Risk Stratification in patients with Heart failure and in patients with Implantable Cardioverter - Defibrillators

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ABSTRACT

Heart failure is a very common medical condition with significant mortality and morbidity. Patients hospitalised with heart failure are at high risk of death in the short term and patients with chronic heart failure in the community are also at a high risk of death in the medium to long term. It is difficult to accurately identify those at a higher risk of death as current methods of risk stratification lack both sensitivity and specificity. The available treatments for prevention of sudden death in patients with heart failure such as Implantable Cardioverter Defibrillators (ICD) are expensive and do not abolish the risk of sudden death completely. Hence it is necessary to improve risk stratification methods in patients with heart failure and identify factors predicting mortality in those patients with ICD protection.

This thesis first describes a series of studies examining the clinical factors that predict increased risk of short-term mortality in patients with a recent hospitalisation for heart failure. These include examination of patient demographics, clinical history and examination, blood tests, electro-cardiographic and echo-cardiographic variables and medication. Based on these variables, I have formulated a simple scoring system to predict short term mortality in hospitalised patients with heart failure. This score was validated in a prospective study of contemporary heart failure population with a recent hospital admission. The relationship of cholesterol and risk of death in heart failure was examined in detail.

Then, the utility of Holter monitoring and signal averaged electro cardiograms (SAECG) for risk stratification were examined based on the prognostic value of abnormalities found by these tests in patients with chronic heart failure.

Finally patients with heart failure deemed at high risk of sudden death and had ICDs implanted were studied and factors predicting shocks and mortality were identified. Two separate studies were done, first in population who had ICDs mainly for secondary prevention and the second in patient population who had ICDs exclusively for primary prevention.

From these studies, I have identified those clinical characteristics that are associated with high risk of death in patients with acute and chronic heart failure and those associated with death in patients with heart failure after ICD implantation.

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CHAPTER 1. INTRODUCTION

1.1 EPIDEMIOLOGY OF HEART FAILURE

The life-time risk of developing heart failure is one in five with little evidence of variation in prevalence between industrialised countries in Europe and North America.[1, 2] Heart failure affects 1-2% of the population, causes about 5% of medical admissions amongst adults and complicates a further 10-15%.[3, 4] Heart failure is usually due to left ventricular systolic dysfunction (LVSD) secondary to ischaemic heart disease or dilated cardiomyopathy. Many cases have preserved LV systolic function with clinical signs of heart failure. This is a poorly understood but common phenomenon, especially in elderly women with stiff hypertrophied ventricles.[5] The mechanism is believed to be due to diastolic dysfunction and it can be paroxysmal.[6] Lack of understanding may reflect the fact that the problem is predominantly vascular rather than cardiac in origin.

1.2 MORTALITY IN HEART FAILURE

Heart failure has a poor prognosis. One third or more of patients will die within 6 months of diagnosis and the annual mortality amongst 6 month-survivors is 10-15%.[7] Patients with heart failure due to left ventricular systolic dysfunction have a worse prognosis. In the CHARM study, patients with LVSD had an annual mortality of 9% whereas those with preserved LV systolic function had an annual mortality of only 4%.[5, 7-10]

1.3 MODE OF DEATH IN HEART FAILURE

Most patients with heart failure will die suddenly or from progressive heart failure. More patients with left ventricular systolic dysfunction will die suddenly before developing heart

failure rather than dying subsequent to a diagnosis of heart failure.[11] The risk of dying from progressive heart failure is particularly high in the early period after diagnosis with over half of all progressive heart failure deaths in the first six months occurring within one month after diagnosis.[12] Sudden death has generally been perceived to be primarily an arrhythmic problem. Whilst this is usually the case, a substantial proportion could be due to other causes such as stroke or myocardial infarction. Acute myocardial infarction is associated with sudden cardiac death due to an arrhythmia and is also likely to precipitate a worsening in progressive heart failure and subsequent death. [13, 14]

1.3.1 Frequency of sudden death versus progressive heart failure death

Randomised clinical trial data showed that in general, sudden death constituted 50% of all deaths, progressive heart failure death accounting for 30% and the rest being non cardiac deaths, although this was not consistent.[15-23]

1.3.2 Functional status and mode of death

The relative importance of these modes of death varies with functional class. Patients in NYHA class II are more likely to die suddenly rather than progressing to end-stage heart failure, whereas patients with NYHA class III or IV are likely to die of progressive deterioration of pump failure (i.e. from a low cardiac output). In the CONSENSUS-I trial heart failure patients with NYHA IV symptoms had progressive heart failure as the mode of death in 65% of cases.[24] In the RALES study which recruited patients with severe symptoms in the prior six months, approximately 50% of all deaths were due to progressive heart failure.[25]

1.3.3 Prediction of sudden cardiac death (SCD) in heart failure

Predicting sudden death in CHF patients remains a big challenge.[26-29] There is no reliable variable which can accurately predict the risk of sudden death. [30] Several risk variables (non sustained ventricular tachycardia, heart rate variability, left ventricular ejection fraction, ECG markers etc) have been shown to predict the risk of SCD in various studies done mainly in post myocardial infarction patients.[31-40] As a result, a number of tests have been developed but the relatively low positive predictive accuracy of these tests adversely affects their usefulness.[41, 42] At best, alone or in combination, these tests reach a positive predictive accuracy of 30%. Although this may not be a problem when low-cost, effective therapy free from adverse effects is possible; unfortunately this is not the case. Moreover many of these studies were done in the pre optimal treatment era when most patients were not on beta blockers and many not on ACE inhibitors. SPECT (single photon emission computed tomography) has been proposed recently as a risk stratifying tool in patients with left ventricular ejection fraction > 35%.[43, 44]

A study by Huikuri et al, has found that these arrhythmia risk variables, particularly the autonomic and standard ECG markers, have limited predictive power in identifying patients at risk of sudden death after acute myocardial infarction, in the beta blocking era.[45] It is not known whether this is applicable to all heart failure patients. Other studies have previously found these methods useful. It is necessary to establish whether these methods are useful in risk stratification for heart failure patients in the current era of optimal treatment with beta blockers and ACE inhibitors.

Recently, imaging of the cardiac sympathetic innervation with ^{123}I-*m*IBG imaging has been found to be helpful in assessing the extent of myocardial injury and remodelling associated with ischemic and nonischemic cardiomyopathy, thus identifying the substrate associated with SCD.[46] The criteria for clinical use are being developed and this may emerge as useful tool for risk stratification in the near future.

1.3.4 Risk prediction models in acute heart failure

In contrast to risk prediction in patients with chronic heart failure where there are extensive data, the prediction of risk of death during hospitalisation for acute heart failure has not received the same amount of attention. There are several reasons which include lack of consistent definition of acute decompensated HF, limited prospective data and use of different statistical techniques to analyse these data. Hence the available evidence in this area is largely derived from major heart failure registries around the world. In the following chapter risk prediction tools derived from three large worldwide registries of patients hospitalised with heart failure are reviewed.

1.4 CURRENT TREATMENT OF HEART FAILURE AND IMPACT ON MODE OF DEATH

Standard treatment for heart failure due to left ventricular systolic dysfunction includes angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), beta-blockers and aldosterone antagonists. The use of ACEI and beta blockers in patients with heart failure is associated with a reduction in deaths due to both sudden death and progressive heart failure.[20, 22, 47, 48] Similarly, aldosterone antagonists have been reported to reduce both progressive heart failure death and sudden death. [18, 25] The use of device therapies such as implantable-cardioverter defibrillators have been reported

to reduce the risk of sudden death.[49-51] Cardiac resynchronisation therapy reduces the incidence of both sudden death and progressive heart failure deaths.[52]

1.5 IMPLANTABLE CARDIOVERTER DEFIBRILLATORS (ICD)

Large multi centre trials (MADIT, MUSTT & AVID) have shown that Implantable Cardioverter Defibrillators (ICD) are beneficial in patients at high risk of sudden cardiac death (SCD) i.e. with a history of myocardial infarction and reduced systolic LV function.[53] ICD therapy was shown to prolong life in this high risk population with heart failure. Although all of these trials included a significant number of patients with heart failure, they did not address specifically the role of ICD in heart failure patients. However, the SCD-HeFT study demonstrated a 7.2% absolute decrease in mortality after 5 years in heart failure patients who had ICD, when compared to those treated with amiodarone.[54]

Despite these advancements in drug and device therapy, there has been no major impact on sudden death. A survey from USA showed that there was only a minor decline in the absolute number of sudden cardiac deaths in the 1990s (unselected population), despite a large increase in the number of ICD implants over the same time.[55] Despite 25 years of technical advances in ICD therapy, ICD-unresponsive SCD remains a problem and pooled analysis of randomised trials indicates a crude rate of ICD-unresponsive SCD of 5%, which comprises about 30% of cardiac deaths.[56] Meta-analyses of RCTs showed that ICD therapy is associated with a relative risk reduction of SCD of approximately 60%, far less than the greater than 90% efficacy that many expect.[57] A critical appraisal by an expert

group suggested that the scientific community might have overestimated the benefits of ICD.[58]

1.6 NEED FOR RISK STRATIFICATION

ICDs prolong life but are expensive. Analyses from 8 randomised trials showed that the use of an ICD was projected to add between 1.01 and 2.99 quality-adjusted life-years (QALY) and between US$68,300 and US$101,500 in cost.[59] It is likely that no more than one patient in 10 will have a life-saving defibrillation over a 2-3 year period, as the annual rate of appropriate shock therapy in the SCD-HeFT trial was 5.1%[60]. In other words 90 out of 100 patients receiving a device do not benefit and may be harmed. In the same trial, the median survival after an appropriate shock was only 168 days.[61] Hence the ICD prolonged life only by 6 months.

With increasing numbers of patients surviving a myocardial infarction but left with LV systolic dysfunction, potential candidates for ICD therapy constitute a large population. Hence, patient selection is now a major issue and it is important to identify those patients at a higher risk of death, hence more likely to derive benefit from ICDs. Inappropriate patient selection is likely to cause more harm due to ICD.

In patients who are at high risk of death despite having an ICD are more likely to benefit from a palliative medical management rather than from the ICD. In other words an ICD would not prolong life in these patients although it is indicated as per guidelines. A retrospective study of device therapy in end stage heart failure found that CRT-D implantation in heart failure patients needing inotropes, did not improve survival.[62, 63]

In patients at the other end of the spectrum (i.e. at a very low risk of death) an ICD is likely to result in harm and should be avoided.

1.7 OUTLINE OF THIS THESIS

Based on the above principles, I have conducted a series of experiments as detailed in the following chapters.

1.7.1 Euro Heart Failure Survey

The Academic Cardiology Department at the University of Hull holds the core data collected from the Euro Heart Failure Survey. I had utilised these data to

- identify factors predicting mortality in patients hospitalised with heart failure,
- study the utility of Electrocardiogram (ECG) to detect and determine the severity of left ventricular dysfunction and
- study the relation between cholesterol and risk of death.

1.7.2 Euro Heart Failure Risk Score

Based on the above studies, I had formulated the Euro Heart Failure Risk score to estimate the risk of death in patients hospitalised with heart failure using few simple clinical variables. I then examined the applicability of this score to a contemporary population by conducting a study in the Liverpool Heart and Chest Hospital in the year 2010.

1.7.3. Hull Life Lab programme

The Hull LifeLab® is a large, longitudinal epidemiologically-based cohort study of patients with heart failure. Patients in this cohort receive optimal medical diagnosis and therapy and attend for regular follow-up visits with regular investigation including symptoms, signs and quality of life score, physical examination, ECG, Echo and neuro-endocrine measurements such as brain natriuretic peptide. These patients were recruited to undergo 24 hour ECG monitoring and Signal Averaged ECG recordings. I then examined the relation between the abnormalities on these tests and mortality.

1.7.4. ICDs in Heart Failure

Finally I have studied patients who had ICDs and identified those factors that were associated with increased risk of mortality. Two separate groups were studied; the first group had ICDs mainly for secondary prevention and the second group for primary prevention.

CHAPTER 2. REVIEW OF RISK PREDICTION MODELS IN ACUTE HEART FAILURE DERIVED FROM LARGE HEART FAILURE REGISTRIES

2.1. INTRODUCTION

Heart failure (HF) is a serious condition, a leading cause of hospitalisation in persons older than 65 years and is associated with significant morbidity and mortality. Although there has been reduction in in-hospital mortality over the last 15 years, there has not been any major improvement in 30 day mortality and hospital re-admission rates have increased.[64, 65] The huge impact of hospitalisations due to heart failure on health care systems has led to research to identify those patients who are at high risk in order to target them for intense therapy or move on to palliative care if appropriate.

There are lot of data in the literature regarding those factors which are associated with higher risk of mortality in outpatients with chronic heart failure. These variables include demographic characteristics, clinical severity of HF, ventricular function, ventricular dyssynchrony, renal function, haematology, neuro-hormonal activation, pulmonary function, and hemodynamics. However the prediction of risk of death during hospitalisation for acute heart failure has not received the same amount of attention. There are several reasons which include lack of consistent definition of acute decompensated HF, limited prospective data and use of different statistical techniques to analyse these data. Hence the available evidence in this area is largely derived from major heart failure registries around the world. In this chapter, risk prediction tools derived from three large worldwide registries of patients hospitalised with heart failure are reviewed.

2.2 EFFECT MODEL

The Enhanced Feedback for Effective Cardiac Treatment (EFFECT) study was a retrospective study of 4031 community based patients presenting with heart failure at multiple hospitals in Canada between 1997 and 2001.[66] The patients included were those newly admitted with a primary diagnosis of heart failure and the study excluded those who had developed heart failure complicating the hospital admission. The derivation cohort comprised of 2024 patients and the validation cohort had 1407 patients. The multivariable predictors of 30 day and 1 year mortality are given in table 2.1. A heart failure risk scoring system was derived from these variables (table 2.2). Patients with very low-risk scores ($\leq$ 60) had a mortality rate of 0.4% at 30 days and 7.8% at 1 year. Patients with very high-risk scores (>150) had a mortality rate of 59% at 30days and 78.8% at 1 year.

This is a simple model meant to give guidance for health care providers during the early stages of hospitalisation with heart failure. It is based on simple clinical observations which could be readily obtained in the community; age, blood pressure and respiratory rate. Blood tests consisted of simple biochemistry comprising blood urea nitrogen and serum sodium concentration. It should be noted that this model is independent of ventricular function, as echocardiography is not immediately available in many settings.

The EFFECT model takes into consideration of the co-morbidities which include dementia, cirrhosis, chronic obstructive airways disease, cerebrovascular disease and cancer. Dementia and cirrhosis score more points than other co-morbidities.

Table 2.1: The multivariable predictors of 30 day and 1 year mortality in the EFFECT model.*

Variable	30 day model		1 year model	
	OR (95% CI)	P value	OR (95% CI)	P value
Age, y (per 10-unit increase)	1.7 (1.45–1.99)	< .001	1.61 (1.45-1.77	< .001
Systolic BP, mm Hg (per 10-unit increase)	0.84 (0.8-0.88)	< .001	0.88 (0.85-0.9)	< .001
Respiratory rate, breaths/min (per 5-unit increase)	1.23 (1.12-1.36)	< .001	1.15 (1.08-1.24)	< .001
Sodium < 136 mEq/L	1.53 (1.14–2.05)	.005	1.46 (1.19-1.80)	<.001
Hemoglobin < 10g/dl	NA	NA	1.37 (1.05-1.78)	.02
Urea Nitrogen, mg/dl (per 10-unit increase)	1.55 (1.42-1.71)	<.001	1.49 (1.39-1.60)	<.001
Cerebrovascular disease	1.43 (1.03-1.98)	.03	1.36 (1.08-1.71)	.01
Dementia	2.54 (1.77-3.65)	<.001	2.00 (1.47-2.72)	<.001
Chronic obstructive pulmonary disease	1.66 (1.22-2.27)	.002	1.41 (1.13-1.75)	.003
Hepatic cirrhosis	3.22 (1.08-9.65)	.04	5.80(2.23-15.11)	<.001
Cancer	1.86 (1.28-2.70)	.001	1.85 (1.4-2.43)	<.001

Table 2.2: EFFECT Risk Scoring system.*

Variable	No of points	
	30 - day score	**1- year score**
Age, y	+ Age (in years)	+ Age (in years)
Respiratory rate/m (min 20; max 45)	+ Rate /m	+ Rate /m
Systolic BP (mm Hg)		
>180	-60	-50
160 – 179	-55	-45
140 – 159	-50	-40
120 – 139	-45	-35
100 – 119	-40	-30
90 – 99	-35	-25
<90	-30	-20
Urea nitrogen (maximum 60 mg/dl)	+ level (in mg/dl)	+ level (in mg/dl)
Sodium <136 meq/l	+10	+10
Cerebrovascular disease	+10	+10
Dementia	+20	+15
Chronic obstructive pulmonary disease	+10	+10
Hepatic cirrhosis	+25	+35
Cancer	+15	+15
Hemoglobin <10g/dl	NA	+10

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The EFFECT model is unique that it not only predicts in-hospital and short term mortality, but also intermediate term mortality at 1 year. However, this model is not very specific to heart failure as too much emphasis is given for the co-morbidities, which themselves indicate poor prognosis even when they are considered on their own. The other disadvantage is that the main determinant of adverse prognosis in heart failure, i.e. the severity of LV systolic dysfunction is not included. Thus the EFFECT model predicts adverse outcome based on the "general" health status of heart failure patients rather than based the actual severity of heart failure.

2.3 ADHERE MODEL

The Acute Decompensated Heart Failure National Registry (ADHERE) model is based on data collected from 65,275 patient episodes of hospitalisation with a primary diagnosis of acute decompensated HF in 263 hospitals across the USA.[67] This model is intended as a "clinical risk prediction tool" for in-hospital mortality.

The predictors of in-hospital mortality were determined from an initial derivation cohort consisting of 33,046 hospitalisations and a validation cohort consisting of subsequent 32, 229 hospitalisations. The mean age was 72.5 years and 52% were female. 58% had coronary artery disease. 46% had preserved left ventricular systolic function. In-hospital mortality was similar in both the derivation (4.2%) and validation (4.0%) cohorts.

These data were subjected to classification and regression tree (CART) analysis. This is an empirical statistical technique based on recursive partitioning analysis helpful in setting up clinical decision rules. Using this technique, 39 clinical variables were analysed. The best single predictor of mortality was high levels of blood urea nitrogen (BUN) (15.35 mmol/l)

followed by low systolic blood pressure (SBP <115 mm Hg) on admission and then by high levels of serum creatinine (> 243 μmol/l). On multivariate logistic regression analysis, BUN level, SBP, heart rate and age were the most significant mortality risk predictors.

The final "tree" generated by the CART analysis is given in figure 2.1 with mortality rates from derivation and validation cohorts indicated. The branch points in this tree permit patient stratification into 5 risk groups (low, intermediate 1, 2, & 3 and high). The mortality risk varied accordingly from 2.1% to 21.9% with statistically significant differences between all groups except between intermediate risk groups 2 and 3.

The ADHERE model has shown that three simple admission clinical and laboratory variables, namely systolic blood pressure, blood urea nitrogen and serum creatinine can readily stratify patients into groups at low, intermediate and high risk for in-hospital mortality. It should be noted that 2 of the 3 variables are based on renal function. Although 39 variables including demographics, clinical and lab data such as qualitative left ventricular ejection fraction were included, they did not improve the predictive accuracy. The complex multivariable model which also included age and heart rate improved the prediction only marginally.

In summary, the renal function (BUN and creatinine) and hemodynamic status (SBP) were the two main determinants of in hospital mortality. These findings are in line with several other studies demonstrating the association of poor outcome in patients with heart failure and renal impairment. Although left ventricular function has been shown to predict mortality in other studies, it did not offer any incremental risk discrimination over renal function and SBP. Thus ADHERE CART analysis provides a practical, user – friendly and

bedside risk prediction tool. However, the disadvantage is that this model relies only on two parameters (renal function and blood pressure), one of which is highly influenced by the dosage of concomitant heart failure medication. Thus a patient who was on maximal dosage of beta blocker and ACEI is likely to have a better prognosis but may be marked as having higher risk due to a lower SBP.

2.4 OPTIMIZE-HF MODEL

OPTIMIZE-HF (Organised Program to initiate Lifesaving Treatment in Hospitalised Patients with Heart Failure) was a national hospital based registry and quality improvement program conducted in 259 hospitals across the USA in 2003-2004.[68] It used a web based registry data collection tool with process-of-care interventions that promoted evidence based therapy for eligible patients. Patients were enrolled if they were 18 years of age or older and the primary reason for admission was new or worsening heart failure or if they developed significant HF symptoms during hospitalisation.

48,612 patients were enrolled with a mean age of 73 years. 52% were women. 46% had ischaemic aetiology and LVSD was present in 49%. In-hospital mortality was 3.8%. Eighteen predictors of mortality were identified (table 2.3) and these included age, heart rate, systolic BP, serum sodium, serum creatinine and presence of LVSD. Presence of co-morbidities such as chronic obstructive pulmonary disease (COPD), peripheral vascular disease (PVD) and liver disease increased the risk of death. A risk prediction nomogram has been derived from the multivariable model and this is available on the OPTIME-HF website. From this nomogram, a score is calculated which is directly associated with the probability of in-hospital mortality.

Figure 2.1: Predictors of in hospital mortality in the ADHERE registry – Mortality in derivation (D) and validation (V) cohorts.

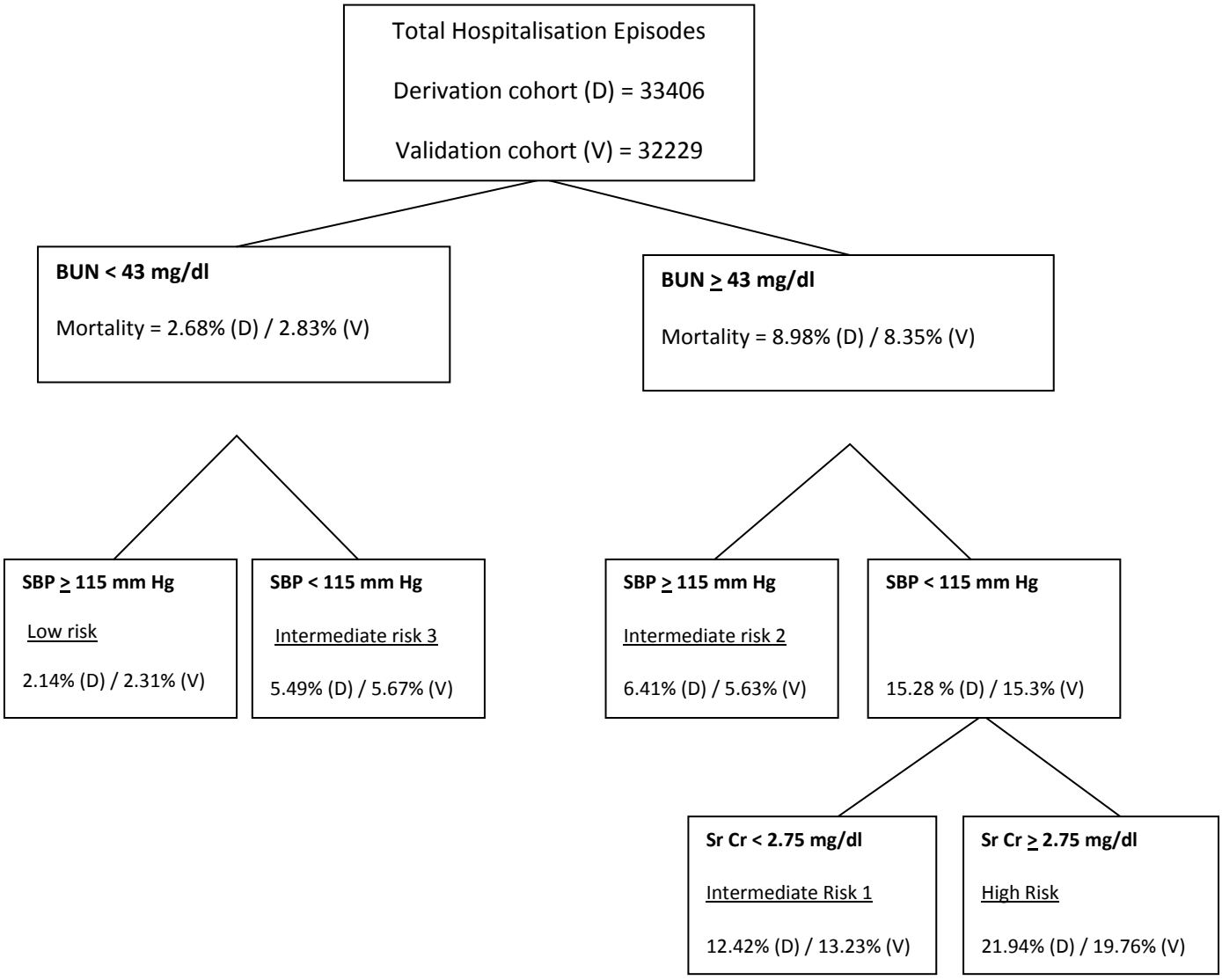


Table 2.3: Predictors of in-hospital mortality from OPTIMIZE-HF model*

Variable	OR	95% CI	p value
Serum Creatinine: per 0.3 mg/dl increase upto 3.5 mg/dl	1.18	1.16 – 1.20	< 0.0001
Systolic BP: per 10 mm Hg increase up to 160	0.83	0.80 - 0.86	< 0.0001
Age: per 10-yr increase	1.34	1.26 – 1.41	< 0.0001
Heart rate: per 10bpm increase between 65-110bpm	1.18	1.13 – 1.24	< 0.0001
Sodium: per 3 mEq/l decrease < 140 mEq/l	1.15	1.10 – 1.20	< 0.0001
Sodium: per 3 mEq/l decrease > 140 mEq/l	0.87	0.78 – 0.97	0.0100
HF as primary cause of admission	0.72	0.60 – 0.88	0.0011
Liver disease	2.33	1.43 – 3.80	0.0007
Prior CVA / TIA	1.37	1.19 – 1.58	<0.0001
Peripheral vascular disease	1.32	1.13 – 1.54	0.0003
Diastolic BP: per 10-mm Hg increase up to 100 mm Hg	0.90	0.85 – 0.95	0.0003
Hyperlipidemia	0.80	0.71 – 0.91	0.0009
Smoker within past year	0.70	0.58 – 0.85	0.0004
No known HF before this admission	0.65	0.51 – 0.85	0.004
African American	0.71	0.57 – 0.87	0.0009
LVSD	1.28	1.13 – 1.46	0.0002
Chronic obstructive pulmonary disease	1.19	1.04 – 1.35	0.0120
ACE inhibitor at admission	0.84	0.75 – 0.95	0.0056
Beta-blocker at admission	0.77	0.68 – 0.87	<0.0001

A CART analysis showed that SBP, serum creatinine (SCr), age and heart rate as the most discriminative variables for predicting in-hospital mortality. In-hospital mortality increased by 18% for every 0.3mg/dl increase in serum creatinine and by 34% for every 10-year increase in age. There was 17% reduction in in-hospital mortality with each 10-mm Hg increase up to 160 mm Hg. Figure 2.2 shows the relationship between SBP and SCr measured at admission and in-hospital mortality.

