Death	22	Pulmonary/Upper Respiratory
9	Dermatology/Skin	23	Renal/Genitourinary
10	Endocrine	24	Secondary Malignancy
11	Gastrointestinal	25	Sexual/Reproductive Function
12	Growth and Development	26	Surgery/Intra-Operative Injury
13	Haemorrhage/Bleeding	27	Syndromes
14	Hepatobiliary/Pancreas	28	Vascular

Appendix 13: Follow up CRF form

EudraCT No.: 2015-005043-13 CONFIDENTIAL WHEN COMPLETE

RATE AF

RATE-AF Follow-Up CRF

UNIVERSITY OF BIRMINGHAM | BCTU

IDENTIFYING DETAILS

Patient initials: ☐☐☐	Trial Number: ☐☐☐☐
Date of visit: ☐☐/☐☐☐/☐☐☐☐	

TIMEPOINTS

Please indicate below, which visit this CRF relates to:

6 months ☐	12 months ☐

QUALITY OF LIFE QUESTIONNAIRES

Has the patient completed the following?	SF-36	No ☐ Yes ☐
	EQ5D-5L	No ☐ Yes ☐
	AF-EQT	No ☐ Yes ☐

BLOOD TESTS

Clinical samples (all bloods to be taken non-fasted)

Test		Not Applicable	Test		Not Applicable
Sodium:	☐☐☐ mmol/L		Albumin:	☐☐ g/L	☐
Potassium:	☐☐.☐ mmol/L		Calcium:	☐.☐☐ mmol/L	☐
Urea:	☐☐.☐ mmol/L		Phosphate:	☐.☐☐ mmol/L	☐
Creatinine:	☐☐☐ micromol/L		Magnesium	☐.☐☐ mmol/L	☐
eGFR	☐☐☐ mL/min/ 1.73m^2		Hb:	☐☐☐ g/L	☐
		Not Applicable	HCT:	☐.☐☐ L/L	☐
INR:	☐☐.☐	☐			

CONCOMITANT MEDICATIONS

Please indicate whether the patient is on any of the following medication:

Anticoagulant medication: No ☐ Yes ☐

If known, please indicate which medication(s) the patient is on from the list below:

Warfarin ☐	Acenocoumarol ☐	Phenindione ☐	Dabigatran ☐	Edoxaban ☐	Rivaroxaban ☐	Apixaban ☐

Trial Number: ☐☐☐☐ Date of Visit: ☐☐/☐☐/☐☐☐☐

Antiplatelet medication: No ☐ Yes ☐				
If known, please indicate which medication(s) the patient is on from the list below (choose as many as required):				
Aspirin ☐	Dipyridamole ☐	Prasugrel ☐	Clopidogrel ☐	Ticagrelor ☐
Antihypertensive medication: No ☐ Yes ☐				
If known, please indicate which medication(s) the patient is on from the list below (choose as many as required):				
ACEi ☐	ARB ☐	Thiazide/loop diuretics ☐	CCBs ☐	Alpha-blockers ☐
Aldosterone antagonists ☐	Others ☐ *Please specify:*			
Inhalers for airway disease: No ☐ Yes ☐				

MEDICAL HISTORY

Please provide details about the patients recent medical history:

Atrial Fibrillation	Modified EHRA score: 1 ☐ 2a ☐ 2b ☐ 3 ☐ 4 ☐ ***Guidance on selecting modified EHRA score:*** **1:** *None; AF does not cause any symptoms* **2a:** *Mild; normal daily activity not affected; patient not troubled by symptoms* **2b:** *Moderate; normal daily activity not affected; patient troubled by symptoms* **3:** *Severe; normal daily activity affected by symptoms relating to AF* **4:** *Disabling; normal daily activity discontinued*
Heart Failure	Has the patient been diagnosed with heart failure? No ☐ Yes ☐ *Please complete the following:* NYHA Functional Classification: I ☐ II ☐ III ☐ IV ☐ ***Guidance on selecting NYHA Functional Classification:*** **I** *No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnoea.* **II** *Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatique, palpitation or dyspnoea.* **III** *Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation or dyspnoea.* **IV** *Unable to carry out any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.*