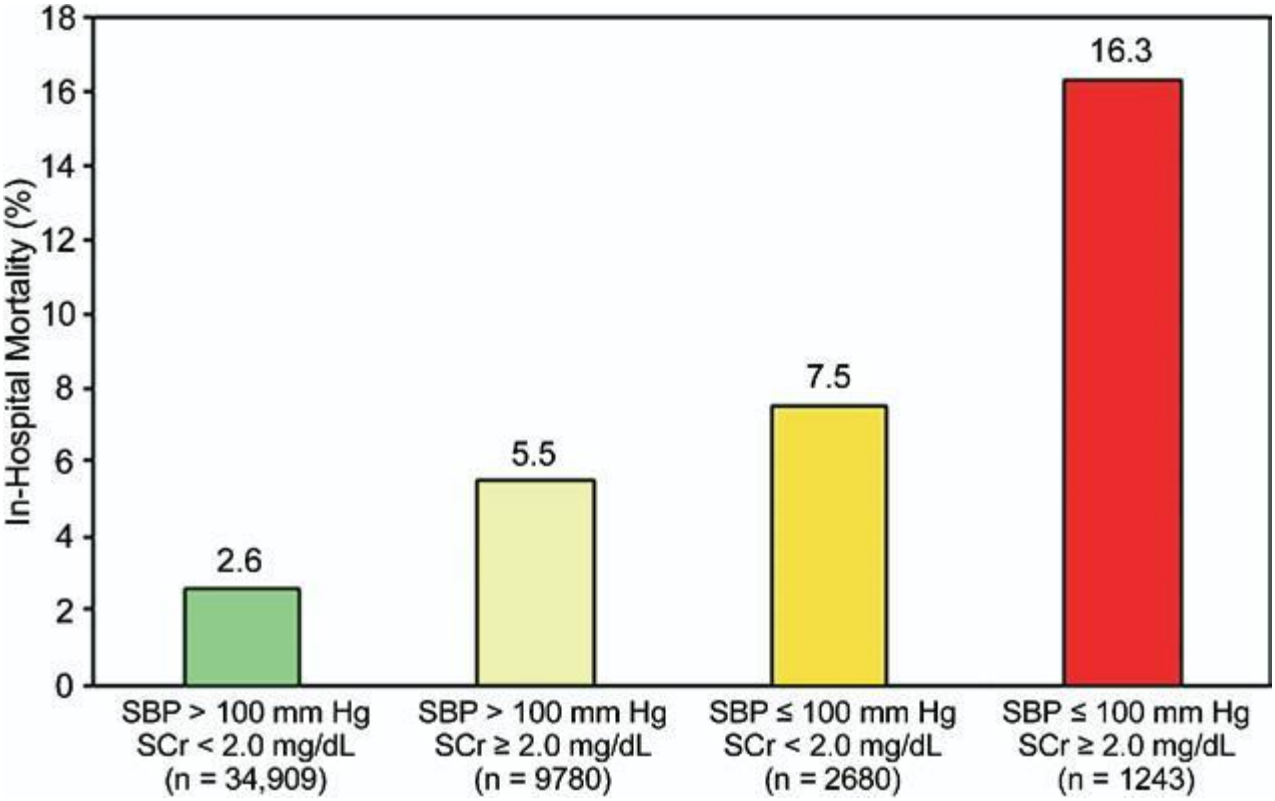
In addition, a few important observations were noted in this study. As with the EFFECT model, presence of co morbidities was predictive of mortality. However diabetes was not significantly associated with excessive risk and hyperlipidemia was associated with lower risk. Patients who were on ACE inhibitor or beta-blocker had a lower risk of in-hospital mortality.

The main disadvantages of this model are that it contains several variables and the need to consult the normogram to calculate the risk. Hence it is more complex than the other two models discussed earlier. However unlike other two models, it is comprehensive and combines the physiological variables and co morbidities with the presence of LVSD.

2.5 SUMMARY

A variety of risk prediction tools are available to predict mortality of patients hospitalised with heart failure. These are based on large heart failure registries and pooled trial data. These tools suggest that mortality can be predicted reasonably well with simple clinical data and routine investigations.

Figure 2.2: The relationship between serum creatinine (SCr) and systolic blood pressure (SBP) as measured at hospital admission and in-hospital mortality in the OPTIMIZE –HF model.*



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However these models do have some limitations. These include oversimplification of a complex pathophysiology and inability to differentiate clearly between those who will improve with aggressive treatment and those likely to die irrespective of whatever therapeutic measures being undertaken. None of these models are specific to heart failure patients as they are based on the overall well being / sickness of the patients and are influenced by the co-morbidities. Hence the results could be similar if these models were applied to any patient population with an acute medical illness.

Around half of those included in these models had preserved LV systolic function and this reflects the inconsistency between clinical diagnosis of heart failure and objective assessment of LV systolic function. Many patients might have had diastolic dysfunction which is hard to establish or right heart failure, although it cannot be excluded that some were misdiagnosed as having heart failure.

Despite these limitations, these models are likely perform well in any group of hospitalised elderly patients with a clinical syndrome of heart failure, due to their general applicability and simplicity of use in the bedside. They will help to improve resource utilisation and to target high risk patients for intense monitoring and treatment.

CHAPTER 3. METHODS OF INVESTIGATIONS, DATA HANDLING AND STATISTICS

In this thesis the various analyses were based on the results of clinical investigations in heart failure. This chapter describes those investigations, methods employed in handling the data and statistical analysis.

3.1 CLINICAL INVESTIGATIONS

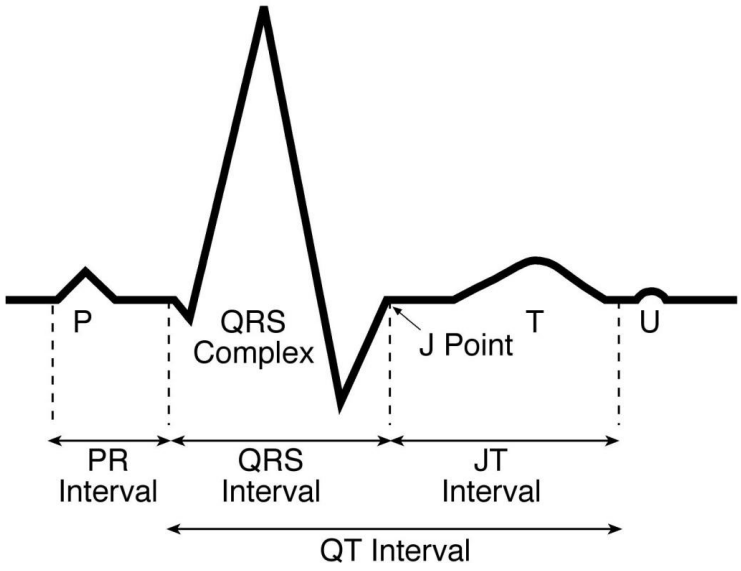
These investigations included 12 lead ECG, signal averaged ECG (SAECG), echocardiography, Holter monitoring and blood tests comprising of routine biochemical and haematological tests.

3.1.1 Electrocardiography (ECG)

A standard 12 – lead ECG was recorded for all cohorts of patients described in this thesis. In the Academic Cardiology Department of University of Hull, a GE-MAC 5000 ECG machine was used to record surface ECGs using standard 12 leads and ECG intervals (PR, RR, QRS, QT, QTc) were automatically calculated by the machine's inclusive software. QTc interval was calculated by Bazett's method.[69] Abnormalities in the ECG were reported by the attending clinician.

In the Euro Heart Failure survey, the ECGs were recorded at the participating hospitals and reported by the attending clinicians locally. All the ECGs were sent to the core lab at Hull and the ECG intervals were measured by a single observer who was blinded to other clinical data. ECG intervals were obtained from three non–infarct chest or limb leads using a digital ruler-calliper (ABSolute digimatic, Mitutoya, UK) and averaged. QTc was calculated by Bazett's method.[69] QRS prolongation was defined as QRS > 120ms. QTc prolongation was defined as QTc > 440ms.

Figure 3.1 ECG intervals



3.1.2 Signal Averaged ECG

Signal-averaged electrocardiography (SAECG) is a special electrocardiographic technique, which enables detection of low amplitude bioelectric potentials at the end of QRS complex (late potentials) which are masked by the noise due to skeletal muscle activity in standard ECG. This is done by averaging many QRS signals to remove interference, amplify the complexes, and letting finer detail of the QRS complexes appear. Late potentials on SAECG are associated with an increased risk of ventricular tachycardia, sudden death and total mortality in patients after myocardial infarction.[70-76]

3.1.2.1 Recording and analysis of SAECG

In addition to the usual 12 leads used for surface ECG, orthogonal XYZ leads are recorded by placing 4 additional electrodes at the following positions; H – back of neck, E – mid sternum (same level as V4), I – right mid axillary line (same level as V4) and M – centre of back (same level as V4). Then the recordings are averaged, filtered and combined into a

vector magnitude called the filtered QRS complex. Analysis of this filtered QRS complex includes a) the filtered QRS duration; b) the root – mean – square (RMS) voltage of the terminal 40 ms of the filtered QRS; and c) the duration that the filtered QRS complex remains < 40 μv.

In normal SAECGs, the filtered QRS duration is ≤ 114 ms, RMS voltage is ≥ 20 μv and the duration that the filtered QRS complex remains < 40 μv is ≤ 38 ms. [77]

3.1.2.2 Criteria for late potential

Late potentials are due to delayed ventricular activation, in areas of myocardial scarring, which form the substrate for ventricular arrhythmias. Patients with sustained ventricular tachycardia during electrophysiological testing are more likely to have late potentials.

Characteristics of a late potential (using a 40Hz high pass bidirectional filter) include a filtered QRS complex duration of > 114 ms; RMS voltage of < 20 μv in the last 40 ms of the filtered QRS complex and the duration that the filtered QRS complex remains < 40 μv is > 38 ms.

SAECG was considered abnormal if filtered QRS is > 114 ms and fulfilled the other two criteria for late potential, provided it was recorded in sinus rhythm and there was no evidence of bundle branch block or marked intra-ventricular conduction delay.

3.1.3 Holter monitoring

Holter monitoring was performed for 24 hours with Life Card CF digital Holter recorder (Del Mar Reynolds Medical Inc.) and data were analysed with Reynolds Pathfinder II program (Del Mar Reynolds Medical Inc.). The predominant Holter rhythm was recorded.

For patients in sinus rhythm, the heart rate variability index SDNN (standard deviation of the average R – R intervals) was recorded. All arrhythmias were captured. Frequent ventricular ectopics (VE's) were defined as > 10 VE's /hour. Non sustained ventricular tachycardia (NSVT) was defined as 3 VE's or more in succession, but less than 30 seconds in duration. Sustained VT was defined as VT occurring for more than 30 seconds.

3.1.4 Echocardiography

This was performed by the attending clinicians or technicians at the Academic Cardiology department using a GE vivid 5 machine by standard technique. Left ventricular dysfunction (LVSD) was qualitatively assessed as being none, mild, moderate and severe. Ejection fraction was measured by Simpson's method.[78]

In the Euro Heart Failure Survey, the echocardiograms were performed and reported by the participating hospitals. Left ventricular systolic dysfunction, dilatation and mitral regurgitation (MR) were assigned qualitatively (by the investigator) to one of four categories; none, mild, moderate and severe.

3.1.5 Biochemical and haematological investigations

Routine tests were carried out for all patients at the local laboratories. Hyponatraemia was defined as Na < 135 mmol/l. Hyperkalaemia was defined as K > 5 mmol/l. Renal impairment was defined as a creatinine of > 127 µmol/l in men or > 107 µmol/l in women. Hypercholesterolemia was defined as > 5 mmol/l (193 mg/dl). Hyperuricaemia was defined as uric acid > 0.42 mmol/l in men or > 0.36 mmol/l in women. The presence of anaemia was defined as Hb < 13 g/dl in men or Hb < 12 g/dl in women.

3.2 STATISTICAL METHODS

The software used for statistical tests was SPSS v16 (SPSS Inc, Chicago, Illinois, USA).

3.2.1 General data handling

I have expressed all continuous data as means with standard deviations (SD) when they are normally distributed. When normal distribution could not be assumed, medians with inter quartile range (IQR) are given. Categorical data are expressed as frequency with percentage. Group means were compared by parametric (students 't' test and analysis of variance – ANOVA) and non parametric tests (Chi-square) as applicable to the relevant data (i.e. continuous or categorical).

3.2.2 Standard Normal Distribution

In the Euro Heart Failure Survey, for the purpose of multivariable analysis, the continuous variables were transformed into a standard normal distribution (with a mean of 0 and SD of +/- 1). This was achieved by subtracting the individual values by the mean and then dividing by standard deviation. This was done so that the effect size could be directly compared with that of other continuous and categorical variables.

3.2.3 Missing Values handling

In the Euro Heart Failure Survey, I excluded those variables with > 10% missing values from multivariable models. For others, missing values were replaced with the series mean. For echocardiographic variables, another category of "no echo" was added when the patient had not had an echocardiogram, thus keeping sample size same for all variables included in the logistic regression models.

3.2.4 Logistic regression

Logistic Regression is one of the most commonly used statistical techniques biomedical research.[79] This technique was employed for both univariate and multivariable analysis in most of the studies described in this thesis.

3.2.4.1 Predictive modelling

Logistic regression is a type of predictive model that can be used when the target variable is a categorical variable with two categories (such as, alive/dead) and the independent variables are continuous, categorical, or both. The relationship between predictor variables and an outcome variable is estimated similar to linear regression, but the difference is that in logistic regression we estimate the probability that the outcome variable assumes a certain value (yes or no), rather than estimating the value itself.

3.2.4.2 Output from Logistic Regression

Logistic regression estimates odds ratios (OR) associated with each independent (predictor) variable with 95% Confidence Intervals (CI). A p value of < 0.05 (two–tailed) was considered statistically significant. The "odds" of an event is defined as the probability of the outcome event occurring divided by the probability of the event not occurring. The "odds ratio" is one set of odds divided by another. The odds ratio for a variable is defined as the relative amount by which the odds of the outcome increase (OR greater than 1) or decrease (OR less than 1) when the value of the predictor variable is increased by 1 unit.

3.2.4.3 Advantages and limitations of Logistic Regression

Unlike linear regression, logistic regression does not assume that the relationship between the independent variables and the dependent variable is a linear one. Nor does it assume

that the predictor variables are distributed normally. However, the predictor variables should not be highly correlated with one another because this could cause problems with estimation.

Although the choice of a statistical model generally depends on biological or clinical considerations in addition to statistical results, large sample sizes are required for logistic regression to provide sufficient numbers in both categories of the dependant variable. If there are many independent variables, a proportionately larger sample size is needed for accurate estimation.

3.2.5 Bootstrapping

In the Euro Heart Failure survey, I used bootstrapping to validate the multivariable model predicting mortality. The bootstrap method is used to estimate the accuracy of an estimator such as the standard error, a confidence interval, or the bias of an estimator. This technique is useful for analysing expensive-to-collect data sets where prior information is sparse, distributional assumptions are unclear, and where further data may be difficult to acquire.[80]

The bootstrap procedure involves choosing random samples with replacement from a dataset and analyzing each sample the same way. Sampling with replacement means that each observation is selected separately at random from the original dataset. So a particular data point from the original data set could appear multiple times in a given bootstrap sample. The number of elements in each bootstrap sample equals the number of elements in the original data set. The range of sample estimates obtained enables us to establish the uncertainty of the quantity we are estimating. In the Euro Heart Failure

survey, bootstrapping was done with re-sampling 1000 times to calculate the 95% confidence intervals.

3.2.6 Log Linear Analysis

Log linear analysis is an extension of the chi-square test of independence and it provides a sophisticated way of looking at cross tables. It not only tests the different factors included in the cross tables, but also tests their interactions for statistical significance. Hence, I have used this analysis in the study of ECG intervals from the Euro Heart Failure Survey.

3.2.7 Poisson Regression[81]

Poisson regression predicts not only the likelihood of an event, but also the number of events in a statistical model. I have used this model to predict the likelihood and incidence of inappropriate shocks in those patients who have heart failure and had an ICD implanted.

3.3 SUMMARY

I have used advanced statistical methods in this thesis to analyse data generated from simple clinical investigations.

CHAPTER 4. PREDICTORS OF SHORT TERM MORTALITY IN HEART FAILURE – INSIGHTS FROM THE EURO HEART FAILURE SURVEY.

4.1 INTRODUCTION

Data from large heart failure registries have demonstrated that simple clinical variables can predict mortality in patients hospitalised with heart failure.[66, 67] Some are modifiable, potential causes of deterioration and death and therefore possible targets for therapy. Others may just be markers of risk but nonetheless identify patients in need of intensive management or, palliative care. Standard treatment for heart failure includes ACE inhibitors, angiotensin receptor blockers, beta-blockers, aldosterone antagonists and, in selected patients, cardiac resynchronisation therapy and implantable defibrillators.[82] These medication and devices have improved the prognosis of heart failure but are often not implemented correctly.[83] New treatments are being developed that target specific problems such as renal dysfunction and anaemia.

4.2. EURO HEART FAILURE SURVEY

The Euro Heart Failure survey investigated whether appropriate tests were being performed and therapeutic interventions done according to European Society of Cardiology guidelines in patients hospitalised with a diagnosis of or suspected heart failure.[4, 84, 85] The Academic Cardiology Department at the University of Hull holds the core data collected from the Euro Heart Failure Survey. I had integrated these extensive data into a single dataset and analysed these data to identify factors that independently predicted short term mortality.

4.3 METHODS

4.3.1 Study Population

In the Euro Heart Failure survey, vital data were collected from 10,701 patients enrolled with suspected heart failure in 115 hospitals across Europe during 2000-2001. The detailed design of this study has been published.[4] In short, consecutive hospital discharges and deaths were screened for 6 weeks and patients enrolled if they fulfilled at least one of the following: (1) a clinical diagnosis of heart failure during admission; (2) a diagnosis of heart failure recorded at any time in last three years; (3) administration of loop diuretic for any reason other than renal failure in the 24 hours prior to death or discharge; (4) pharmacological treatment for heart failure or ventricular dysfunction in the 24 hours prior to death or discharge. Data were collected on co-morbid conditions and results of following investigations were recorded: ECG, echocardiogram, serum electrolytes, creatinine, haemoglobin (during this admission), uric acid and cholesterol (most recent results). Details of medication used any time during this admission were also recorded. Deaths within 12 weeks of admission, either in hospital or after discharge were recorded.

4.3.2 Clinical Investigations

4.3.2.1 ECG

The 12 lead ECGs were analysed in the core laboratory at University of Hull by a single observer, blinded to other results. ECG intervals were measured from three non–infarct chest or limb leads using a digital ruler-calliper (ABSolute digimatic, Mitutoya, UK) and

averaged. QTc was calculated by Bazett's method.[69] QRS prolongation was defined as QRS > 120ms. QTc prolongation was defined as QTc > 440ms.

4.3.2.2 Echocardiography

The echocardiograms were performed and reported by the participating hospitals. Left ventricular systolic dysfunction (LVSD), dilatation and mitral regurgitation (MR) were assigned qualitatively (by the investigator) to one of four categories; none, mild, moderate and severe.

4.3.2.3 Blood Tests

The results of routine blood tests were recorded and were considered abnormal if outside the laboratory reference range, as defined in the previous chapter.

4.3.3 Statistical Analysis

The clinical, laboratory, ECG and echocardiographic variables were subjected to univariate analysis by binary logistic regression to predict death within 12 weeks of admission and odds ratios (OR) with 95% confidence intervals (CI) were calculated. A p value of < 0.05 (two–tailed) was considered statistically significant. Those variables with a p value of < 0.001 on univariate analysis were included in a multivariable stepwise logistic regression model. The continuous variables were transformed into a standard normal distribution (with a mean of 0 and SD of +/- 1). Odds ratios were calculated per unit change in standard deviation. Those variables with > 10% missing values were excluded from multivariable model. For others, missing values were replaced with series mean. For echo

variables, another category of “no echo” was added, thus keeping sample size same for all variables. This model was validated by bootstrapping (resample = 1000).

A risk score to predict mortality was derived by using the simple variables obtained from the multi variable model. Statistical analysis was carried out using SPSS v16 (SPSS Inc, Chicago).

4.4 RESULTS

4.4.1. Death

Vital status was available for 10,701 patients at 12 weeks after admission. 1404 (13%) had died during this period. Most patients fulfilled three or more enrolment criteria, 84% of patients had a diagnostic label of heart failure and only 10% were enrolled solely because they received loop diuretics, as previously reported.[84] Of 1,603 patients who were not enrolled with a diagnostic label of heart failure, 145 (8.3%) died, compared to 1259 (14.1%) of 7,694 patients with a reported diagnosis of heart failure ($p<0.001$ on univariate analysis).

4.4.2 Clinical Investigations

The results of routine laboratory tests were available for 92% (9833) of patients and abnormalities were common, especially anaemia and renal dysfunction (table 4.1). ECGs were available for 83% (n = 8863) of patients, 18% of which showed atrial fibrillation and 27% of which showed a QRS interval >120msec. Echocardiography results were available for 65% (n = 6993) of patients, 71% of which showed LVSD and 27% showed moderate or severe MR. In the investigator’s opinion major valve disease was present in 23% of

patients. The mean (SD) ejection fraction in the four qualitative categories of LVSD were as follows: no LVSD – 62 (8) %, mild LVSD – 50 (7) %, moderate – 41 (7) % and severe 27 (8) %. Most patients were treated with a diuretic with about two thirds of patients taking ACE inhibitors and one third on beta-blockers.

4.4.3 Univariate analysis

On univariate analysis (table 4.1), four variables were associated with an odds ratio >2.0 of dying, hyponatraemia, renal impairment, need for IV inotropic agents and hyperkalaemia, whilst the upper confidence limit was >2.0 for anaemia (1.9; 1.7-2.1) and severe MR (1.7; 1.3 – 2.2). Treatment with ACE inhibitors (0.4; 0.4-0.5), angiotensin receptor blockers (0.3; 0.2-0.5), beta blockers (0.5; 0.4-0.5), nitrates (0.8; 0.7-0.9), anti-thrombotics (0.6; 0.5-0.7) and lipid lowering drugs (0.3; 0.3-0.4) were associated with a better prognosis. Patients who were on loop diuretics (1.5; 1.3 – 1.8) or intravenous inotropic agents (5.1; 4.4 – 6.0) had a worse prognosis.

4.4.4 Multivariable analysis

Multivariable analysis (table 4.2) was performed with the following variables, included in the model; sex, presence of severe LVSD, mitral regurgitation, major valvular disease, hypertension, atrial fibrillation, treatment with ACEI, ARB, beta-blockers, loop diuretic, thiazide diuretic, calcium channel blockers, digitalis, nitrates, inotropic agents, anti thrombotic agents, anti arrhythmic drugs and lipid regulators as categorical variables and age, sodium, potassium, cholesterol, Hb, urea, creatinine, urate, QTc & QRS durations as continuous variables. Odds ratios were given for a change of +/- 1 SD for continuous variables and odds ratios obtained by comparing Yes vs No for categorical variables.

TABLE 4.1: Univariate Analysis by binary logistic regression predicting mortality within 12 weeks of admission with heart failure.

Variable	Descriptive Statistics *μ + SD / n (%)*	Wald Statistic	Odds Ratio (95% CI)	P value
Demographic profile (n = 10701)				
Age (years)	71 + 13	234.0	**1.7** (1.6 – 1.8)	< 0.001
Female Sex	5021 (47)	14.0	**1.2** (1.1 – 1.4)	< 0.001
Hypertension	5679 (53)	17.5	**0.8** (0.7 – 0.9)	< 0.001
Diabetes	2907 (27)	0.4	**1.0** (0.9 – 1.2)	0.537
Echocardiogram (n = 6993)				
LV dilatation	2771 (26)	0.8	**1.1** (0.9 – 1.3)	0.369
Severe LVSD	2087 (20)	32.5	**1.6** (1.4 – 1.9)	< 0.001
Moderate or severe LVSD	3736 (35)	13.9	**1.3** (1.2 – 1.6)	< 0.001
Major valve disease	2501 (23)	37.4	**1.6** (1.4 – 1.9)	< 0.001
Mild MR	2525 (24)	1.2	**0.9** (0.7 – 1.1)	0.274
Moderate MR	1453 (14)	10.6	**1.5** (1.2 – 1.8)	< 0.001
Severe MR	454 (4)	17.0	**1.7** (1.3 – 2.2)	< 0.001
ECG (n = 8863)				
Heart rate (bpm)	83 + 22	231.2	**1.6** (1.5 – 1.6)	< 0.001
QRS prolongation (> 120ms)	2360 (22)	8.2	**1.2** (1.1 – 1.4)	0.004
QTc prolongation (>440ms)	4763 (45)	16.0	**1.3** (1.1 – 1.4)	< 0.001
AF	1595 (15)	28.5	**1.5** (1.3 – 1.7)	< 0.001
Ventricular Arrhythmias	239 (2)	1.2	**1.2** (0.9 – 1.7)	0.275

Treatment profile (n = 10701)				
ACE or ARB	6995 (65)	241.3	**0.4** (0.4 – 0.5)	< 0.001
ACE (in those not on ARB)	6610 (62)	195.1	**0.4** (0.4 – 0.5)	< 0.001
ARB(in those not on ACEI)	481 (5)	13.6	**0.3** (0.2 – 0.5)	< 0.001
Beta Blocker	3944 (37)	122.3	**0.5** (0.4 – 0.5)	< 0.001
Loop Diuretic	8627 (81)	26.2	**1.5** (1.3 – 1.8)	< 0.001
Thiazide	1179 (11)	10.6	**0.7** (0.6 – 0.9)	0.001
Spironolactone	2197 (21)	2.5	**0.9** (0.8 – 1.0)	0.115
CCBlocker	2265 (21)	34.3	**0.6** (0.5 – 0.7)	< 0.001
Digoxin	3825 (36)	7.3	**1.2** (1.0 – 1.3)	0.007
Nitrates	5069 (47)	9.2	**0.8** (0.7 – 0.9)	0.002
Anti Arrhythmic agents	1574 (15)	1.6	**1.1** (0.9 – 1.3)	0.211
Aspirin / Anti Platelet drugs	5593 (52)	99.7	**0.6** (0.5 – 0.6)	< 0.001
Heparin	2682 (25)	69.5	**1.7** (1.5 – 1.9)	< 0.001
Warfarin & other coumadin drugs	2450 (23)	56.3	**0.6** (0.5 – 0.6)	< 0.001
IV Inotropic agents	767 (7)	408.9	**5.1** (4.4 – 6.0)	< 0.001
Lipid Regulators	2187 (20)	128.4	**0.3** (0.3 – 0.4)	< 0.001
Laboratory tests (n = 9833)				
Sodium < 135 mmol/l	1477 (14)	150.1	**2.4** (2.1 – 2.7)	< 0.001
Potassium > 5 mmol/l	997 (9)	96.9	**2.2** (1.9 – 2.6)	< 0.001
Renal Impairment (Cr >127µmol/l in Male ; >107µmol/l in Female)	3398 (32)	220.6	**2.5** (2.2 – 2.8)	< 0.001
Cholesterol > 5mmol/l	2768 (26)	29.8	**0.6** (0.5– 0.7)	< 0.001
Uric acid (>0.42-M 0.36-F mmol/l)	2355 (22)	0.03	**1.0** (0.8 – 1.3)	0.861
Anaemia (<13g/dl M; <12g/dl F)	4180 (39)	109.7	**1.9** (1.7 – 2.1)	< 0.001

The following factors provided independent prognostic information: increasing age, severe LVSD, serum creatinine, sodium, Hb and treatment with ACEI, beta blockers, statins, calcium channel blockers, warfarin, heparin, anti-platelet drugs and need for inotropic agents.

The relation between mortality, cholesterol and its therapy was examined further (chapter 7) and I found that low cholesterol levels carry an adverse prognosis (figure 4.1). Among those on lipid lowering therapy, the mortality was higher in those with cholesterol in the lowest and highest quintiles (figure 4.2 - U shaped relation).

4.4.5 Derivation of Risk Score

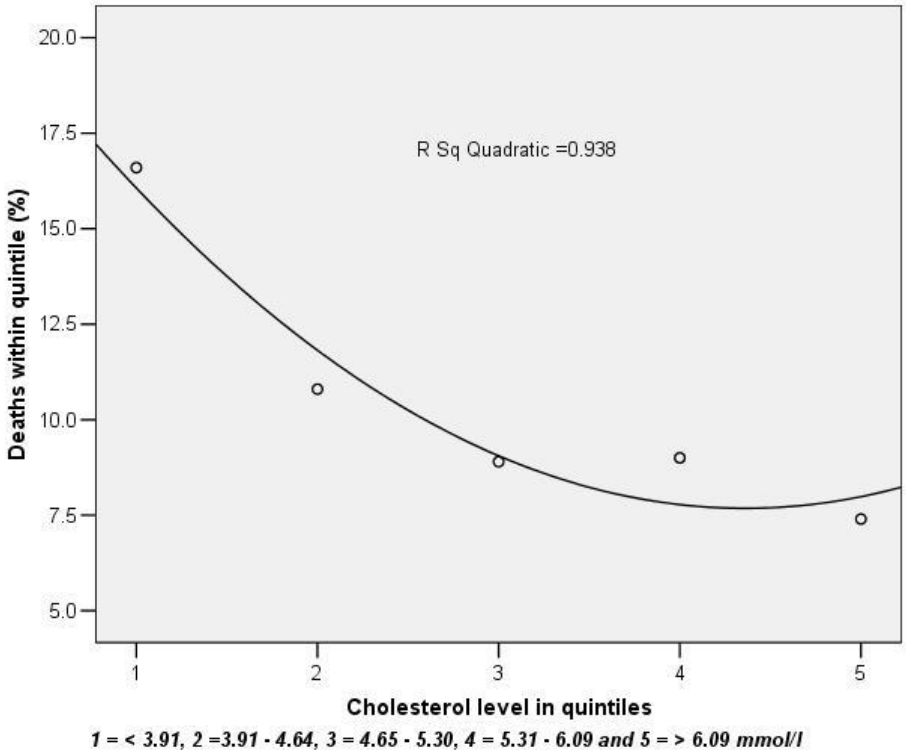
A crude risk score was derived from the variables in the multivariable model, after examining their relative ability to predict mortality. The variables were then examined in various combinations by stepwise logistic regression and the best combination that predicted mortality with the least number of variables was chosen and a score assigned based on their odds ratios.

A final risk score was obtained (**0-11**) with the following variables only: Age: 71-75 (**1**), 76 – 80 (**2**) and > 80 (**3**), LVSD: Mild (**1**), Moderate (**2**) and severe (**3**), Not on beta blocker (**2**), Not on ACEI/ARB (**2**) and elevated serum creatinine (**1**). Increase in risk score was associated with a linear increase in mortality (table 4.3 and figure 4.3) throughout the range with R square = 0.952. Other variables from multivariable analysis were excluded as they did not improve the predictive ability any further.

TABLE 4.2: Multivariable analysis predicting mortality within 12 weeks of admission with heart failure.

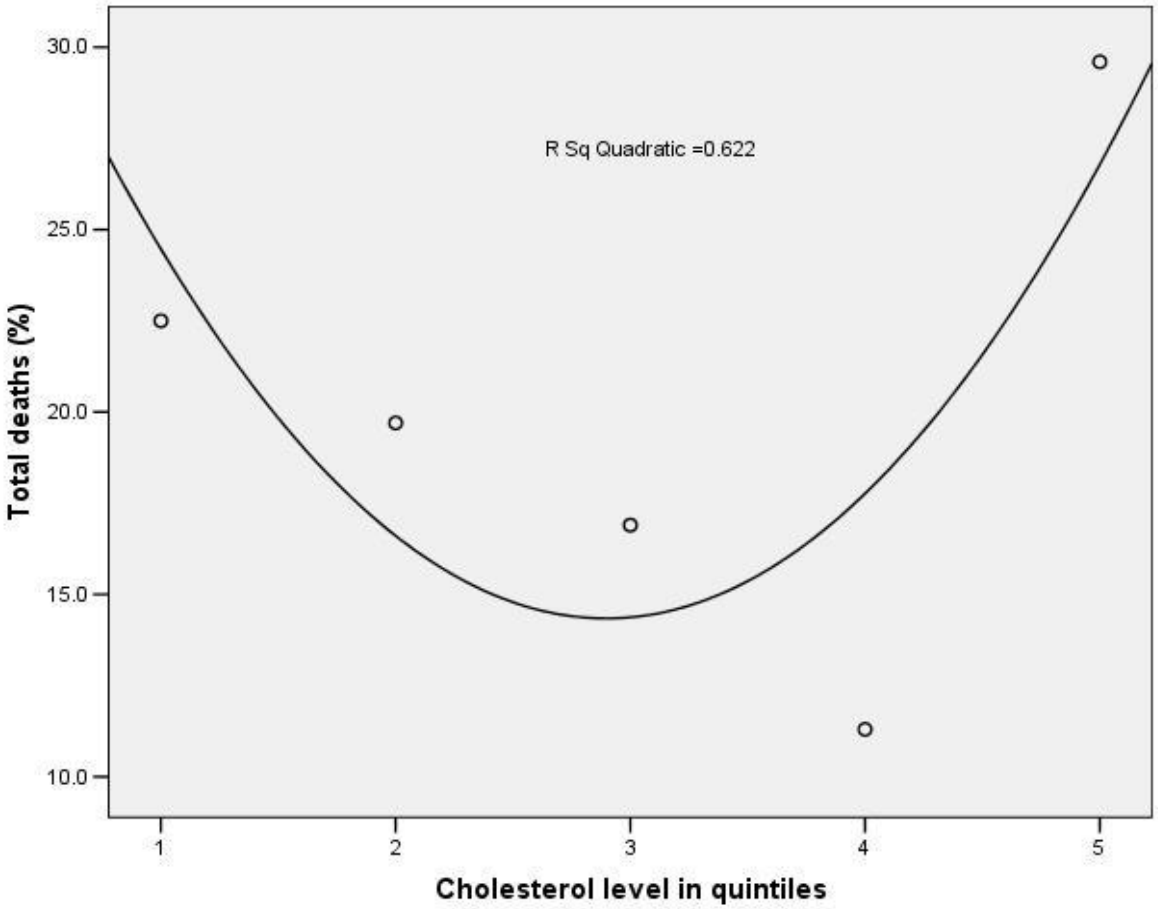
Variable	p	Wald Statistic	Odds Ratio	95% CI	Bootstrap p (97.5%)
Age* (SD = 13 years)	< 0.001	127.2	**1.5**	1.4 – 1.6	< 0.001
Haemoglobin* (SD = 2.2 g/dl)	< 0.001	27.9	**0.9**	0.8 – 0.9	0.003
Creatinine* (SD = 103 µmol/l)	< 0.001	79.2	**1.2**	1.2 – 1.3	< 0.001
Sodium* (SD = 5 mmol/l)	< 0.001	19.8	**0.9**	0.8 – 0.9	0.035
Severe LVSD (20% of all patients)	< 0.001	35.7	**1.8**	1.5 – 2.1	< 0.001
Atrial Fibrillation (15%)	0.001	10.9	**1.3**	1.1 – 1.6	0.205
ACE therapy (62%)	< 0.001	85.4	**0.5**	0.5 – 0.6	< 0.001
ARB therapy (5%)	0.001	11.9	**0.5**	0.4 – 0.8	0.073
Beta blocker therapy (37%)	< 0.001	19.1	**0.7**	0.6 – 0.8	0.006
Calcium channel blocker therapy (21%)	< 0.001	15.7	**0.7**	0.6 – 0.8	0.018
Lipid lowering therapy (20%)	< 0.001	24.8	**0.6**	0.5 – 0.7	0.001
Aspirin and anti platelet drugs (53%)	< 0.001	69.1	**0.6**	0.5 – 0.6	< 0.001
Warfarin (23%)	< 0.001	54.5	**0.5**	0.4 – 0.6	< 0.001
Heparin (25%)	< 0.001	53.1	**1.7**	1.4 – 1.9	< 0.001
Need for IV inotropic agents (7%)	< 0.001	325.4	**5.5**	4.6 – 6.6	< 0.001

Figure 4.1 Relation between cholesterol level and mortality



1 = < 3.91, 2 =3.91 - 4.64, 3 = 4.65 - 5.30, 4 = 5.31 - 6.09 and 5 = > 6.09 mmol/l

Figure 4.2. Mortality related to cholesterol level in patients on lipid lowering drugs.



1 = < 3.91, 2 =3.91 - 4.64, 3 = 4.65 - 5.30, 4 = 5.31 - 6.09 and 5 = > 6.09 mmol/l

Figure 4.3. Relation between Euro Heart Failure Risk Score and mortality at 12 weeks of hospital admission

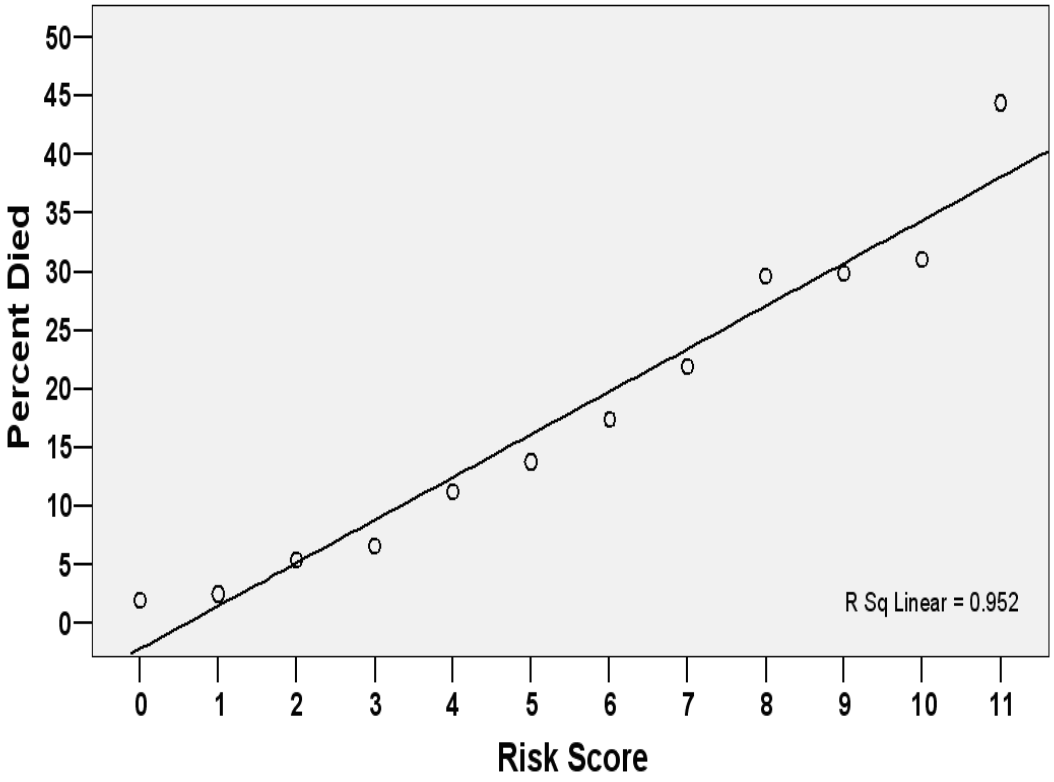


Table 4.3 Euro Heart Failure Score and mortality

Risk Score	No (%)	Died (%)
0	306 (2.9)	6 (2)
1	357 (3.3)	9 (2.5)
2	1066 (10)	58 (5.4)
3	1429 (13.4)	94 (6.6)
4	1587 (14.8)	177 (11.2)
5	1757 (16.4)	242 (13.8)
6	1281 (12)	223 (17.4)
7	956 (8.9)	209 (21.9)
8	672 (6.3)	199 (29.6)
9	157 (1.5)	47 (29.9)
10	58 (0.5)	18 (31)
11	27 (0.3)	12 (44.4)

4.5 DISCUSSION

This analysis shows that simple clinical information acquired during hospitalisation in an international clinical survey can be used to risk-stratify patients with suspected heart failure. The scoring system was able to identify patients with a 12 week mortality risk as low as 2% and as high as 44%. This information may help with planning of care. Patients at higher risk may benefit from more intense monitoring and therapy during and after hospitalization. Alternatively, patients with poor scores and symptoms recalcitrant to conventional therapy might be selected for palliative care. Some markers of risk may also be targets for therapy.

Treatment with established heart failure drugs such as ACEI and beta blockers were independently associated with a lower mortality. It is unclear whether the higher mortality in those who were not treated with these agents reflects important omissions of medical care or inability to tolerate therapy. However, important co-morbidities such as renal dysfunction that might contra-indicate such treatment were included in the model but did not eliminate treatment effects. This suggests that the association between treatment with these agents and outcome may indeed reflect their therapeutic benefits. Many patients in this survey did not receive optimal treatment, even if they had documented LVSD.[86] This survey suggests that further efforts to ensure that patients are initiated on life-saving treatment during hospitalization are required to reduce the high mortality observed during this period. A similar association was observed with nitrates, consistent with the outcomes of the V-HeFT-I and A-HeFT trials.[87, 88] It is difficult to explain the association between the use of thiazide diuretics and lower mortality as there have been concerns such as thiazide induced hypokalemia,

ventricular ectopics and elevation of uric acid levels.[89, 90] This could reflect use in younger patients with less severe LVSD or in those with hypertension, as supported by evidence from ALLHAT trial, although adjustment for these co-variates (age and hypertension) did not eliminate the effect.[91] The same could be true for calcium channel blockers, predominantly amlodipine, which were associated with lower mortality in this study.

The relation between low cholesterol level and increased mortality observed in this study (figure 4.2) has been well recognized as part of "reverse epidemiology" when low body mass index, low blood pressure and low cholesterol are associated with adverse prognosis in HF. This is thought to be due to malnutrition and inflammation in severe heart failure. [92] The higher number of deaths observed in patients with high cholesterol despite being on lipid lowering therapy (figure 4.3) was probably due to increased risk of ischemic events due to refractory hypercholesterolemia. However, the association between lipid lowering therapy and better outcome was independent of cholesterol and might be due to the pleiotropic effects of statins.[93-95] But, two large randomised trials, CORONA and GISSI-HF did not find any mortality benefit with statin therapy in patients with ischaemic heart failure.[96, 97]

Anti platelet drugs and warfarin were associated with good outcome, although two randomized controlled trials in this setting (WASH and WATCH) were unable to identify benefits.[98, 99] It is also not clear why heparin, which presumably was used mainly in patients confined to bed and only during hospitalization, was not associated with a favorable outcome. It is likely that heparin was used more often in patients who had an acute coronary syndrome, atrial

fibrillation, valve disease/replacements, factors which are associated with an independent risk of death and possibly the additional risk of bleeding contributed to increased mortality.

The association of use of inotropic drugs with poor outcome observed in this survey is consistent with previous observations that inotropic agents are associated with increased mortality, although used in severe heart failure to improve cardiac output.[100] However, this may simply be a marker of end stage decompensated HF rather than having any independent mechanistic effect on increasing the mortality. The lack of association of ventricular arrhythmias with adverse outcome is probably due to the small number of patients (2%) with documented arrhythmias. It is highly likely that the true prevalence of non sustained ventricular arrhythmias was much higher and the detection rate was low as most of these patients would not have been on continuous ECG monitoring during their admission.

Severe heart failure is commonly associated with electrolyte abnormalities such as hyponatraemia, hyperkalaemia, elevated urea and creatinine. These abnormalities can be made worse by treatment with loop diuretics. All these factors were associated with a higher mortality in this survey on univariate analysis and hyponatraemia and creatinine on the multi-variable analysis. Arginine vasopressin receptor antagonists can improve hyponatraemia and cause weight loss by aquaresis with modest improvement in symptoms and quality of life.[101] However there is no evidence that these agents reduce either short or long term mortality.

Renal impairment is an important marker of cardiovascular morbidity and mortality risk in patients with both systolic and diastolic heart failure, an observation to which this analysis provides additional support.[102-104] At present our understanding of the mechanism of this

cardio-renal syndrome is rudimentary and the question of whether renal dysfunction is a marker or mediator of death due to worsening heart failure awaits the outcome of effective therapies targeted at this problem. Adenosine is an important determinant of renal function in patients with heart failure and there were encouraging reports that adenosine A1 receptor antagonists may improve renal function in this setting.[105-109] The PROTECT pilot study showed that in 301 patients, compared with placebo treatment with rolofylline, improved dyspnea over the first 48 hours, prevented increases in serum creatinine of 0.3 mg/dL or greater on days 7 and 14, and tended to reduce 60-day mortality or readmission for cardiovascular or renal causes in patients with ADHF.[110] However, the PROTECT clinical trial failed to confirm this and there was no difference in death or readmission due to cardiovascular or renal causes at 60 days between study and placebo groups (31 vs 32%).[111] Hence the search for effective agent to treat patients hospitalised with heart failure and renal dysfunction is still ongoing.

Anaemia is common among patients with heart failure. The prevalence increases with age, increasing severity of heart failure and declining renal function, which themselves are independently associated with a poor prognosis.[112] Anaemia is consistently associated with increasing mortality and the more severe the anaemia, the higher the mortality.[113] Erythropoietin has been shown to improve the hemoglobin and exercise capacity in these patients.[114] It has been shown that that heart failure patients with persistent anemia have a worse prognosis when compared to those with resolved anemia.[115]

Non modifiable risk factors such as increasing age and female sex (on univariate analysis) were associated with an unfavorable outcome as expected and this is significant, as frail elderly population is not adequately represented in randomized trials in heart failure. It is surprising that diabetes was not associated with a worse outcome in this study, as other observational studies have demonstrated poor outcome with diabetes in hospitalised patients in heart failure.[116, 117] However this has been observed in previous similar studies such as EFFECT, ADHERE and OPTIME-HF.[66-68] It is likely that adverse impact of diabetes is limited to those with ischemic etiology as shown in a previous study. [118] In this study of 1246 patients with LV systolic dysfunction by de Groote et al, diabetes was an independent predictor of cardiovascular mortality in ischaemic patients but it was associated with a statistically significant decrease in cardiovascular mortality in non-ischaemic patients.

The findings of the SHAPE (Study group on HF Awareness and Perception in Europe) study, showed that adherence of guideline management therapies in HF was quite low among internists, geriatricians and primary care physicians.[119] For example, in this study only 39% internists/geriatricians used a β-blocker in >50% of their patients (vs. 73% of cardiologists, $p < 0.0001$). Hence findings from Euro Heart Failure Survey are truly relevant in contemporary medical practice, emphasising the need to prescribe therapies such as β-blocker and ACEI in patients with HF.

4.6 LIMITATIONS

I acknowledge that surveys, unlike randomised trials, cannot distinguish whether the association between treatment and better outcome reflects the likelihood that patients with an

intrinsically better prognosis will receive treatment or reflects a true therapeutic effect. In the survey, 16% of patients had markers of heart failure, such as use of loop diuretics, but were not given a diagnosis of heart failure and 29% of those who had echocardiograms had preserved LV systolic function. Data on physical signs such as blood pressure, admission BNP and other non conventional risk factors such as microalbuminaemia and fibrinogen were not collected in this survey and might have changed the predictive power of the variables included. Echocardiographic data were reported from individual hospitals and not validated. However any potential error due to these limitations has probably been overcome to some extent by the large patient numbers in this study.

4.7 CONCLUSIONS

Simple and readily available clinical variables and a risk score using this information may be useful to identify patients at high risk of dying during or soon after hospital discharge.

CHAPTER 5. VALIDATION OF EURO HEART FAILURE SCORE IN A CONTEMPORARY HEART FAILURE POPULATION

5.1 INTRODUCTION

The Euro Heart Failure Survey Score (table 5.1) was derived from the Euro Heart Failure Survey data as discussed in last chapter.[120] This simple score may be useful to predict short term mortality in patients hospitalised with signs and symptoms of heart failure and evidence of left ventricular systolic dysfunction. In this chapter, I have prospectively evaluated the usefulness of this score in a contemporary patient population with heart failure.

5.2 AIM

To assess the usefulness of Euro Heart Failure Survey score to predict 12 week mortality in patients admitted with symptoms or signs of heart failure associated with evidence of left ventricular systolic dysfunction on echocardiography.

5.3 PATIENTS AND METHODS

This is a prospective, observational study of consecutive patients admitted to Liverpool Heart Chest Hospital, Liverpool, UK between January – March 2010 with symptoms or signs of heart failure and found to have evidence of left ventricular systolic dysfunction. The study was prospectively approved by the R&D department of Liverpool Heart and Chest Hospital NHS Foundation Trust, Liverpool.