Has the patient undergone any cardiovascular procedures since their last study visit? No ☐ Yes ☐

If yes, please retrieve a relevant summary of procedure and file in the investigator site file

Trial Number: ☐☐☐☐ Date of Visit: ☐☐/☐☐☐/☐☐☐☐

Pacemaker

Has the patient had a pacemaker fitted since their last trial visit? No ☐ Yes ☐

If yes, please complete the following section:

When was the pacemaker fitted? ☐☐☐/☐☐☐☐

Type of pacemaker: Single chamber ☐ Dual chamber ☐

Is the pacemaker? Pacing only ☐ ICD ☐ CRT-D ☐ CRT-P ☐

Is the patient pacemaker dependant? No ☐ Yes ☐

Reason for implantation: Bradycardia ☐ Atrial fibrillation (e.g. with tachy-brady syndrome) ☐ Heart failure ☐ Syncope ☐

Please provide details of any oral medications that the patient is currently taking to normalise their heart rate:

Oral medication				Current dose & frequency		
Type	Agent/ Brand	No	Yes	Dose	Units	Frequency
Digoxin		☐	☐			
β-blocker		☐	☐			
Diltiazem		☐	☐			
Verapamil		☐	☐			
Amiodarone		☐	☐			
Others (*please specify*)		☐	☐			
		☐	☐			

FOLLOW-UP PROCEDURES AND ASSESSMENTS

12-lead ECG:

Heart rate ☐☐☐ bpm | QRS duration ☐☐☐ ms | QT interval ☐☐☐ ms

Office blood pressure and heart rate. To be taken whilst patient is at rest, in a seated position:

BP 1: ☐☐☐/☐☐☐ mmHg | BP 2: ☐☐☐/☐☐☐ mmHg

Radial artery heart rate: ☐☐☐ bpm | Apical heart rate: ☐☐☐ bpm

Calculate heart rate from at least 30 second measurement

Trial Number: ☐☐☐☐ Date of Visit: ☐☐/☐☐☐/☐☐☐☐

Physical examination:	
Does the patient have any signs of heart failure?	No ☐ Yes ☐
If yes, please indicate which ones below:	
Lung crepitations consistent with heart failure	No ☐ Yes ☐
Peripheral oedema	No ☐ Yes ☐
Raised jugular vein pressure	No ☐ Yes ☐
Abnormal heart sounds	No ☐ Yes ☐
Please specify:	

Anthropometric measurements:	
Weight: ☐☐☐ kg, to nearest kg	Waist circumference: *taken above the hip bones in expiration, to nearest cm* ☐☐☐ cm

Please provide details of the patients recent (within the last 7 days) physical activity:	
During the last 7 days, how much time did the patient spend sitting on a week day?	☐☐☐☐ minutes per weekday
During the last 7 days, on how many days did the patient walk for at least 10 minutes at a time?	☐ days per week
What is the total amount of time the patient spent walking over the last 7 days?	☐☐☐☐ minutes per week
During the last 7 days, on many days did the patient undertake moderate physical activities?	☐ days per week
How much time in total has the patient spent over the last 7 days doing moderate physical activities?	☐☐☐☐ minutes per week
During the last 7 days, on how many days did the patient undertake vigorous physical activities?	☐ days per week
How much time in total has the patient spent over the last 7 days doing vigorous physical activities?	☐☐☐☐ minutes per week

Guidance on completing physical activity fields:

Sitting	*Ask the patient to think about the time they spent sitting on week days during the last 7 days. Include time spent at work, at home, while doing course work, and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television.*
Walking	*Ask the patient to think about the time they spent walking in the last 7 days. This includes at work and at home, walking to travel from place to place, and any other walking that they might have done solely for recreation, sport, exercise, or leisure.*
Moderate physical activities	*Ask the patient to think about the time they spent undertaking activities which take moderate physical effort over the last 7 days. Moderate physical activities are those that made them breathe somewhat harder than normal and may have included carrying light loads, bicycling at a regular pace, or doubles tennis. Do not include walking. Again, ask that the patient thinks about only those physical activities that they did for at least 10 minutes at a time.*
Vigorous physical activities	*Ask the patient to think about all the vigorous activities which take hard physical effort that they did in the last 7 days. Vigorous activities are those that made them breathe much harder than normal and may include heavy lifting, digging, aerobics, or fast bicycling. Ask that the patient thinks about only those physical activities that they did for at least 10 minutes at a time.*

Trial Number: ☐☐☐☐ Date of Visit: ☐☐/☐☐☐/☐☐☐☐

Six-minute walk test:	
Did the patient undergo the six-minute walk test? No ☐ Yes ☐	
Total time spent undertaking the test: ☐:☐☐ min/s	Total distance covered: ☐☐☐ m, to nearest m
Was the test stopped prematurely? No ☐ Yes ☐	
If yes, please specify the reason the procedure was stopped (choose one option):	Breathlessness ☐ Fatigue ☐ Claudication ☐ Chest pain ☐ Other pain e.g. joint ☐ Other (please specify) ☐ .....
Peak heart rate: ☐☐☐ bpm	

Mini mental state examination (please refer to RATE-AF Worksheet). Record only the total test score on this CRF:
MMSE total test score: ☐☐/30

TREATMENT COMPLIANCE

Has the patient been compliant with drugs used to control heart their rate? All ☐ Some ☐ None ☐
Assessed by asking the participant how much of their medication they've taken

If some, how compliant has the patient been? > 75 % ☐ > 50 – 75 % ☐ > 25 – 50 % ☐ ≤ 25 % ☐
Assessed by asking the participant

ADVERSE EVENTS

Please record patient reported adverse events:

Since the last visit, has the participant been unwell or experienced any side-effects or other adverse events? No ☐ Yes ☐

If 'yes', please complete below:
If a previously recorded AE has resolved or changed since the last visit, please update the AE records.

Did the event include any of the following?

	No	Yes		No	Yes
Gastrointestinal upset	☐	☐	Dizziness	☐	☐
Blurred vision	☐	☐	Headache	☐	☐
Rash	☐	☐	Lethargy	☐	☐
Peripheral oedema	☐	☐	Upper respiratory tract symptoms	☐	☐
Symptomatic bradycardia	☐	☐	Symptomatic hypotension	☐	☐

Trial Number: ☐☐☐☐ Date of Visit: ☐☐/☐☐☐/☐☐☐☐

Other (*please specify*) .....

.....

.....

.....

Has the patient stopped taking trial medication because of **adverse event(s)?** No ☐ Yes ☐

If yes, has the medication been stopped? Temporarily ☐ Permanently ☐

If medication has been stopped **permanently**, what date was the last dose of medication taken? ☐☐/☐☐☐/☐☐☐☐

If medication has been stopped temporarily, please provide dates:
Date stopped: ☐☐/☐☐☐/☐☐☐☐
Date restarted: ☐☐/☐☐☐/☐☐☐☐

If the patient has stopped taking medication for **any reason other than adverse events,** please provide details below, including the date medication was stopped:

.....

Date stopped: ☐☐/☐☐☐/☐☐☐☐

Serious adverse events

SAE: Any adverse event, reaction or unexpected adverse reaction, respectively that: Results in death; is life threatening; requires hospitalisation or prolongation of existing hospitalisation; results in persistent or significant disability or incapacity; consists of a congenital anomaly.

Since the last visit, has the participant experienced any serious adverse events? No ☐ Yes ☐

If 'yes', please complete an SAE form

Follow-Up CRF completed by:
You **must** have signed the trial signature and delegation log

Name: .....
(please print)

Date: ☐☐/☐☐☐/☐☐☐☐ **Signature:** .....