Baseline clinical characteristics, details of therapeutic intervention, laboratory test results and details of medication (once medical therapy has been optimised) were recorded. Vital status (alive or dead) was determined at 12 weeks, by reviewing the follow up data and a telephone call to the patient.

Table 5.1. Euro Heart Failure Survey score

Variable	**Risk Score**
Age (years)	
71 – 75	1
76 – 80	2
> 80	3
LVSD on echocardiogram	
Mild	1
Moderate	2
Severe	3
Elevated serum creatinine	1
Not on ACEI /ARB	2
Not on beta blocker	2

Minimum score = 0; Maximum score = 11

5.4 RESULTS

75 patients were enrolled during a study period of 8 weeks between 25th January 2010 and 18th March 2010. 61 (81%) were male. The mean age was 66 (SD 12) years. The primary reason for hospital admission is given in table 5.2. 69 (92%) had ischaemic heart disease, 51 (68%) had hypertension and 18 (24%) had diabetes. 19 (25%) had renal impairment. Details of medical therapy are given in table 5.3.

Table 5.2: Reason for hospital admission

Primary reason for hospital admission	**No (%)**
Worsening of heart failure	6 (8)
Angina	5 (7)
Acute coronary syndrome	6 (8)
Myocardial Infarction	53 (71)
Valvular heart disease	3 (4)
Atrial Fibrillation	1 (1)
Ventricular arrhythmia	1 (1)

Table 5.3: Details of medication

Medication	**No (%)**
Beta blockers	51 (68)
ACEI	55 (73)
ARB	4 (5)
Inotropes	7 (9)

47 patients (63%) underwent PCI and 10 (13%) had CABG. 3 (4%) had CRT implantation and 1 (1%) had CRT-D implantation. Two patients had previously undergone CRT device implantation.

In-patient echocardiography was performed in all patients. 23 (31%) had mild LV systolic dysfunction, 34 (45%) had moderate LV systolic dysfunction and 18 (24%) had severe LV systolic dysfunction.

9 (12%) patients died during the 12 week follow up period. The Euro Heart Failure Survey Score was calculated for all patients. The relationship between the score and risk of death before 12 weeks from admission is given in table 5.4. None of the patients with a risk score below 5 died. In patients with a risk score of $\geq$ 5, there was almost a linear relation between increasing score and increasing risk of death.

Table 5.4. Frequency distribution of Euro Heart Failure Survey score and death in this study population

Risk Score	**No (%)**	**Died (%)**
1	11 (15)	0 (0)
2	18 (24)	0 (0)
3	6 (8)	0 (0)
4	8 (11)	0 (0)
5	9 (12)	2 (22)
6	8 (11)	2 (25)
7	10 (13)	2 (20)
8	4 (5)	2 (50)
9	1 (1)	1 (100)

5.5 DISCUSSION

This validation study of the Euro Heart Failure Survey score shows that this score can predict the risk of death within 12 weeks of hospital admission with heart failure. A risk score below 5 indicates good prognosis with a very low risk of death in the short term whereas a score of 5 or above indicates worse prognosis with a substantial risk of death within 3 months.

This reiterates the observation from other large registries such as ADHERE, OPTIME-HF and EFFECT that a few simple clinical variables that are readily available can reliably predict short term mortality in hospitalised patients with heart failure.[66-68] Although some variables such as age are non modifiable, other variables such as renal impairment can be modified by adjusting the fluid status and the dose of diuretic medication. Left ventricular impairment may be improved at least in some patients with appropriate medical or device therapy.

While, some patients may be truly unable to tolerate beta blockers and ACE inhibitors due to severe hypotension caused by low-output cardiac state, most would be able to take these medication in at least small doses. It is still common to withhold beta blockers in patients with airways disease and decompensated heart failure. However the evidence is for the contrary. In the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization (ESCAPE) trial, consistent beta-blocker use during hospitalization of patients with decompensated heart failure was associated with a significant reduction in the rate of re-hospitalization or death within six months after discharge (odds ratio 0.27, 95% confidence interval 0.10 to 0.71; $p < 0.01$).[121] The same observation was noted in the OPTIME-HF program and in addition withdrawal of beta-blocker therapy during hospitalisation for

decompensated heart failure was associated with worse risk and propensity-adjusted mortality. [122]

A study from University of Hull has shown that the majority of patients with heart failure and obstructive airways disease can safely tolerate low dose initiation and gradual up titration of beta blockers.[123] The population with true absolute contraindication for beta blocker therapy such as bronchial asthma is like to be very small. Hence we should endeavour to get everyone on these life saving medication prior to discharge from hospital.

Finally the risk score may help us to identify those patients who are candidates for palliative therapy. As very elderly patients with severe left ventricular and renal impairment who are unable to tolerate beta blocker or ACE inhibitor therapy clearly have a grave prognosis, they are better managed by palliative therapy rather than referred for CRT or ICD therapy.

5.6 LIMITATIONS

The sample size for this study was small. However, the patient population is representative of a "real life" heart failure in-patient cohort seen every day in an average UK hospital.

5.7 CONCLUSIONS

The Euro Heart Failure Survey risk score is useful in predicting short term mortality in contemporary patients admitted to hospital with heart failure.

CHAPTER 6. CHOLESTEROL LEVEL AND RISK OF DEATH IN HEART FAILURE –A REVIEW OF LITERATURE ABOUT THE CHOLESTEROL PARADOX

6.1 INTRODUCTION

Heart failure is caused by left ventricular systolic dysfunction in more than half of the cases and this is usually due to coronary artery disease (CAD) or dilated cardiomyopathy. Hypercholesterolemia is a major risk factor for CAD. Statins (3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors) are highly effective in reducing Low Density Lipoprotein (LDL) cholesterol levels by reducing the endogenous synthesis of cholesterol. Statins have been shown to reduce mortality and morbidity in large randomised controlled trials in patients with CAD.[124-127] Retrospective analyses of data from clinical trials of other agents, database analysis and re-analysis of data from statin trials have suggested that there might be a benefit from statins in patients with heart failure.[128-133] Statins have other biological effects apart from cholesterol lowering which are of potential benefit for patients with HF.[93, 94, 134-138] Paradoxically, however, low cholesterol level is an adverse prognostic marker in patients with chronic heart failure. [139-141]

6.2 STATINS IN CORONARY HEART DISEASE

Large randomised controlled trials such as Scandinavian Simvastatin Survival Study (4S), CARE and LIPD have demonstrated that statins can reduce the rate of vascular events in patients who have actual or circumstantial evidence of stable atherosclerotic vascular disease.[125-127] The Heart Protection Study (HPS) showed that adding simvastatin to existing treatments safely

produces substantial additional benefits for a wide range of high-risk patients, irrespective of their initial cholesterol concentrations.[142] However, the evidence for primary prevention of cardiovascular events by statin therapy is not as strong as for secondary prevention. The WOSCOPS study showed that in men with moderate hypercholesterolemia and no history of myocardial infarction, treatment with pravastatin significantly reduced the incidence of myocardial infarction and death from cardiovascular causes although there was no reduction in overall mortality.[143] More recent trials have demonstrated that statins are effective in the treatment of patients presenting with acute coronary syndromes and statins are now part of standard treatment of acute coronary syndrome and stable CAD.[144, 145]

6.3 STATINS IN HEART FAILURE

Many patients with CAD have left ventricular systolic dysfunction, either symptomatic or asymptomatic, as a result of previous acute coronary events or chronic myocardial ischaemia. In these patients, statins may indirectly help to preserve left ventricular function by preventing further acute coronary events. However, all the major randomised controlled trials of statins in CAD have specifically excluded patients with heart failure by design. Retrospective analysis of 4S study found that simvastatin reduced the occurrence of heart failure in a cohort of patients with coronary heart disease without previous evidence of congestive heart failure.[146] Analyses from PROVE IT-TIMI 22 and TNT studies suggested that intensive statin therapy reduced the risk of hospitalisations with HF,[147, 148] but there is no direct evidence that statins might be useful for patients with established heart failure.

6.4 PLEIOTROPIC EFFECTS OF STATINS IN PATIENTS WITH HEART FAILURE

6.4.1 Beyond lipid lowering

Statins have many effects beyond simply lowering cholesterol (the so called pleiotropic effects) including improvement in endothelial function, reduction in oxidative stress, anti inflammatory and anti thrombotic properties, regulation of autonomic function, anti arrhythmic effects, reduction of myocardial hypertrophy, reduction of angiotensin II mediated vasoconstriction, induction of angiogenesis and reduced apoptotic rate.[135]

6.4.2 Anti-oxidant properties

Statins interact with the nitric oxide (NO) pathway and increase NO bioavailability. There is evidence from animal experiments and a few human studies to support this hypothesis.[149, 150] Oxidative stress by increased production of oxygen free radicals in patients with HF is linked with the development of myocardial hypertrophy and progression of heart failure in animal studies.[151] Statins have antioxidant properties and reduce NADPH dependent superoxide formation which may contribute to the beneficial effect of statins in HF.[152] Statins also inhibit the synthesis of isoprenoids, thereby decreasing vascular and myocardial oxidative stress.[153]

6.4.3 Anti-inflammatory actions

Increased circulating levels of tumour necrosis factor alpha (TNF-α), interleukin-6, and the soluble TNF receptors have been shown to be independent predictors of higher mortality

in patients with advanced heart failure.[154] In small studies, statins appear to interfere in

Table 6.1: Trials of statins and heart failure

Study	**Patients**	**Follow-up & outcome**	**Results** Hazard Ratios (HR) for outcome with Statin therapy
Horwich et al. [155] Observational A University centre	N=551 LVEF <= 40% Referred for HF treatment and/or transplant evaluation 45% IHD Mean age 52 ± 13 years	1 year All-cause mortality or urgent heart transplant	HR 0.44 (95% CI 0.30 – 0.67), p=0.0001 *[All-cause mortality: HR 0.52 (95% CI 0.30 – 0.90), p=0.017]*
Sola et al. [137] Observational	N=446 Stable HF treatment LVEF <=35% NYHA II/III 44% IHD Mean age (Statin) 55.4 ± 6.4 & (No statin) 53.8 ± 5.7 years.	2 years All-cause mortality HF hospitalisation	Statin 38/255 (15%) vs No statin 63/191 (33%), p<0.0001 Statin 57/255 (22%) vs No statin 72/191 (37%), p<0.0001
Anker et al. [156] Observational	1) N=3132 [397 (13%) on statin] in ELITE II Study Median FU 559 days	1-year All-cause	Statin 8% (5-10%) vs No Statin 12% (11-

Analyses of 2 studies	mean age 71.5 ± 6.8 yrs LVEF 31.1 ± 6.9% 71.3% IHD 2) N=2068 [from HF clinics in 5 EU tertiary centres, *max. n=693 from Ludwigshafen, Germany*; 705 (34%) on statin] Median FU 742 (486-1331) days Age 61.7 ± 0.3 years LVEF 30.1 ± 0.3% 58.1% IHD	mortality 1-year All-cause mortality 3 year All-cause mortality	13%), p<0.001 HR 0.61, 95% CI 0.44-0.84, p=0.0028) corrected for age, sex, LVEF, cholesterol, beta-blockers (at baseline) and BMI. Statin 7% (6-9%) vs No Statin 14% (12-16%), (χ^2 = 20.1, p < 0.0001) Statin 22% (16-29%) vs No statin (31-35%), (χ^2 = 26.6, p < 0.0001)
Foody et al. [130] Observational	N=54960 (16.7% received statin) USA -Medicare beneficiaries Between 4/1998 & 3/1999 and 7/2000 & 6/2001	All-cause mortality 1-year	HR 0.80 (95% CI 0.76 – 0.84), p<0.001

	Age >= 65 years Discharge from hospital with new HF diagnosis	 3-year	HR 0.82 (95% CI 0.79 – 0.85), p<0.001
Ray et al. [157] Observational	N=28828 (4.0% received statin) Ontario, Canada Age 66 – 85 yrs (mean 76.5 yrs) Survived > = 90 days following hospitalisation for newly diagnosed HF.	7 years Death/AMI/Stroke	 Statin 13.6 vs No statin 21.8 per 100 person-years. HR 0.72 (95% CI 0.63 – 0.83)
Kjekshus et al. [146] Retrospective analysis of 4S	N=4444 All IHD	Median 5.4 years New HF (n=412) [mean age 61 yrs] New HF and died	Simvastatin 184/2221 (8.3%) vs Placebo 228/2223 (10.3%), p<0.015 Simvastatin 47/2221 vs 73/2223, RR 0.63 (95% CI 0.44 – 0.91, p=0.014) For the 412 who developed new HF, simvastatin was associated with 19% reduction in mortality.
Mozaffarian et al. [158] Retrospective analysis of PRAISE	N=1153 LVEF <= 30% & NYHA IIIB/IV 134 (12%) had statin at baseline or during follow-up	Mean 15 months All-cause mortality	 Statin 12 vs No statin 31 deaths/100 person-years, p<0.001 [HR 0.38 (95% CI 0.23 – 0.65, p<0.001)]Statin was also associated with lower sudden death and pump failure death

Scirica et al.[148] PROVE IT – TIMI 22 Randomised trial	N = 4162 North America, Europe and Australasia. Age 58 +/- 11 yrs Recent hospitalisation with ACS	2 years HF admission 30 days after randomisation	Atorvastatin 80 mg od: 1.6% vs. Pravastatin 40 mg od: 3.1%, HR (Atorvastatin 80 mg) 0.55, (95% CI 0.35 to 0.85), p = 0.008
Khush et al.[147] TNT study Randomised trial	N = 10,001 Age 35 – 75 yrs; mean = 61 yrs Stable coronary artery disease	4.9 years Hospitalization for HF	Atorvastatin 80 mg: 2.4% vs 10 mg: 3.3% HR (Atorvastatin 80 mg) 0.74, (95% CI 0.59 to 0.94), p=0.0116
CORONA trial[96]	N = 5011 Age = 73 $\pm$ 7 (at least 60 years) NYHA II – IV LVSD secondary to IHD (EF = 0.31 $\pm$ 0.07)	32.8 months Death from CV causes, non fatal MI or stroke Death	HR (Rosuvastatin) 0.92 (95%CI 0.83 – 1.02) p = 0.12 HR (Rosuvastatin) 0.95 (95%CI 0.86 – 1.05) p = 0.31
GISSI-HF trial [97]	N = 4574 Age = 68 $\pm$ 11 (at least 18 years) Chronic heart failure of NYHA II – IV, irrespective of cause and LV ejection fraction	3.9 years Death Death or hospitalisation for CV causes	HR (rosuvastatin) 1·00 (95% CI 0·9 1·1), p=0·943. HR (rosuvastatin) 1·00 (95% CI 0·9 1·1), p=0·903

the inflammatory pathway leading to reductions in serum levels of high sensitivity C-reactive protein, IL-6, brain natriuretic peptide and TNF-α receptor II.[93, 153] Statins may have an antithrombotic effect.[159] It is also postulated that statins might reduce the vasoconstrictor effect of angiotensin II by downregulating the AT1 receptors in vascular smooth muscle cells.[135]

6.4.4 Statins and apoptosis

Animal studies suggest that statins can decrease the rate of apoptosis, thereby reducing the development of cardiac hypertrophy and fibrosis.[160] Statins may also modulate the remodelling process of heart failure through effects on matrix metalloproteinases.[161] Whether these experimental data will translate into a clinical effect is not yet clear. Sola et al showed that atorvastatin improved left ventricular function and serum markers of inflammation in non ischaemic heart failure.[162] However in the UNIVERSE trial, high dose rosuvastatin did not beneficially alter LV remodelling in patients with HF. [163]

6.4.5 Left ventricular function

Several observational studies and retrospective analyses of randomised controlled trials have suggested that statins might be beneficial in patients with heart failure (table 6.1) with and without CAD. In observational short term studies, statin use was associated with improvement in left ventricular ejection fraction, peak oxygen consumption and attenuation of adverse left ventricular remodelling even in patients who had dilated cardiomyopathy.[153, 164]

6.4.6 Anti-arrhythmic properties

Vrtovec et al showed that in a group of 40 patients who received atorvastatin 10 mg od for a period of 3 months, statin therapy increased heart rate variability (HRV), decreased QT variability, and shortened QTc interval as compared to the control group. Several small studies and analyses of the MADIT -2 and DEFINITE trials done in post MI patients have suggested that statins have anti-arrhythmic properties leading to reduction in sudden death due to arrhythmias in both ischemic and non ischemic cardiomyopathy.[165-167]

However, the majority of the evidence suggesting the benefit of statin therapy in heart failure was derived from studies with small number of patients. It is also possible that in all these observational studies, statins might have been prescribed to younger patients with less severe disease and an apparently better prognosis and statin prescribing may be a marker of better access to healthcare systems.[168]

6.5 ADVANCED HEART FAILURE AND CHOLESTEROL

Chronic heart failure may lead to a catabolic state and eventually cachexia in advanced cases.[169] The mechanisms underlying cachexia are poorly understood but appear to reflect increased resting energy consumption. There is preferential loss of fat but also a decline in lean body mass. This can only partially be explained by increased myocardial work, increased work of breathing or sympathetically mediated increases in thermogenesis by brown fat. Reduced efficiency of ATP production by mitochondria, reduced appetite, malabsorption and reduced levels of anabolic steroids may play a role. [169]

Patients with advanced heart failure have severe symptoms, a high mortality and a low cholesterol.[139] This may be due to inflammation, endotoxins, adrenergic activation, oxidative stress, tissue injury, hepatic dysfunction and cachexia.[134, 138] A similar constellation of factors is likely to be responsible for low cholesterol and the catabolic state. Higher cholesterol levels were noted to be associated with better survival in patients with chronic heart failure (figure 6.1).[139]

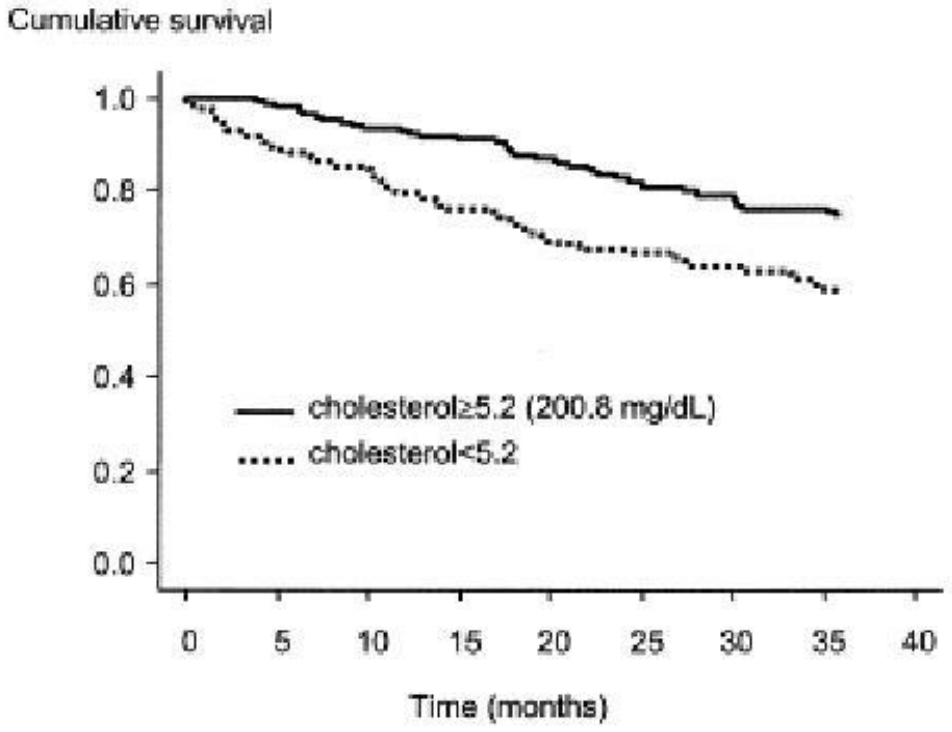
6.5.1 Reverse Epidemiology

In patients with advanced heart failure, the traditional risk factors of poor clinical outcome and mortality in the general population such as obesity, hypercholesterolemia, and high values of blood pressure have been associated with greater survival.[92, 170] The association between low cholesterol and increased mortality in HF is part of this "reverse epidemiology", which is also seen in other patient populations such as those with end stage renal disease. [171] However, the mechanism is not clear. Malnutrition, immunologic reaction and inflammation have been postulated as causes of low cholesterol and adverse prognosis.[92] Circulating lipoproteins help to neutralize bacterial lipopolysaccarides (LPS) and endotoxins which may be sources of inflammatory activation. [139]

However, low cholesterol might simply reflect more advanced illness and thus be a marker of worse prognosis rather than be a mediator. The low cholesterol may reflect reduced food intake, reduced intestinal absorption due to bowel oedema and as a result of increased metabolic stress.[172] This is supported by the observation that the possible benefit of statin therapy in heart failure may be independent of cholesterol levels.[156]

Figure 6.1: Relation between cholesterol level and mortality in a cohort of 114 patients with chronic heart failure, followed up to 3 years.

(Reproduced with permission: Rauchhaus M, Clark AL et al. JACC 2003;**42**:1933-40)



6.6 STATINS AND COENZYME Q10

Theoretically, statins might have adverse effects in patients with heart failure for several reasons. Further reductions in cholesterol and lipoproteins could have adverse consequences as noted above. Statins can affect coenzyme Q10 (CoQ10). This is a component of the mitochondrial electron transport chain and participates in aerobic cellular respiration, generating energy as ATP. The heart and the liver have high CoQ_{10} concentrations under normal circumsatnces. Statins reduce circulating levels of CoQ10, as this is transported in lower-density lipoproteins.[173, 174] COQ10 levels in serum and the myocardium have been shown to be low in HF patients, with potential for further decrease in these levels with a statin, particularly in the elderly.[175, 176] Coenzyme Q10 deficiency may exacerbate the poor contractility of myocardial cells in CHF patients because, in the setting of LV dysfunction, the myocardium demonstrates oxidative stress and coenzyme Q10 can reduce this oxidative stress and improve energy production in the mitochondria. [176-179] There have been claims that CoQ10 supplementation could improve LV function, but other studies were neutral.[179-183] CoQ10 reduction with statin therapy has been postulated as one of the mechanisms for the neutral outcome of UNIVERSE trial, where rosuvastatin did not improve adverse cardiac remodelling in chronic heart failure.[184]

6.7 DRUG INTERACTIONS

Several drug interactions have been noted between statins and other heart failure drugs. In experimental studies in humans, atorvastatin has decreased the inhibitory effect of clopidogrel on platelet aggregation.[185] Most statins have been reported to increase the anticoagulant effect of warfarin, requiring slight warfarin dosage reduction.[185] High doses of some statins (eg, simvastatin and atorvastatin) can

slightly increase the plasma concentrations of digoxin (up to 20%).[185] The mechanism of these interactions is poorly understood, but the clinical significance of these interactions is likely to be limited in routine clinical practice.

6.8 RECENT RANDOMISED TRIALS OF STATIN THERAPY IN HEART FAILURE

CORONA was a large, multi- centre trial of 5011 patients of at least 60 years of age (mean = 73 $\pm$ 7) with NYHA II-IV class symptoms and heart failure due to left ventricular systolic dysfunction (mean ejection fraction = 0.31 $\pm$ 0.07) secondary to underlying ischaemic heart disease.[96] Patients were randomised to rosuvastatin 10 mg or placebo. Median follow up was 32.8 months. Rosuvastatin did not reduce the number of deaths from any cause or the primary outcome, a composite endpoint comprising death from cardiovascular causes, non fatal myocardial infarction or stroke. As expected with a potent lipid lowering drug, there was a substantial reduction in the levels of low density lipoprotein (LDL) cholesterol and high sensitivity C reactive protein in the rosuvastatin group. There was no reduction in the number of patients hospitalised, but a significant reduction in the total number of hospitalisations was noted in the rosuvastatin group. There was no excess of muscle related or other adverse events observed with rosuvastatin.

Although the results of CORONA were neutral, a number of questions remain unanswered. A class effect of statins cannot be assumed, as learnt from experience with cerivastatin, which did not lower LDL cholesterol to the same extent as other statins, but higher incidence of rhabdomyolysis was observed.[186, 187] CORONA was limited to patients with ischaemic heart failure, already on evidence based therapy with beta blockers and angiotensin converting enzyme blockers or angiotensin receptor blockers. It is possible that some beneficial effect of rosuvastatin might be

more important in patients with non ischemic heart failure or those with heart failure and preserved left ventricular function. It is also possible that there might be a small benefit of rosuvastatin in younger patients with a better prognosis who are hence going to be followed up for a longer time, such that there was no benefit in older patients with a shorter follow up.

GISSI-HF is a multicenter, randomized, double-blind clinical trial examining the effect of n-3 polyunsaturated fatty acids and rosuvastatin at a dose of 10 mg versus placebo on the cardiovascular morbidity and mortality of patients with chronic symptomatic HF.[97] In this trial, patients with heart failure of NYHA class II-IV, irrespective of cause and left ventricular ejection fraction, were randomly assigned to rosuvastatin 10 mg daily (n=2285) or placebo (n=2289) and followed up for a median of 3.9 years. Primary endpoints were time to death, and time to death or admission to hospital for cardiovascular reasons. 29% died in rosuvastatin group and 28% died in placebo group. Rosuvastatin 10 mg daily did not affect clinical outcomes in patients with chronic heart failure of any cause.

6.9 CONCLUSIONS

Statin therapy to lower LDL cholesterol is established in the treatment of coronary artery disease. The assumption that statins will also be useful in treatment of heart failure, for which coronary artery disease is the main contributing factor, is supported by only a number of small studies. However the mechanisms for the potential benefit of statin therapy in heart failure seem different as advanced heart failure is a highly catabolic state and is associated with adverse prognostic factors such as cardiac cachexia, elevated inflammatory markers and low cholesterol levels. These studies have shown evidence of beneficial pleiotropic effects of statins in heart failure, beyond

lipid lowering. However this hypothesis was not proven in large randomised controlled trials such as the CORONA and GISSI-HF. It is still possible that statins may have role in the treatment of heart failure in patient populations different to those recruited in these trials, but they are currently not included as standard therapy in the guidelines for treatment of heart failure.

CHAPTER 7. CHOLESTEROL LEVEL AND RISK OF DEATH IN HEART FAILURE – THE FINDINGS FROM EURO HEART FAILURE SURVEY

7.1 INTRODUCTION

7.1.1 Cholesterol levels in heart failure

As reviewed in the last chapter, patients with heart failure often have low cholesterol and this is usually associated with more advanced symptoms and increased mortality.[188] It is not clear whether low cholesterol is a marker or mediator of adverse prognosis. On the other hand many patients with heart failure may have hypercholesterolemia, as this is an important cause of ischemic heart disease, the most common etiology of heart failure.

7.1.2 Causes of low cholesterol in heart failure

Low cholesterol level in heart failure may be due to reduced food intake or due to metabolic stress caused by factors such as inflammation, endotoxins, adrenergic stimuli, oxidative stress and tissue injury due to cachexia.[134, 138, 172, 189]

7.1.3. Role of statin therapy in heart failure

Statin therapy has been advocated in both ischemic and non-ischemic heart failure.[155, 156, 190] This apparent paradox of recommending a treatment that lowers cholesterol for a condition where low cholesterol is an indicator of poor prognosis is supported by the evidence for the beneficial pleiotropic effects of statins. These include reduction of inflammatory factors, improvement of endothelial function, nitric oxide potentiation, angiogenesis, improvement in autonomic function and anti arrhythmic effects.[94, 95, 149, 159, 160, 164, 166] However statins could cause harm

by diminishing the ability of lipoproteins to bind endotoxins and can reduce levels of coenzyme Q10, an important factor in mitochondrial electron transport chain.[176]

7.2. AIMS

In this study, the following were examined in a patient population hospitalised with or suspected heart failure.

1. Relation between cholesterol level and short term (12 week) mortality

2. Relation between statin therapy, cholesterol level and mortality.

7.3 METHODS

The data from Euro Heart Failure Survey, held at the University of Hull were used for this analysis. This survey was conducted on 10,701 patients, hospitalised with or suspected heart failure in 115 hospitals from 24 ESC countries during 2000-2001. Data on clinical profile, investigations and treatment were collected and vital status determined at 12 weeks after admission. Lipid lowering therapy was assumed as statin therapy in view of contemporary practice at the time of survey.

7.4 RESULTS

7.4.1 Cholesterol levels

Serum total cholesterol level (mmol/l) was available for 5729 patients. Hence this study population consists of these 5729 patients. The mean cholesterol was 5.04 mmol/l (SD 1.44). The cholesterol levels were normally distributed (figure 7.1). 1506 (26%) patients were on lipid lowering therapy, assumed with statins. Patients on lipid lowering treatment were likely to have a higher cholesterol (5.2 mmol/l vs 5.0 mmol/l; $p < 0.001$) than those who were not on treatment (table 7.1).

Figure 7.1. Distribution of cholesterol level in Euro Heart Failure Survey

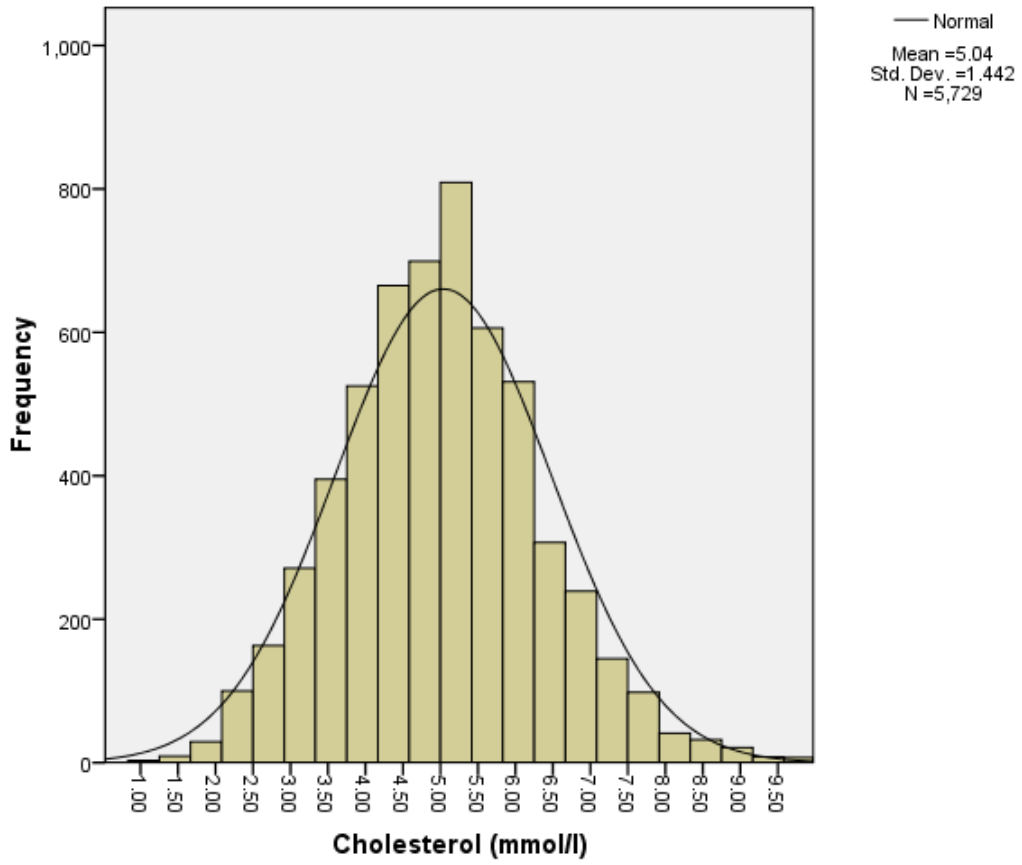


Table 7.1 Cholesterol levels (mmol/l), treatment and survival

Group	N (%)	Mean (mmol/l)	SE	p
Alive *vs* Dead				
Alive	5123 (89)	5.1	0.02	< 0.001
Dead	606 (11)	4.7	0.06	
Lipid lowering treatment				
No	4223 (71)	5.0	0.02	< 0.001
Yes	1506 (29)	5.2	0.04	

7.4.2 Mortality and cholesterol level

606 patients (11%) had died by 12 weeks from admission. These patients had lower cholesterol when compared to those who were alive at 12 weeks after admission (4.7 vs 5.1 mmol/l; $p < 0.001$) (table 7.1). Patients who died had lower cholesterol irrespective of whether they were on lipid lowering therapy or not (table 7.2). The difference was statistically significant in those not on lipid lowering therapy ($p < 0.001$) but not in the group which was on lipid lowering therapy ($p = 0.526$).

TABLE 7.2 Survival vs Lipid lowering treatment and mean cholesterol levels

Status	Total N (cholesterol)	Lipid Regulators	
		No	Yes
Total	5729 (5.0 mmol/l)	4223 (5.0 mmol/l)	1506 (5.2 mmol/l)
Alive	5123 (5.1 mmol/l)	3688 (5.0 mmol/l)	1435 (5.2 mmol/l)
Dead	606 (4.7 mmol/l)	535 (4.6 mmol/l)	71 (5.1 mmol/l)
P value	< 0.0001	< 0.0001	0.526

When the cholesterol level was divided into quintiles, I found a linear association between the level of cholesterol and risk of death. The lower the cholesterol, the higher the risk of death (table 7.3.A and figure 7.2). Among those on lipid lowering therapy, the relationship was “U” shaped (table 7.3.B and figure 7.3), as higher rates of death were observed in those with a very low cholesterol level and in those with a high cholesterol level despite lipid lowering therapy.

TABLE 7.3. Relation between cholesterol levels in quintiles and mortality

A: All patients

Vital Status		*Cholesterol - mmol/l (mg/dl) - Quintiles*					**Total**
		< 3.91 (<151)	**3.91 - 4.64 (151 - 179)**	**4.65 - 5.30 (180 – 205)**	**5.31 - 6.09 (206 – 235)**	**> 6.09 (> 235)**	
Alive	Count	1001	978	1090	1019	1046	**5134**
	% of total survivors	19.5%	19.0%	21.2%	19.8%	20.4%	100%
	Survivors within quintile	83.4%	89.2%	91.1%	91.0%	92.6%	89.4%
Dead	Count	199	119	106	101	83	**608**
	% of total deaths	**32.7%**	**19.6%**	**17.4%**	**16.6%**	**13.7%**	100%
	Deaths within quintile	**16.6%**	**10.8%**	**8.9%**	**9.0%**	**7.4%**	10.6%

B: Patients on lipid lowering drugs

Vital Status		*Cholesterol - mmol/l (mg/dl) - Quintiles*					**Total**
		< 3.91 (<151)	**3.91 - 4.64 (151 - 179)**	**4.65 - 5.30 (180 – 205)**	**5.31 - 6.09 (206 – 235)**	**> 6.09 (> 235)**	
Alive	Count	262	253	285	253	385	1438
	% of total survivors	18.2%	17.6%	19.8%	17.6%	26.8%	100.0%
	Survivors within quintile	94.2%	94.8%	96.0%	96.9%	94.8%	95.3%
Dead	Count	16	14	12	8	21	71
	% of total deaths	**22.5%**	**19.7%**	**16.9%**	**11.3%**	**29.6%**	100.0%
	Deaths within quintile	**5.8%**	**5.2%**	**4.0%**	**3.1%**	**5.2%**	4.7%

Figure 7.2. Relation between cholesterol level in quintiles and mortality within each quintile.

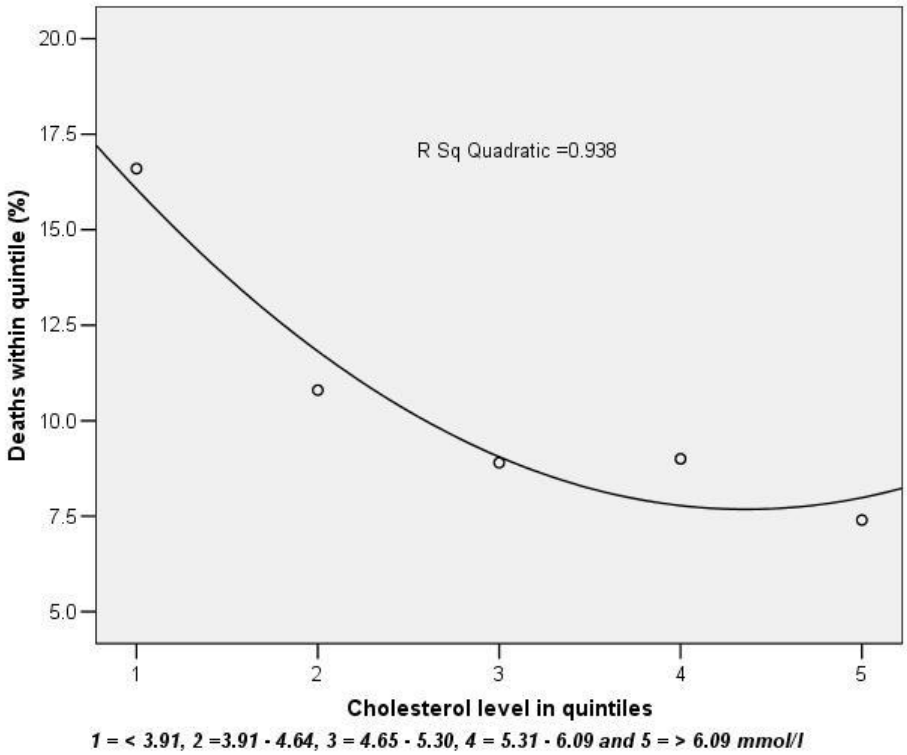
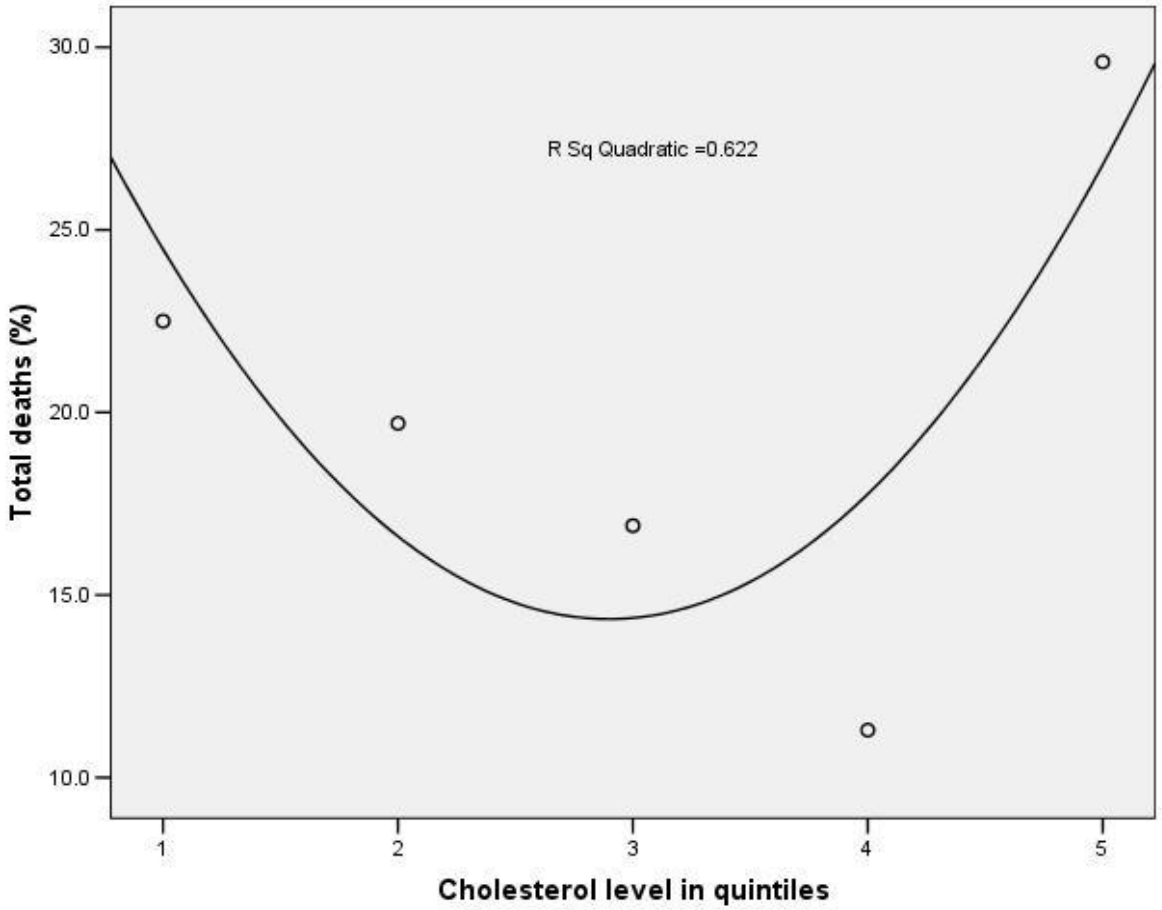


Figure 7.3. Mortality related to cholesterol level in patients on lipid lowering drugs.



1 = < 3.91, 2 =3.91 - 4.64, 3 = 4.65 - 5.30, 4 = 5.31 - 6.09 and 5 = > 6.09 mmol/l

On univariate analysis, a cholesterol level of > 5mmol/l was associated with a lower risk of death (OR 0.6, 95%CI 05 – 0.7; p < 0.001) and statin therapy was also associated with a better prognosis (OR 0.3, 95%CI 0.3 – 0.4; p < 0.001).

In a multivariable model, predicting mortality (chapter 4), statin therapy was independently associated with mortality. The following factors were included in the model; sex, presence of severe LVSD, mitral regurgitation, major valvular disease, hypertension, atrial fibrillation, treatment with ACEI, ARB, beta-blockers, loop diuretic, thiazide diuretic, calcium channel blockers, digitalis, nitrates, inotropic agents, anti thrombotic agents, anti arrhythmic drugs and lipid regulators as categorical variables and age, sodium, potassium, Hb, urea, creatinine, cholesterol, urate, QTc & QRS durations as continuous variables.

7.4.3 Cholesterol level and left ventricular systolic dysfunction.

Echocardiogram results were available for 4213 patients (out of a total study population of 5729 patients). Among these, 702 (17%) had mild LV systolic dysfunction, 1009 (24%) had moderate LV systolic dysfunction and 1320 (31%) had severe LV systolic dysfunction.

Those patients who had significant (moderate or severe) LV dysfunction had slightly lower cholesterol as compared to those without significant LV dysfunction (4.98 mmol/l vs 5.08 mmol/l; p = 0.046) (figure 7.4). When the population was divided into two groups, alive and dead, this relation with LV function was still observed (figure 7.5).

Figure 7.4. Relation between cholesterol level and LV systolic dysfunction

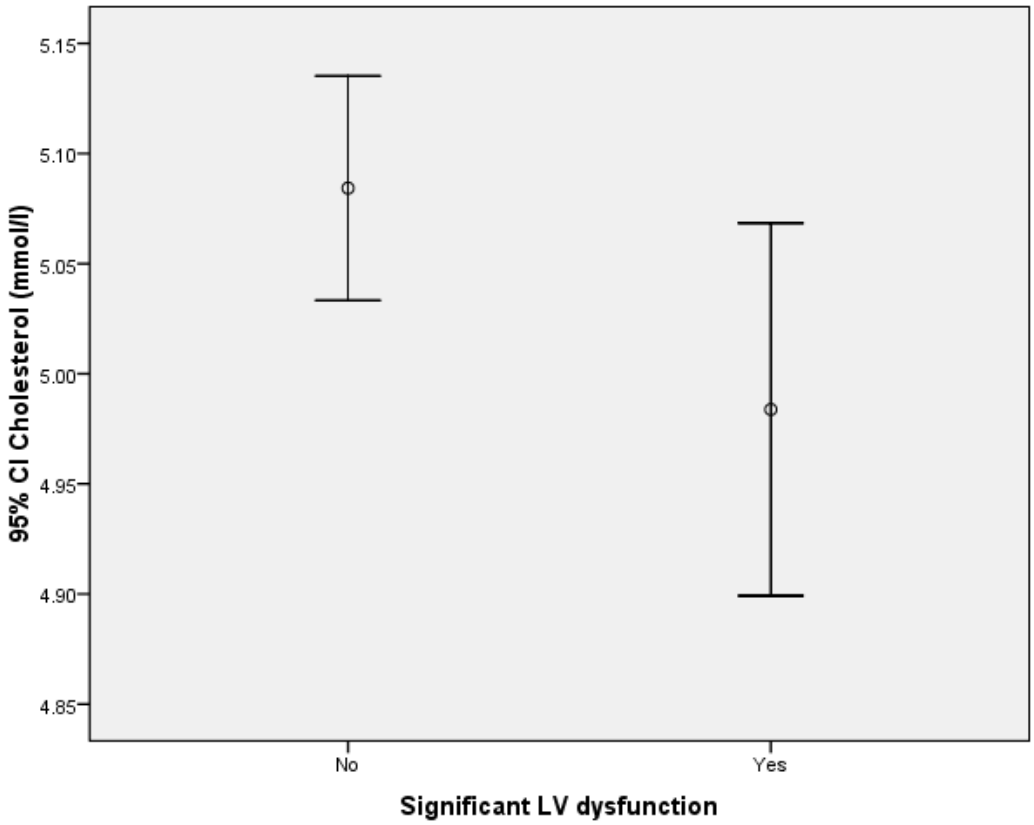
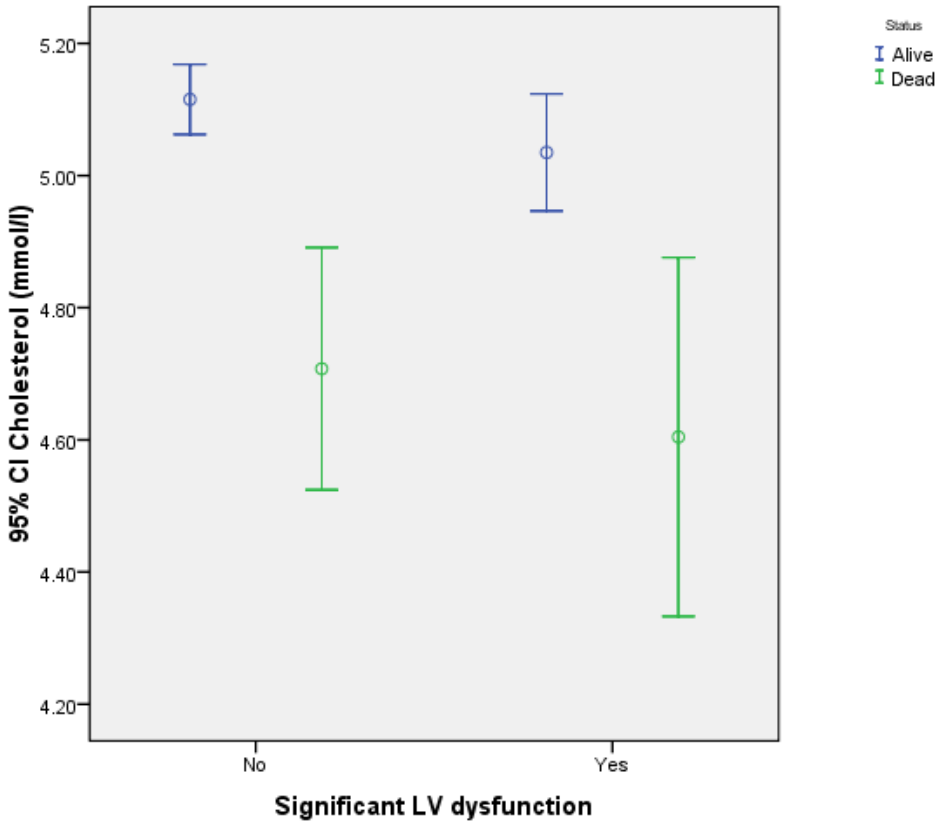


Figure 7.5 Relation between cholesterol level, LV systolic dysfunction and mortality



7.5 DISCUSSION

The findings from this large international survey demonstrate an inverse association between cholesterol level and risk of death but a better prognosis with statin therapy, thus showing the “cholesterol paradox”.

The linear association between cholesterol level and risk of death contributes further evidence to the “reverse epidemiology” in heart failure. This is most likely a part of general cardiac cachexia, such that low cholesterol is simply a marker rather than mediator of poor prognosis.

The beneficial effect of statin therapy could be explained in two ways. As discussed in the last chapter, statin therapy has been shown to have pleiotropic beneficial effects in heart failure independent of lipid lowering. The other possibility is that statins contributed to reduction in ischemic events mediated by lipid lowering in patients with hypercholesterolemia and atherosclerotic plaque stabilisation. This is supported by the observation that patients who had hypercholesterolemia despite taking statin therapy had a higher risk of death (figure 7.3 and table 7.3B). However it should be noted that only a quarter of all patients were on lipid lowering therapy as the mean cholesterol level in this population was not high (5 mmol/l).

Two large randomised trials (CORONA and GISSI-HF) did not show evidence of benefit from statin therapy in patients with heart failure, thus contradicting evidence from observational studies, including this one.[96, 97] However there remains a possibility that a statin therapy might be beneficial in some select groups, not well represented in these randomised trials.

A weak relation between cholesterol level and severity of left ventricular dysfunction has been observed, Again, it is likely that low cholesterol in patients with significant LV dysfunction is simply a marker of higher risk group.

7.6 LIMITATIONS

I acknowledge that this analysis has several limitations. This is an observational study and only total cholesterol levels were studied with no differentiation between random and fasting lipid levels. The lipid regulator therapy had been assumed as statins. However the large patient numbers would have offset some of these limitations.

7.7 CONCLUSIONS

In the Euro Heart Failure survey, there was an independent inverse association with cholesterol level and risk of death. This relationship was linear as those with the lowest cholesterol levels appear to be at the highest risk of death. A weak association was observed between cholesterol level and severity of LV systolic dysfunction.

CHAPTER 8. ECG AS A PREDICTOR OF SEVERITY OF HEART FAILURE - RELATIONSHIP BETWEEN REPOLARISATION ABNORMALITIES ON THE SURFACE ELECTROCARDIOGRAM AND SEVERITY OF LEFT VENTRICULAR SYSTOLIC DYSFUNCTION – A REPORT FROM THE EURO HEART FAILURE SURVEY.

8.1 BACKGROUND

Electrocardiography (ECG) is a simple investigation, routinely performed in all cardiac patients. It may be useful to risk stratify patients suspected to have heart failure since those without an abnormal ECG are less likely to have left ventricular dysfunction. ECG abnormalities such as evidence of previous myocardial infarction, left ventricular strain and bundle branch block can suggest presence of left ventricular dysfunction. Other ECG abnormalities such as QT prolongation are known to be associated with increased risk of coronary heart disease and cardiovascular death.[191-193].

8.2 QT PROLONGATION

The QT interval, which represents the duration of ventricular electrical systole, i.e., the time required for completion of both ventricular depolarisation and repolarisation, has been a variable of particular interest in cardiology and may provide information about ventricular function. Although a high prevalence of QT prolongation has been reported in patients with heart failure, its mechanism and significance are uncertain.[194] Whether QT interval is related to the severity of left ventricular dysfunction or poor prognosis in patients with heart failure remains controversial.[194-198] However, as the QT interval includes the duration of activation as well as repolarisation of the left

ventricle, it will be influenced by QRS width, which has already been shown to predict both increased mortality and sudden death in patients with heart failure.[199] In this study, I have examined the relationship between ECG intervals and the presence and severity of LV dysfunction.

8.3 AIMS

In this study I have examined the following hypotheses using the data from Euro Heart Failure Survey.

1. The QT interval is prolonged in patients with left ventricular systolic dysfunction (LVSD).
2. The degree of QT prolongation is related to the severity of LVSD.
3. QRS prolongation and QT prolongation are independently associated with LVSD.

8.4 METHODS

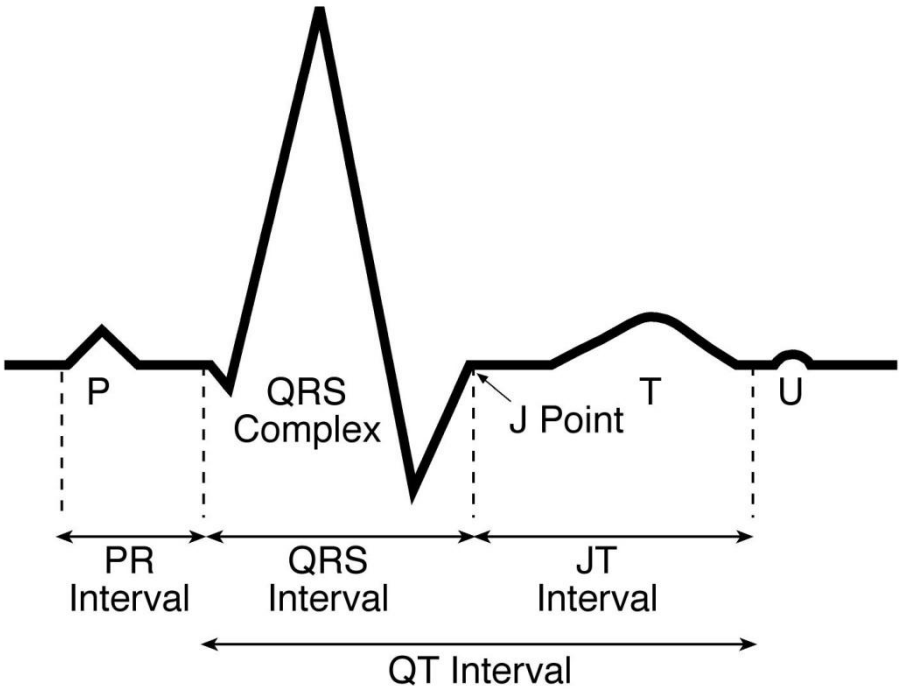
In the Euro Heart Failure survey, data were collected from 10,701 patients with suspected heart failure in 115 hospitals across 24 European countries during 2000-2001, over 6 weeks. The detailed design of this study has been published previously.[4] In short, all consecutive discharges and deaths in the departments of cardiology, cardiovascular surgery, general internal medicine and care of the elderly were screened for 6 weeks and patients were enrolled if they fulfilled at least one of the following criteria: (1) a clinical diagnosis of heart failure during the admission; (2) a diagnosis of heart failure recorded at any time in the last three years; (3) administration of a loop diuretic for any reason other than renal failure in the 24 hours prior to death or discharge; (4) pharmacological treatment for heart failure or

ventricular dysfunction in the 24 hours prior to death or discharge. Data were collected on co-morbid conditions including hypertension, diabetes and renal impairment. Investigations included a 12 lead ECG, echocardiogram and routine blood tests. Vital status (dead or alive) was determined at 12 weeks after discharge.

8.4.1 ECG analysis

The PR, RR, QT, QRS and JT intervals (figure 8.1) were measured from the original 12 lead ECGs with a digital ruler-calliper (ABSolute digimatic, Mitutoya UK Ltd) by a single observer (my coworker, Dr Nasrin Khan), who was blinded to the patients' clinical characteristics and the results of other investigations including echocardiography. Bazett's method of correction for heart rate was used to calculate the QTc interval.[69] JTc interval was defined as QTc minus QRS duration.[200]

Figure 8.1 ECG intervals



The normal QTc is generally accepted to be less than or equal to 440 milliseconds (ms). However the ARIC study, which included 14,672 healthy middle aged men and women, suggested that many apparently healthy people have values > 440 ms and that QTc and JTc durations are greater in women than in men.[192] Accordingly, I identified sex-specific cut-off values for QTc (men; 464 ms and women; 481 ms) and JTc (men: 365 ms and women: 387 ms) of 2SD above the mean of a large population (n=14,240) study of healthy subjects without QRS prolongation.[192]

8.4.2 Echocardiography

The echocardiograms were performed in the participating hospitals to assess left ventricular function and reported by the local cardiologists. Left ventricular systolic dysfunction was classified qualitatively into one of four categories; none, mild, moderate and severe.

The data from 12 lead ECGs analysed as described above and echocardiographic data were available in the University of Hull. I had integrated these data by matching the ECG and Echocardiographic findings. I included 5934 patients who had both 12 lead ECG and echocardiogram results available for this analysis.

8.4.3 Data Analysis

I examined the relation between the ECG variables and the degree of LV systolic function. The group means were compared for significant differences by analysis of variance (ANOVA) or its non parametric equivalent, depending on the distribution of the data. The interaction of beta blocker treatment with LVSD was examined by log linear analysis. Correlation coefficients were calculated for interrelationship between QT variables and for any relation between QT variables with age and heart rate. Each

QT variable was arbitrarily divided into 5 categories of 20 ms intervals (QRS: ≤ 100, 100-120, 121-140, 141-160 and >160 ms. QTc: ≤ 440, 441-460, 461-180, 481-500 and >500 ms. JTc < 330; 331-350, 351-370, 371-390 and >390 ms) and each category was examined by a multivariable logistic regression model to predict the severity of left ventricular systolic dysfunction. From this model, odds ratios (predicting moderate or severe LVSD) with 95% confidence intervals were obtained by comparing each category to the average effect of previous categories. A nominal level of 5% statistical significance was assumed (two-tailed). SPSS v16 software (SPSS Inc, Chicago, IL, USA) was used for statistical analysis.

8.5 RESULTS

The detailed patient characteristics and treatment profile have been published previously.[84, 85] In the present study group (n = 5934), the mean age was 69 (SD: 13) years; 41% (n = 2445) were women; 65% (n = 3874) had coronary disease; 26% (n = 1572) had diabetes; 47% (n = 2784) had hypertension and 16% (n = 962) had renal dysfunction. 44% (n=2598) were treated with beta blockers. The patient characteristics were similar to that of the whole study population.

The mean (SD) QT interval was 389 (55) ms; QTc = 447 (41) ms; QRS = 112 (29) ms; JT = 277 (50) ms; JTc = 334 (37) ms; RR = 774 (189) ms and PR = 178 (36) ms. In 55% (n=3236) of patients the QTc was more than 440 ms. 32% of men and 17% of women had QTc prolongation 2SD above that of a healthy population. The higher proportion of men with QTc prolongation reflected the higher proportion with LVSD (81% of men versus 57% of women). 17% of men and 9% of women had JTc values 2SD above that of the healthy population. 29 % (n=1709) had QRS > 120 ms. 20 % (n = 1200) had LBBB pattern.

LVSD was present in 71% (n=4213); mild in 17% (n=1012), moderate in 23% (n=1374) and severe in 31% (n=1827). Patients with LVSD had prolonged QT (392 *v* 383 ms; p < 0.001), QTc (449 *v* 439 ms; p < 0.001) and QRS (117 *v* 102 ms; p < 0.001) but not JT intervals. The QT, QTc and QRS intervals were longer with increasing severity of LVSD (see table 8.1 and figures 8.2 and 8.3). The JT and JTc intervals were shorter as LVSD increased in severity (figure 8.4).

Table 8.1: ECG variables related to severity of LVSD

Interval **Median (IQR)**	**No LVSD (n = 1721)**	**Mild LVSD (n = 1012)**	**Moderate LVSD (n = 1374)**	**Severe LVSD (n = 1827)**	**p value**
QT	384 (70)	390 (72)	391 (70)	395 (73)	< 0.001
QTc	437 (45)	439 (46)	442 (49)	453 (52)	< 0.001
QRS	**95** (23)	**101** (30)	**104** (31)	**118** (43)	**< 0.001**
JT	281 (66)	280 (69)	279 (69)	269 (61)	< 0.001
JTc	339 (43)	333 (42)	334 (45)	331 (47)	< 0.001
RR	778 (248)	820 (258)	796 (247)	761 (246)	0.824
PR	168 (45)	172 (44)	172 (47)	179 (44)	0.213

Figure 8.2: Relation between QRS and severity of left ventricular systolic dysfunction (LVSD)

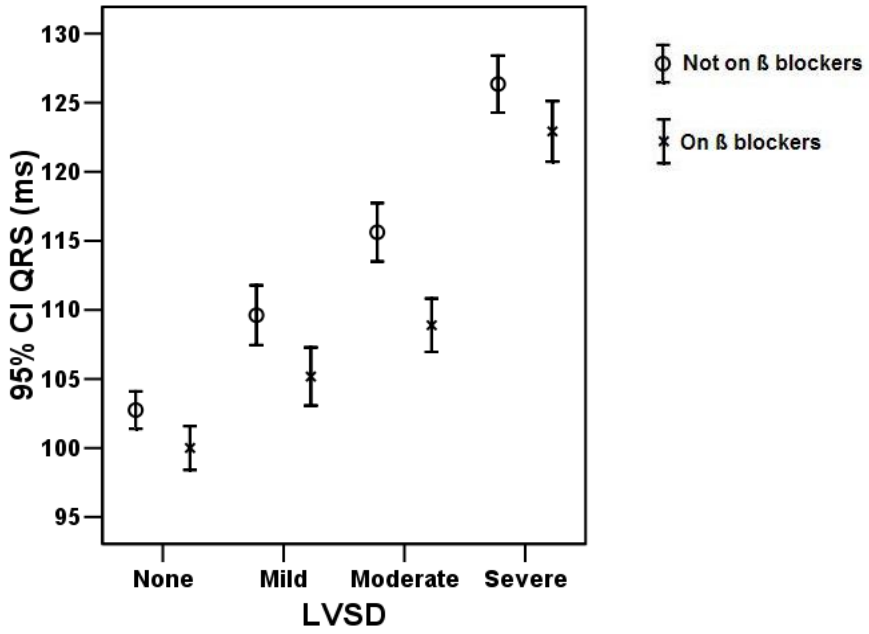


Figure 8.3: Relation between QTc and severity of left ventricular systolic dysfunction (LVSD)

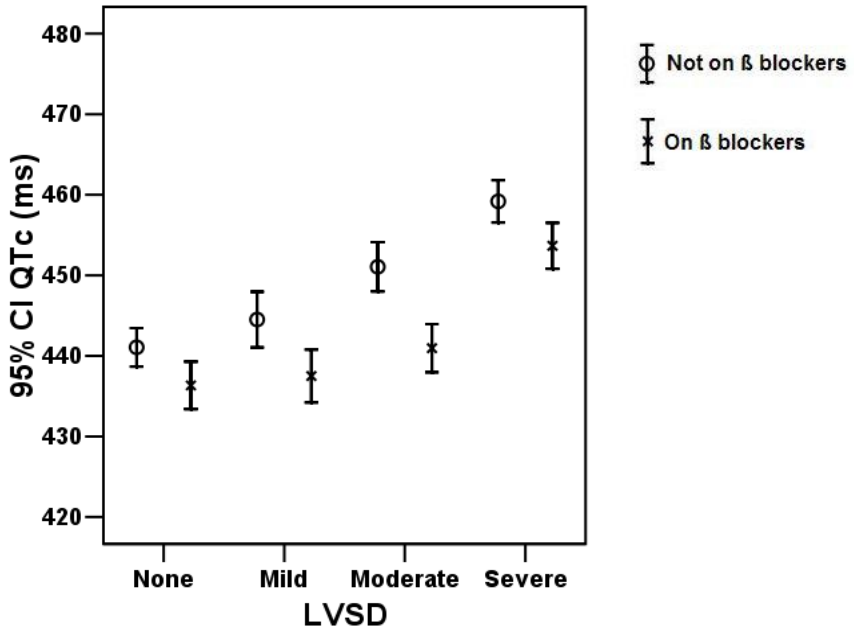
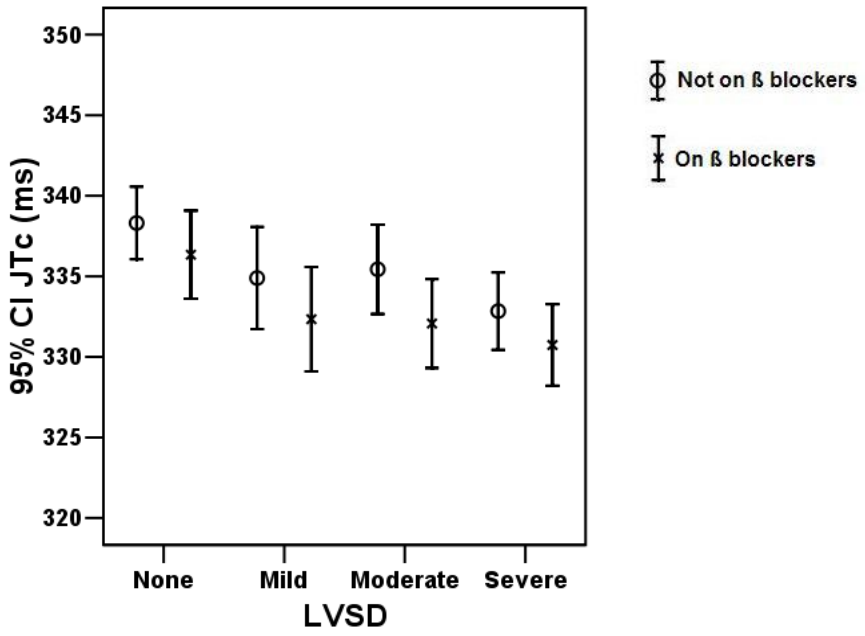


Figure 8.4: Relation between JTc and severity of left ventricular systolic dysfunction (LVSD)



Patients treated with beta-blockers (n=2598; 44%) had a shorter QRS interval (110 *v* 114 ms; p < 0.001) but a longer QT interval (396 *v* 384 ms; p < 0.001). When corrected for heart rate, beta-blocker treatment was associated with shorter QTc (443 *v* 449 ms; p < 0.001) and JTc intervals (333 *v* 336 ms; p = 0.005). This difference was consistent within all categories of LV systolic dysfunction (figures 8.2, 8.4 and 8.4). Patients treated with beta blockers were younger (66 *v* 70 years; p < 0.001) and had a lower heart rate (78 *v* 86 bpm; p < 0.001) than those who were not on them. On log linear analysis there was no significant interaction between the severity of LVSD and beta blocker treatment. QRS duration did not show any association with age (r = 0.04) or heart rate (r = -0.12). QRS interval was strongly correlated with QTc (r = 0.42; p < 0.001), but the association of QRS interval with JTc (r = - 0.25) and RR (r = 0.12) intervals were weak.

When the QT variables were subjected to multivariable logistic regression analysis (that also included age, sex and beta blocker effect), I found that only QRS prolongation was an independent predictor of moderate to severe LV dysfunction. There was a "dose-response" effect with QRS interval prolongation, so that the odds of having moderate or severe LVSD increased with increasing QRS interval (table 8.2). No such effect was seen for QTc interval prolongation.

Table 8.2: QRS and QTc prolongation predicting moderate or severe LVSD

QRS (ms)	**Odds Ratio**	**95 % CI**
≤ 100 (n=2509)	Reference category	
100-120 (n=1716)	**1.6**	1.4 - 1.8
121-140 (n=694)	**2.1**	1.7 - 2.3
141-160 (n=551)	**2.3**	1.7 – 2.6
> 160 (n=441)	**3.5**	2.6 – 4.4

QTc (ms)	**Odds Ratio**	**95 % CI**
≤ 440 (n=2698)	Reference category	
441-460 (n=1207)	1.1	0.9 – 1.2
461-480 (n=866)	1.1	1.0 – 1.4
481-500 (n=566)	1.0	0.9 – 1.3
> 500 (n=594)	0.8	0.8 – 1.2

8.6.DISCUSSION

This analysis from a large epidemiologic study shows that there is a relationship between QT prolongation and the presence and severity of LVSD, but this relationship is due to QRS prolongation. Indeed, the JT interval shortened with increasing severity of LVSD. This could reflect heightened sympathetic activity or it may be an artifact due to extension of the QRS interval into the start of the repolarisation phase.

The QRS interval reflects the duration of ventricular electrical activation and increased QRS width indicates prolonged or delayed activation and is an approximate guide to cardiac dyssynchrony. There are several possible interconnected reasons for the association between QRS width and the severity of LVSD: (1) an increase in myocardial mass, (2) dilated ventricles, leading to longer activation pathways and (3) altered electrical conduction through the His-Purkinje system and/or myocardium.

Dyssynchrony is more common in patients with longer duration of QRS, and may lead to worsening of the pre existing LVSD.[201] Thus, QRS prolongation may reflect both the cause and consequence of LVSD. In the presence of cardiac dyssynchrony, cardiac resynchronisation therapy (CRT) improves synchrony, left ventricular ejection fraction, symptoms, morbidity and mortality. [52, 202]

Use of beta blockers was associated with shorter QRS and QTc intervals, the mechanism of which is not clear. Beta blocker toxicity is associated with prolonged QRS duration, and it is generally believed that beta blockers have no effect on QRS duration at therapeutic doses.[203] Hence this finding is surprising, and it is not known whether this is one of the mechanisms for the prognostic benefit observed with beta blockers in heart failure. However studies have shown that beta-blockers improve cardiac dyssynchrony, although the effect may be modest compared to CRT.[204, 205]

It is also possible that those patients with severe heart failure (and marked QRS prolongation) might not have tolerated beta blocker therapy and those on beta blockers were relatively healthy and hence had a shorter QRS interval. However, it should be noted that the association of shorter QRS interval with beta blocker therapy was seen independent of the severity of LV dysfunction. To date, no randomized controlled trial has reported a shortening of QRS with beta-blocker therapy. However, the effect is modest (about 4 ms) and could very easily have been missed.

8.7 CONCLUSIONS

The ECG is useful in identifying the presence of left ventricular dysfunction and estimating its severity in patients suspected to have heart failure. The QRS interval appears to be the main determinant of QT interval in patients with heart failure and the best electrocardiographic marker of the severity of LV systolic dysfunction.

The relationship between beta blocker treatment with QRS duration and dyssynchrony needs further study.

CHAPTER 9. THE UTILITY OF SIGNAL AVERAGED ECG IN RISK STRATIFICATION OF HEART FAILURE PATIENTS

9.1 INTRODUCTION

Randomised clinical trial data have shown that in general, sudden death constituted around 50% of all deaths in patients with heart failure.[14-22] Patients who have only minimal symptoms (NYHA 2) are those more likely to die from sudden death than those with severe symptoms (NYHA 3/4) in whom death from progressive heart failure is more common.[22] Thus patients with heart failure who are apparently quite well are those who may be at risk from sudden death. Hence it is important to accurately identify these patients in order to prevent sudden cardiac death in heart failure.

Sudden cardiac death in patients with heart failure is commonly due to ventricular tachycardia (VT) or ventricular fibrillation (VF), as patients with heart failure are more prone to these arrhythmias.. Most life-threatening ventricular arrhythmias are due to re-entry phenomena which require an area of slow conduction to allow the perpetuation of an arrhythmia.[206] Following myocardial infarction, fibrosis results in areas of delayed ventricular activation which form the substrate for ventricular arrhythmias. The delayed ventricular activation may extend beyond the end of the QRS complex on the surface ECG forming so called “late potentials”. Patients with sustained monomorphic ventricular tachycardia during electrophysiological testing are more likely to have late potentials.[207]

There is “noise” in surface ECGs generated by skeletal muscle activity ranging in amplitude from 8 to 10 μv. This noise may mask the presence of late potentials which appear after the end of the QRS complex, as detected on the surface ECG. Signal-

averaged electrocardiography (SAECG) allows the detection of low amplitude bioelectric potentials which are masked on surface ECG by averaging many QRS signals to remove interference, amplify the complexes, and letting finer detail of the QRS complexes appear.

Abnormalities in the signal-averaged ECG are detected rarely in normal subjects, in only a small percentage of patients who have had myocardial infarction but not ventricular tachycardia and in up to 93% of patients with a history of sustained monomorphic VT[208]. The presence of late potentials is also associated with inducible sustained VT during electrophysiological testing.[209, 210] In contrast, late potentials are detectable in only 21% to 65% of patients with ischemic heart disease and a history of previous ventricular fibrillation.[208] Late potentials on SAECG are associated with an increased risk of ventricular tachycardia, sudden death and total mortality in patients after myocardial infarction.[70-76] The SAECG might thus be a useful tool for risk stratification in predicting sudden death in patients with chronic heart failure (CHF). However it may be limited to those at risk of monomorphic VT, as the association of late potentials with VF was not strong as with monomorphic VT.

9.2 HYPOTHESES

1. SAECG provides information on left ventricular systolic function.

2. Abnormal SAECG is independently associated with higher risk of death in patients with heart failure.

9.3 PATIENTS AND METHODS

Consecutive patients with clinical symptoms and/or signs of chronic heart failure, being seen in a community heart failure clinic serving the population of Hull and the

East Riding of Yorkshire were recruited into the study. Fully informed written consent was obtained. The study was approved by the local ethics committee and by the Hull and East Yorkshire NHS Trust board.

A total of 845 patients who were in sinus rhythm were recruited. SAECG recordings were made in every patient on one of two GE Mac 5000 machines during 2004-2005. 315 patients were excluded due to the presence of bundle branch block or marked intra-ventricular delay with QRS duration > 150 ms, leaving 530 patients in the study. This was necessary to reduce the number of false positives that can occur in these patients, for whom standard criteria for late potentials are not applicable and different criteria have been proposed.[211]

Left ventricular function was qualitatively assessed. Significant LV systolic dysfunction was defined as moderate or severe LV impairment. Any deaths (all cause mortality) were recorded during the follow up period. Follow up was censored on 01 April 2010. The status of all patients was known at this date. This status was cross checked with the national database.

9.3.1 12 Lead ECG

Standard 12 lead ECG intervals were calculated automatically by the ECG machine's included software. The QTc interval was derived by Bazett's method.[69]

9.3.2 Signal Averaged ECG

9.3.2.1 Recording Technique

In addition to usual 12 leads used for surface ECG, orthogonal XYZ leads were recorded by placing 4 additional electrodes at the following positions; H – back of neck, E – mid

sternum (same level as V4), I – right mid axillary line (same level as V4) and M – centre of back (same level as V4). At least 100 consecutive QRS complexes were recorded and the recordings averaged, filtered and combined into a vector magnitude termed the filtered QRS complex. Analysis of the filtered QRS complex included a) unfiltered QRS duration; b) filtered QRS duration c) root – mean – square (RMS) voltage of the terminal 40 ms of the filtered QRS; and d) duration that the filtered QRS complex remains < 40 μv. These variables were measured automatically by the software of the ECG machines.

9.3.2.2 Criteria to define presence of late potentials

Characteristics of an abnormal late potential include the following [208]

- a filtered QRS complex duration > 114 ms;
- a signal < 20 μv in the last 40 ms of the filtered QRS complex and
- voltage < 40 μv in the terminal QRS complex for > 38 ms.

Late potential was considered present when all the above three criteria were fulfilled.

9.3.3 Statistical analysis

Continuous variables were expressed as mean with standard deviation or median with inter quartile range, depending on their distribution. Categorical variables were expressed as frequency with percentage. Difference between groups was tested with independent samples "t" test for continuous variables or chi square test for categorical data. All the clinical variables were tested by univariate logistic regression to predict mortality, after excluding those who had an ICD. Those predictor variables with a significance level of < 0.05 on univariate analysis were included in the multivariable

analysis. In addition, QRS duration on 12 lead ECG, filtered QRS duration, late potentials on SAECG, beta blocker and amiodarone therapy were also entered. Statistical software used was SPSS v 16 (SPSS inc, Chicago, IL, USA).

9.4 RESULTS

The patients were followed up for a median of 65 (IQR = 8) months. All survivors were followed for a minimum of 5 years. A total of 135 patients (25%) died during follow up. Crude mortality rate at 5 years was 51 per 1000 per year. All were in sinus rhythm. None had a pacemaker or cardiac re-synchronisation device. Significant (moderate or severe) left ventricular impairment was present in 138 patients (26%).

33 (6%) had an ICD in situ, but none was paced at the time of assessment. 7 (21%) patients had died despite having an ICD and there was no difference in the rate of death between those with or without an ICD ($p = 0.562$).

The detailed patient characteristics of those who died during follow up as compared to the survivors, are shown in table 9.1. The clinical factors associated with death on univariate and multivariable analysis by logistic regression are shown in tables 9.2 and 9.3. Those who had an ICD were excluded from the model, to avoid the confounding effect of appropriate potentially life-saving therapy from the device. The benefit of aspirin therapy was observed only in patients with ischaemic heart disease.

9.4.1 12- lead ECG

The mean heart rate was 67 (15) bpm. The mean QRS duration was 95 (13) ms and mean QTc interval was 437 (52) ms. 205 patients (39%) had presence of Q waves on 12 lead ECG, consistent with previous myocardial infarction.

Table 9.1 Patient characteristics of survivors compared with those who had died by 5 years of follow up.

Patient characteristic N (%)	Vital status at 5 years		
	Alive 395 (75%)	**Dead** 135 (25%)	**p value**
Age (yrs) – Median (IQR)	67 (14)	75 (10)	< 0.001
Sex			
Male	273 (79%)	74 (21%)	0.003
Female	122 (67%)	61 (33%)	
Ischaemic Heart Disease	273 (74%)	95 (26%)	0.829
PCI	52 (84%)	10 (16%)	0.087
CABG	79 (79%)	21 (21%)	0.308
Hypertension	178 (74%)	62 (26%)	0.920
Diabetes	72 (65%)	39 (35%)	0.010
NYHA			
I	128 (86%)	21 (14%)	< 0.001
II	193 (73%)	73 (27%)	0.296
III	67 (63%)	39 (37%)	0.003
IV	7 (78%)	2 (22%)	0.821
Smoking			
Never smoked	113 (75%)	38 (25%)	0.919
Ex smoker	230 (74%)	79 (26%)	0.953
Current	52 (74%)	18 (26%)	0.960
Renal Impairment (serum creatinine of > 127 µmol/l in men or > 107 µmol/l in women)	83 (60%)	56 (40%)	< 0.001

Left ventricular impairment			
Mild (or less)	312 (80%)	80 (20%)	< 0.001
Moderate	73 (60%)	48 (40%)	<0.001
Severe	10 (59%)	7 (41%)	0.131
Medication			
Loop diuretic	197 (64%)	109 (36%)	< 0.001
Aspirin	238 (79%)	63 (21%)	0.007
Warfarin	43 (71%)	18 (29%)	0.438
Beta blocker	271 (77%)	81 (23%)	0.073
Amiodarone	24 (73%)	9 (27%)	0.837
Digoxin	13 (57%)	10 (43%)	0.051
ACEI	250 (75%)	82 (25%)	0.073
ARB	63 (72%)	24 (28%)	0.592
Thiazide	37 (80%)	9 (20%)	0.381
Spironolactone	55 (62%)	34 (38%)	0.003
Statin	266 (77%)	80 (23%)	0.095

Table 9.2. Univariate predictors of mortality

Variable	Wald statistic	Odds Ratio	95% CI	P value
Age (years)	45.7	1.1	1.1 – 1.1	< 0.001
Use of loop diuretic	35.9	4.5	2.8 – 7.4	< 0.001
Haemoglobin (g/dl)	34.8	0.7	0.6 – 0.8	< 0.001
Urea (mmol/l)	19.3	1.1	1.1 – 1.2	< 0.001
Elevated serum creatinine (> 127 µmol/l in men or > 107 µmol/l in women)	18.3	2.6	1.7 – 3.9	< 0.001
Significant (moderate/severe) LVSD	17.8	2.6	1.7 – 4.0	< 0.001
QTc interval (ms)	14.4	1.01	1.004 – 1.012	< 0.001
NT-pro BNP (log)	14.2	3.3	1.8 – 6.1	< 0.001
Heart rate (bpm)	12.5	1.02	1.01 – 1.04	< 0.001
Spironolactone	7.5	2.0	1.2 – 3.3	0.006
NYHA III/IV	7.0	1.9	1.2 – 3.0	0.008
Aspirin	7.0	0.6	0.4 – 0.9	0.008
Diabetes	6.1	1.8	1.1 – 2.9	0.014
Filtered QRS duration on SAECG (ms)	0.7	1.0	0.9 – 1.0	0.42
QRS duration on ECG (ms)	0.7	1.0	0.9 – 1.0	0.39
Presence of late potentials on SAECG	0.04	1.0	0.7 – 1.6	0.83

*OR (odds ratio) calculated per unit change for continuous variables.

Table 9.3. Multivariable predictors of mortality*

Variable	Wald	OR^	95% CI	P value
Age (years)	16.3	1.1	1.04 – 1.11	< 0.001
Heart rate (bpm)	7.2	1.03	1.01 - 1.05	0.007
NT-pro BNP (log)	6.6	2.5	1.2 – 5.1	0.010
Use of loop diuretic	6.0	2.3	1.2 – 4.4	0.015

*by stepwise logistic regression model that included all variables shown in table 9.2 and in addition, ischemic heart disease, beta blocker and amiodarone therapy.

^ OR (odds ratio) calculated per unit change for continuous variables.

The relation between the 12 lead ECG intervals and presence of significant left ventricular systolic dysfunction (LVSD) on echocardiography is given in table 9.4. The QRS duration was significantly longer in patients with LVSD. Similar association with LVSD was noted with QTc interval but this was weaker than QRS duration.

The relation between 12 lead ECG variables and vital status at 5 years is shown in table 9.5. The heart rate was higher and QTc interval was longer in those who had died within 5 years, but there was no significant difference in the QRS duration. When the QRS duration was divided into tertiles and examined in relation to survival at 5 years, no significant difference was detected (figure 9.1).

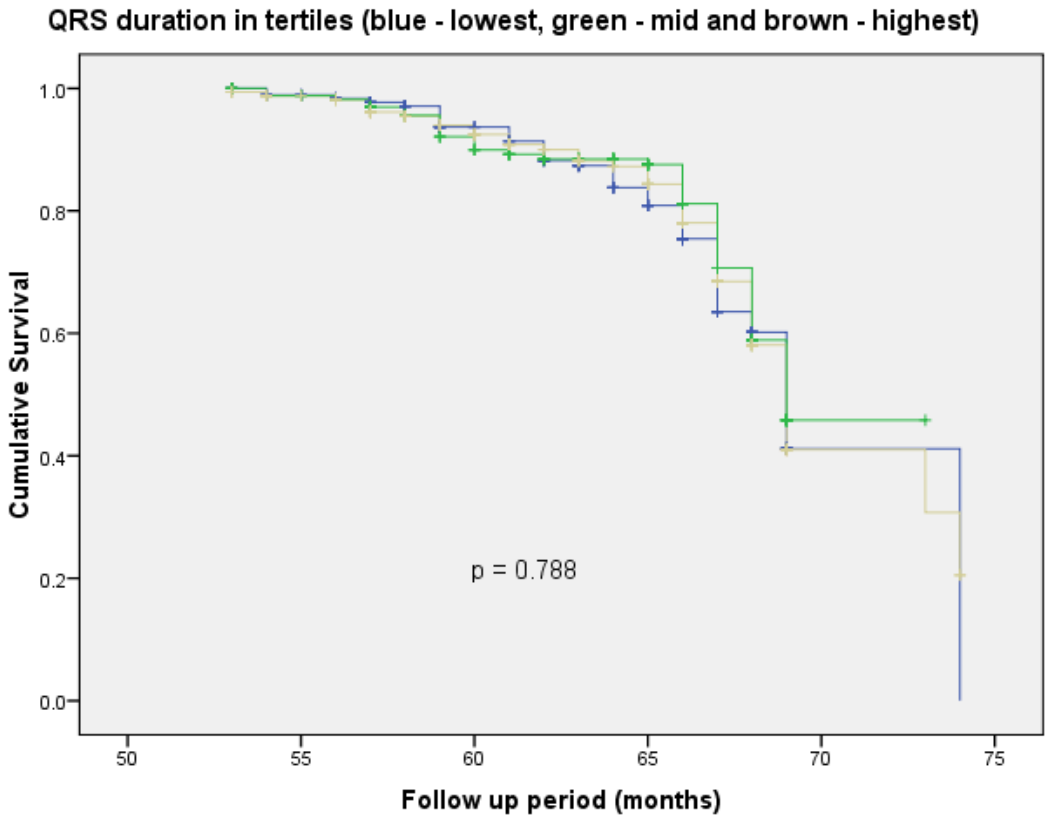
Table 9.4. Relation between ECG intervals and presence of significant LVSD on echocardiography.

Variable Mean (SD)	**Significant LVSD on echo**		
	No	**Yes**	**p value**
12 – lead ECG			
Heart rate	67 (14)	68 (15)	0.423
QRS (ms)	92 (13)	102 (12)	< 0.001
QTc (ms)	434 (54)	444 (47)	0.045
SAECG			
Unfiltered QRS (ms)	95 (13)	106 (15)	< 0.001
Filtered QRS (ms)	114 (25)	129 (31)	< 0.001
Late potentials – N (%)	107 (27%)	57 (41%)	0.002

Table 9.5. Relation between ECG intervals and survival at 5 years.

Variable Mean (SD)	**Vital Status at 5 years**		
	Alive	**Dead**	**p value**
12 – lead ECG			
Heart rate	66 (14)	71 (17)	0.001
QRS (ms)	95 (13)	96 (14)	0.483
QTc (ms)	432 (45)	452 (60)	0.001
SAECG			
Unfiltered QRS (ms)	97 (14)	99 (17)	0.239
Filtered QRS (ms)	117 (27)	119 (29)	0.424
Late potentials – N (%)	121 (31%)	43 (32%)	0.791

Figure 9.1. Kaplan – Meier curve showing the relation between QRS duration (in tertiles) on 12 lead ECG and survival.



9.4.2 SAECG

9.4.2.1 QRS duration on SAECG

The mean (SD) unfiltered QRS duration was 98 (14) ms and the mean filtered QRS on SAECG was 118 (28) ms. There was modest correlation between standard QRS duration on 12 lead ECG and unfiltered QRS duration on SAECG (Pearson's coefficient $r = 0.69$; $p < 0.001$). However, there was only weak correlation between standard QRS duration on 12- lead ECG and filtered QRS duration on SAECG ($r = 0.33$; $p < 0.001$). The Bland-Altman plot demonstrating this correlation between QRS duration on ECG and filtered QRS duration on SAECG is shown in figure 9.2.

The relation between QRS intervals on SAECG and presence of significant left ventricular systolic dysfunction (LVSD) on echocardiography is given in table 9.4. Both filtered and unfiltered QRS durations were significantly longer in patients with significant LVSD. The filtered QRS duration was also progressively longer with increasing severity of LVSD (figure 9.3).

There was no significant difference in the filtered or unfiltered QRS duration between those who were alive and those who were dead at 5 years of follow up (table 9.5). When the filtered QRS duration was divided into tertiles and examined in relation to survival at 5 years, no significant difference was detected (figure 9.4).

Patients with an ICD (6%) had a longer QRS (103 vs 94 ms), unfiltered QRS (109 vs 97 ms) and filtered QRS durations (138 vs 116 ms) when compared to those without an ICD and the difference was statistically significant ($p < 0.01$) for all three comparisons. This is probably due to the fact that patients with an ICD had a higher prevalence of moderate or severe LV impairment (52% vs 24%).

Figure 9.2. Bland – Altman plot showing correlation between QRS measured from 12 lead ECG and filtered QRS measured from SAECG

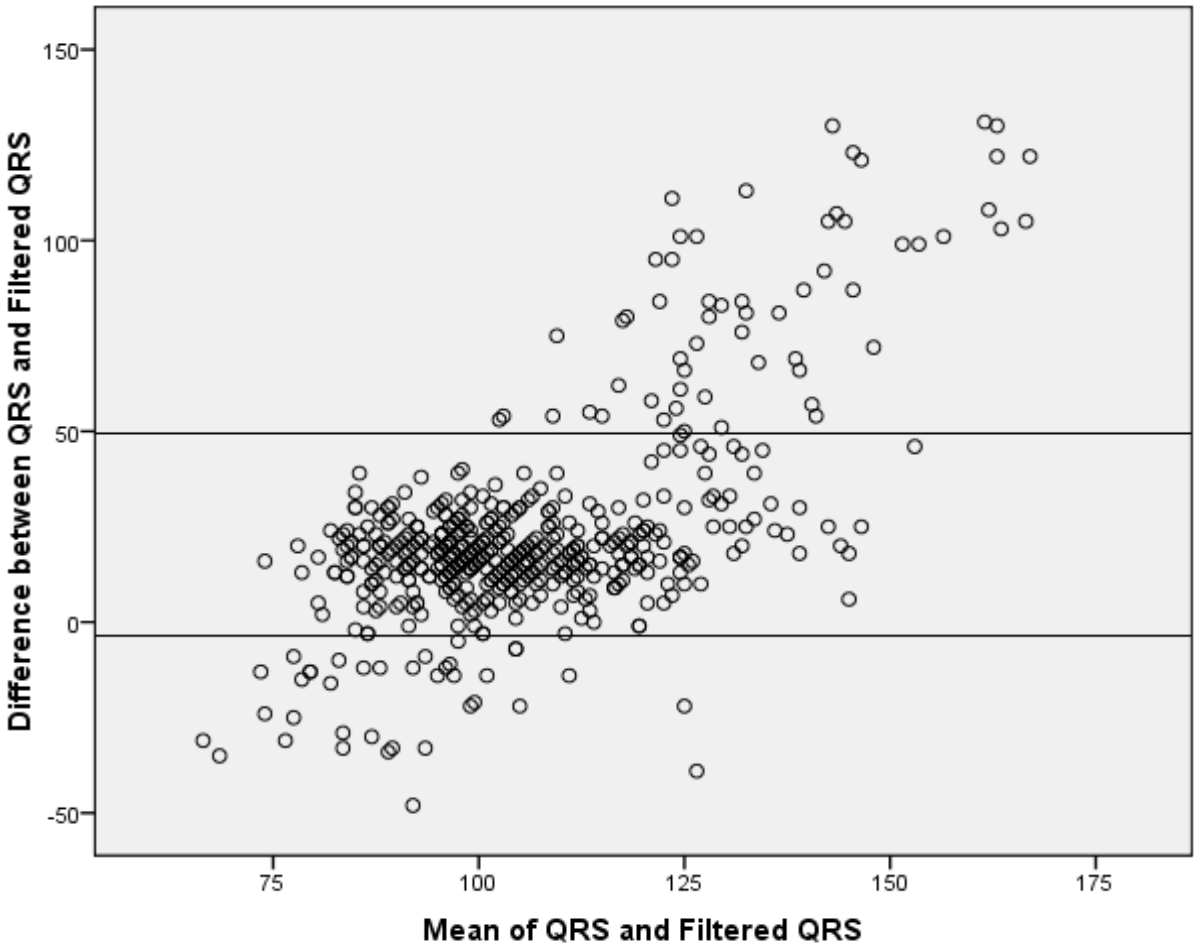


Figure 9.3. Relation between severity of LV dysfunction and filtered QRS duration on Signal Averaged ECG.

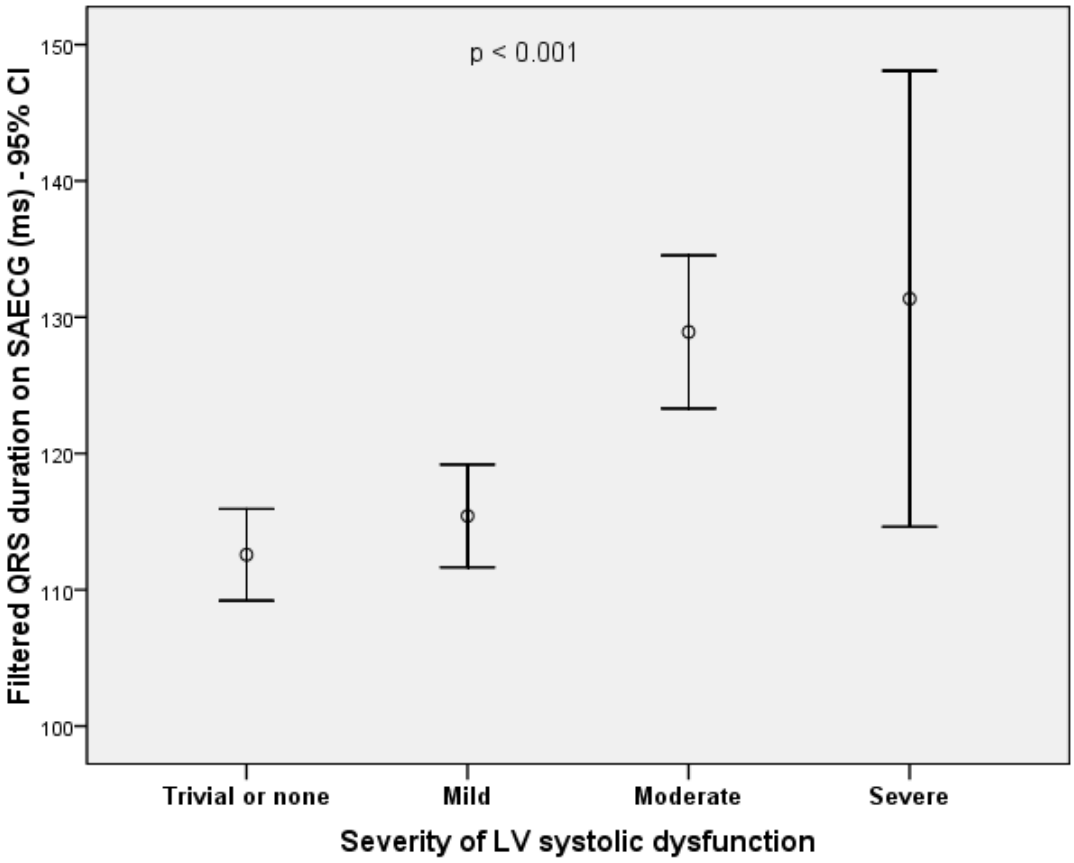
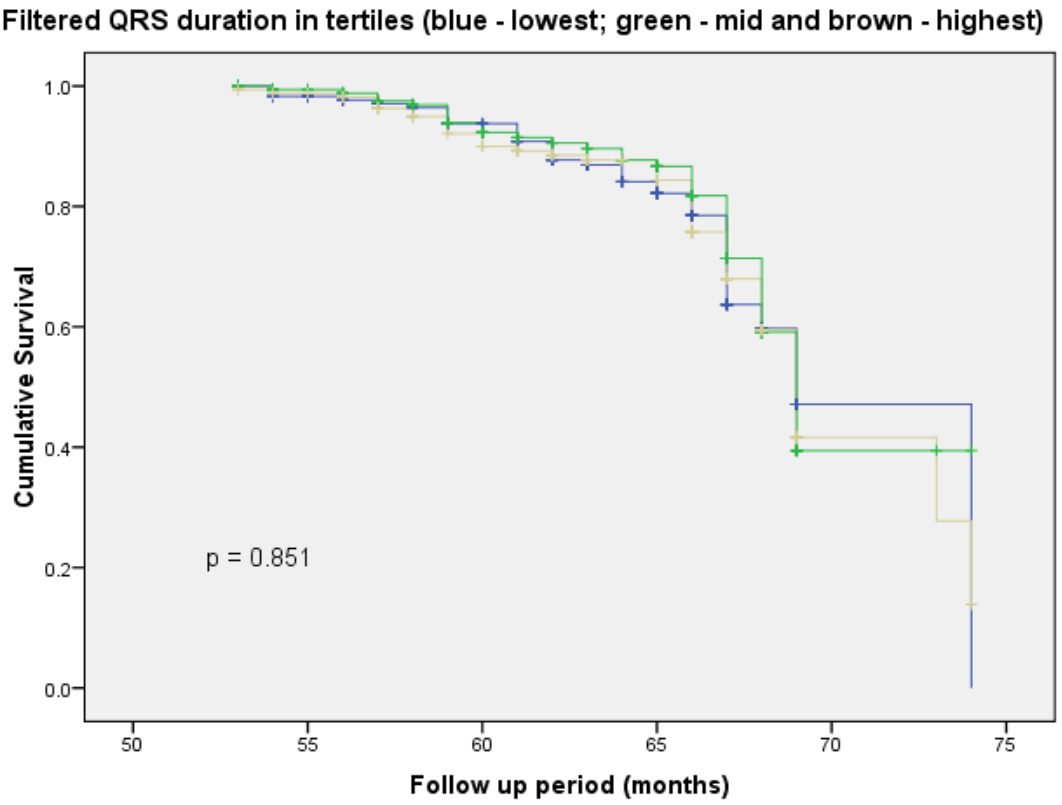


Figure 9.4. Kaplan – Meier survival graph showing the relation between filtered QRS duration (in tertiles) and mortality within 5 years.



9.4.2.2 Late potentials on SAECG

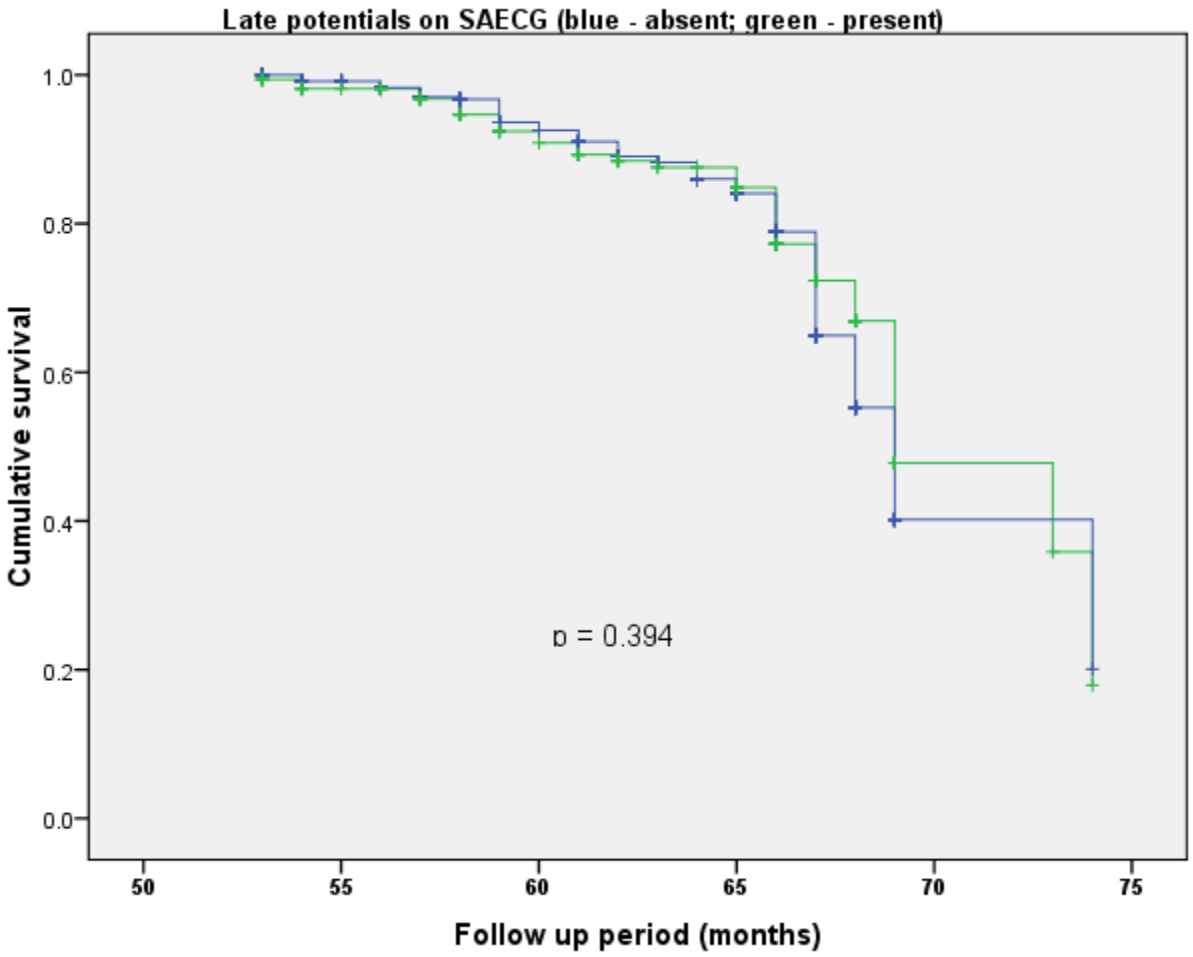
164 patients (31%) had late potentials detected on SAECG. There was no significant difference in the frequency of late potentials between those who were alive and those who were dead at 5 years of follow up (table 9.6) and the presence of late potentials on the SAECG was not associated with increased risk of death on either univariate or multivariable analysis. There was no difference in the survival between those who did or did not have late potentials on SAECG (figure 9.5). The positive predictive value of presence of late potentials on the SAECG in predicting death within 5 years was only 26%, although the specificity was 69%. The sensitivity was only 32% but the negative predictive value was 75%. There was also no association between any of the individual criteria for defining late potentials and the risk of death.

Table 9.6. Relation between death and presence of late potentials on Signal Averaged ECG.

Vital Status (at 5 years)	Late Potentials on SAECG	
	No	Yes
Alive	274	121
Dead	92	43

p = 0.791

Figure 9.5. Kaplan – Meier plot showing lack of association between presence of late potentials on SAECG and survival



However, there was a significant association between presence of significant left ventricular systolic dysfunction (LVSD) on echocardiography and the presence of late potentials on SAECG, as a linear increase in the prevalence of late potentials was observed with increasing severity of LVSD (figure 9.6).

9.4.3 NT –pro BNP

NT-pro BNP level was significantly higher in patients with LVSD and there was an almost linear relation with increasing severity of LVSD (figure 9.7). When the NT-pro BNP was divided into tertiles and examined in relation to survival, there was a significant association, as those with NT-pro BNP in the highest tertile had the worst survival (figure 9.8). Patients with late potentials on SAECG had higher level of NT-pro BNP when compared to those who did not have late potentials (figure 9.9). However there was no correlation between filtered QRS duration on SAECG and NT-pro BNP levels (figure 9.10).

9.5 DISCUSSION

This study has assessed the usefulness of Signal Averaged ECG as a tool for predicting significant left ventricular dysfunction and for risk stratification in predicting mortality in the medium term, in a contemporary population with heart failure.

Previous studies have demonstrated that late potentials on SAECG had a low sensitivity in predicting sudden death, but high negative predictive value. In this study, there was no statistically significant association with death and the negative predictive value was only modest (75%). This supports the view that SAECG can no longer be recommended as a risk stratification tool in predicting death in heart failure.[212]

Figure 9.6. Relation between severity of LVSD and prevalence of late potentials on SAECG

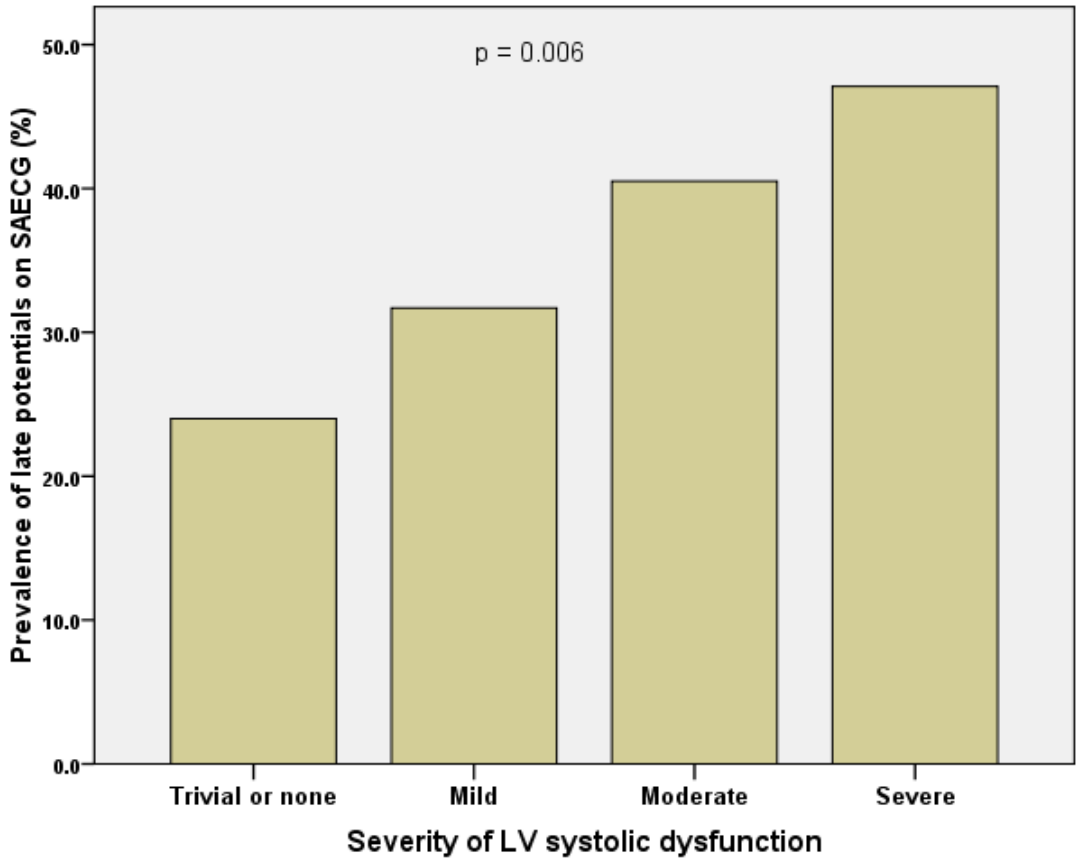


Figure 9.7. Relation between NT-pro BNP level and severity of LV systolic dysfunction on echocardiography.

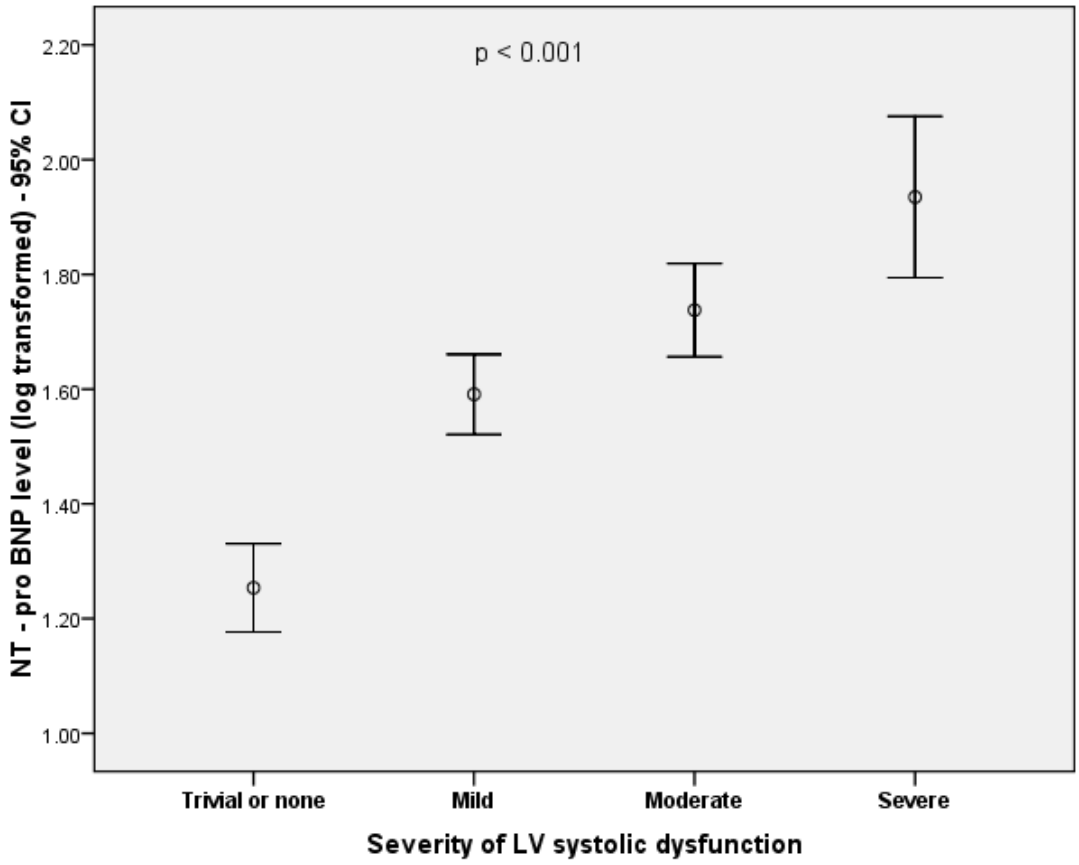


Figure 9.8. Kaplan - Meier survival graph showing the relation between NT pro – BNP level (in tertiles) and mortality within 5 years.

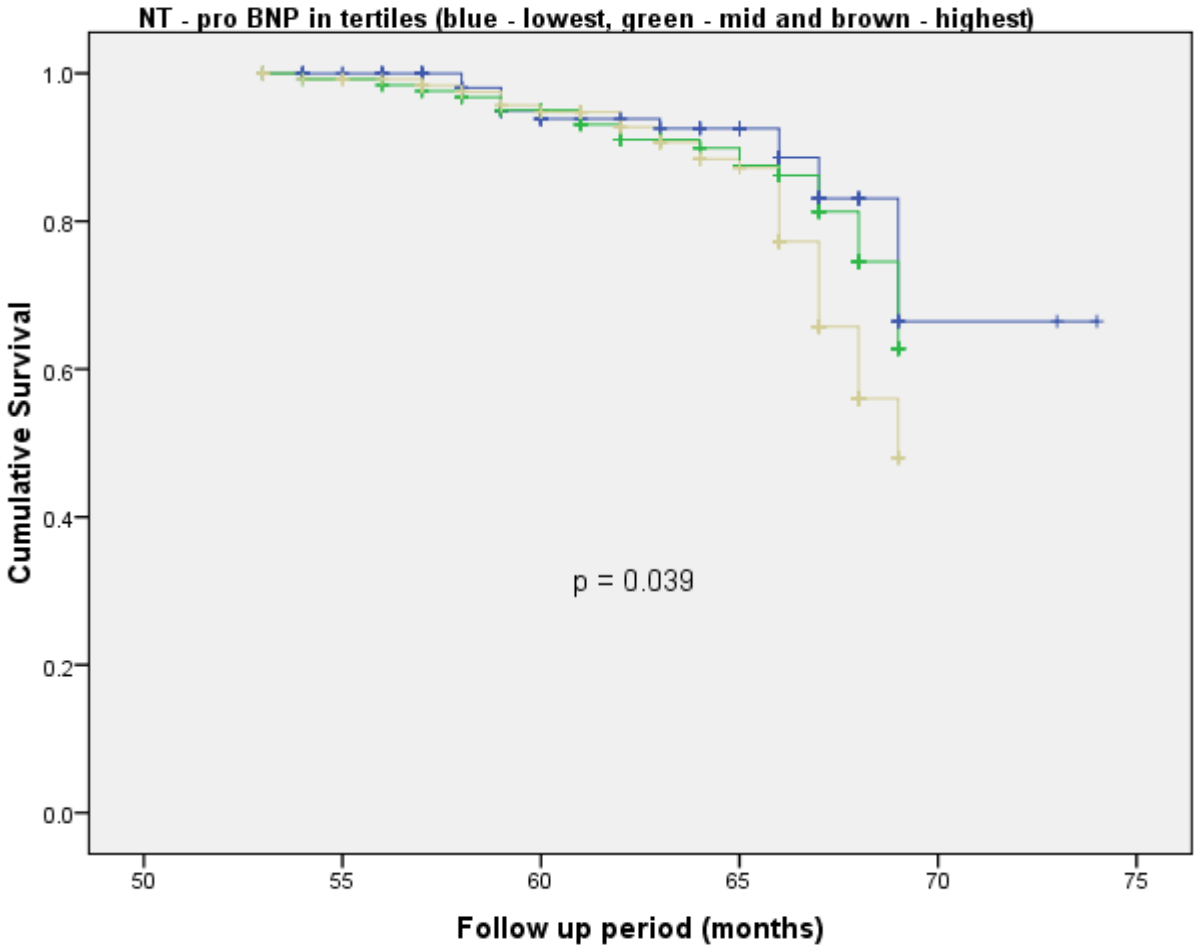


Figure 9.9. Relation between presence of late potentials on SAECG and NT-pro BNP level.

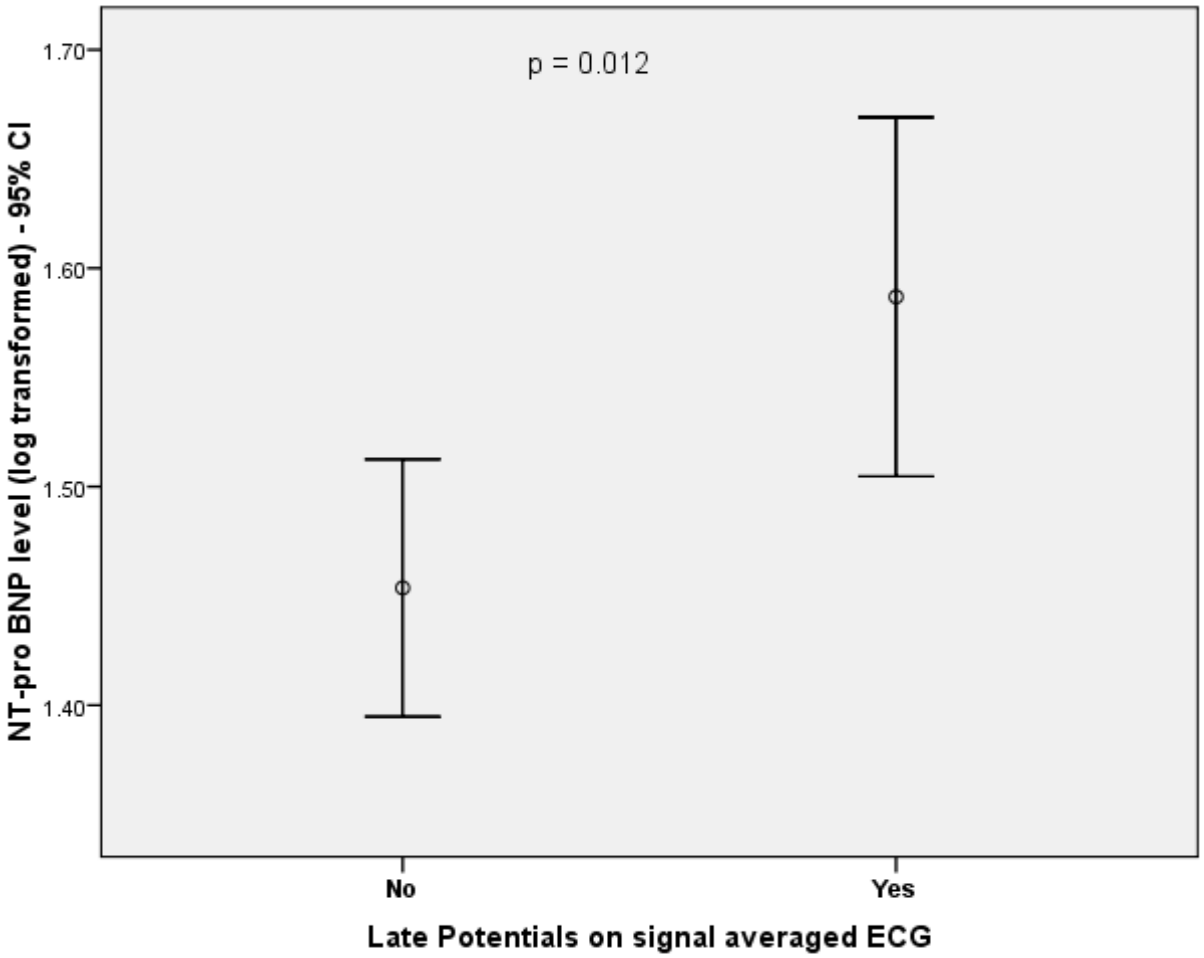
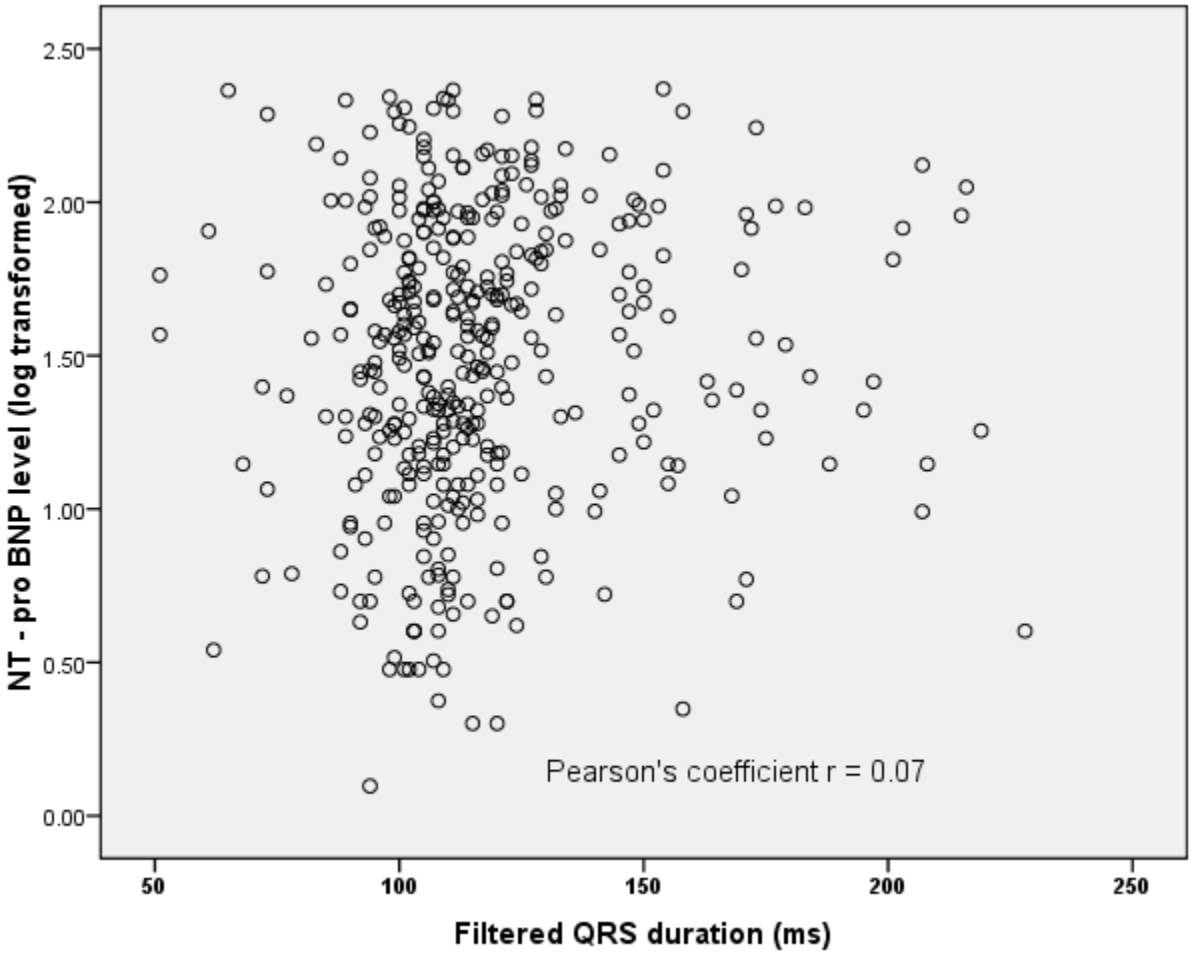


Figure 9.10. Correlation between filtered QRS duration on SAECG and NT-pro BNP level.



In an earlier study from the Euro Heart Failure survey data, I had demonstrated that increasing QRS duration on standard 12-lead ECG was associated with presence of significant LV dysfunction on echocardiography.[213] In the present study group where patients with gross QRS prolongation on 12 lead ECG were excluded, SAECG was able to identify patients with significant LV dysfunction on the basis of prolonged filtered QRS duration. The prevalence of late potentials increased with increasing severity of LV systolic dysfunction. Hence it could be used in settings where echocardiography is not immediately available (such as outpatient clinics) as recording SAECG does not usually require additional hardware (in modern equipment) and takes only an extra of 2 - 3 minutes. Nevertheless, SAECG can obviously not replace echocardiography as only 41% of those with moderate or severe LVSD were found to have late potentials. Further, 27% of patients without significant LVSD had late potentials. Thus, whilst there was a statistically significant relation between abnormal SAECG and LVSD, SAECG is not clinically useful as a screening test to either diagnose or exclude LVSD.

In addition to evaluating the SAECG variables, several other important observations were noted from this study. Elevated level of NT-pro BNP was associated with the presence of late potentials in this study, indicating a higher risk. It was also associated with presence of significant LV systolic dysfunction and increased risk of death in the medium term. In 1994, a seminal paper by Davis et al found that plasma BNP was raised in dyspnoeic patients with heart failure but not in acutely breathless patients with primary lung disorder.[214] Since then, numerous publications have confirmed the relation between raised BNP and left ventricular systolic or diastolic dysfunction and its prognostic significance.[215, 216] This study also found that raised NT-pro BNP predicted increased risk of death in the medium term. This would be consistent with the well-known ability of BNP to predict prognosis, thus increasing the confidence in

the results of this study, even though the number of patients recruited was relatively small.

The heart rate was higher in those who had died within 5 years. The relation between heart rate and prognosis in heart failure has been well established, explaining at least in part why beta blocker therapy would have prognostic benefit patients with all degrees of heart failure. [20, 22] The BEAUTIFUL study assessed the morbidity and mortality benefits of the heart rate-lowering agent ivabradine.[217] The placebo arm of the BEAUTIFUL trial was a large cohort of patients with stable coronary artery disease and LV dysfunction. Patients with heart rates of 70 beats per minute (bpm) or more had increased risk for cardiovascular death, admission to hospital for heart failure or MI, and coronary revascularisation.[218] Subsequently, the large SHIFT study confirmed the prognostic value for using ivabradine in addition to beta blocker therapy in patients whose heart rate exceeds 70 bpm.[219] Ivabradine reduced cardiovascular death, death from heart failure and hospitalisation for heart failure. The present study has found heart rate to be a significant predictor of all-cause mortality after heart failure, independent of beta blocker use. Thus, if a patient attends the heart failure clinic and is found to have a relatively fast heart rate despite beta blocker use, one should consider additional therapy for better heart rate control, such as with ivabradine, provided they are in sinus rhythm.

Use of loop diuretic therapy to control heart failure symptoms had been associated with increased risk of death in both univariate and multivariable analysis. This may be partially explained by the fact that patients with severe symptoms are more likely to be on loop diuretic therapy. However, the dose dependent association between loop diuretic therapy and adverse prognosis has been well recognised.[220-222] The

potential mechanisms are deterioration in renal function and severe electrolyte abnormalities leading to arrhythmias.[223, 224]

QTc interval was longer in patients who died within 5 years in univariate but not multivariate analysis in this study. It has long been known that QT dispersion predicts cardiac death in heart failure.[225] QTc dispersion reduction may be one of the mechanisms why ACE-inhibitor therapy improves prognosis in heart failure.[226] Long QTc *per se* has also been shown to predict cardiac death in other populations, such as stroke survivors.[227] Long QTc may identify silent but potentially lethal cardiac abnormalities which are often treatable.[228] In the present study, QTc was longer in patients with significant LV systolic dysfunction. This observation was noted previously (chapter 8) in the Euro Heart Failure survey data, but it was found to be mainly driven by the QRS prolongation.[213]

By comparison, QRS duration did not appear to predict 5-year survival, despite my observation that patients with increasing severity of LV systolic dysfunction had progressively longer QRS duration. This is intriguing especially since cardiac resynchronisation therapy is particularly effective in patients with prolonged QRS duration, although there is an ongoing debate about whether cardiac imaging (such as with echocardiography) may be superior in the selection of patients for CRT. [52, 229] However, this could be explained by the fact that in my cohort, patients with bundle branch block and gross QRS prolongation due to marked intra-ventricular conduction delay were excluded, as SAECG in these patients are known to have severe abnormalities mimicking late potentials, leading to a high false positive rate. If these were included in the study, it is likely that the relation between QRS duration and survival would have reached statistical significance.

One of the most important findings of this study is the observation that the QRS duration measured from a 12-lead ECG was only weakly correlated with QRS duration derived from signal averaged ECGs. In current clinical practice, if a patient has lots of ventricular ectopics, occasionally SAECG would be used to obtain a “filtered” QRS, which may over-estimate the true QRS duration. This is important because trials demonstrated the importance of QRS duration in selecting patients for CRT and implantable defibrillator therapies, and subsequently NICE guidelines recommended their use based on QRS duration measured from the 12-lead ECG. It can be argued that instead of using the filtered QRS duration, one should examine the 12-lead ECG for QRS duration from beats which are not ventricular in origin (and excluding beats which immediately follow a compensatory pause).

9.6 LIMITATIONS

The major limitation of this study is that SAECG was examined to predict all cause mortality, rather than only sudden cardiac death. However the fact that late potentials on SAECG were equally prevalent in those who died and in those who were alive, suggests that the role of SAECG in predicting death is very limited, if any.

9.7 CONCLUSIONS

The QRS duration measured from a 12-lead ECG is only weakly correlated with QRS duration derived from signal averaged ECGs. Late potentials on signal averaged ECG are associated with the presence of left ventricular systolic dysfunction, in patients presenting with symptoms and signs of heart failure. However SAECG is not useful in predicting all-cause mortality in patients who suffer from heart failure.

CHAPTER 10. RELATION BETWEEN PREVALENCE OF ARRHYTHMIAS ON HOLTER MONITORING AND RISK OF DEATH IN PATIENTS WITH HEART FAILURE

10.1 BACKGROUND

The prognosis of heart failure remains poor. Approximately one half of deaths are classified as sudden and cardiac (SCD) and are presumed to be due to arrhythmias. Although these deaths could be prevented by Implantable Cardioverter-Defibrillators (ICD), it is necessary to identify patients at risk of SCD, as ICDs are expensive and are associated with significant adverse events. Primary ICD prevention studies suggest that less functionally impaired patients with HF have the greatest gain in overall survival from prophylactic ICD placement.[54] This reflects the high mortality from causes other than SCD in patients with advanced heart failure or important co-morbidities such as lung or renal diseases. Although an ICD may prevent SCD in such cases the patient may survive only for a short period before dying of something else. Also, it is possible that ICD shocks accelerate deterioration in myocardial function.[230] This fact underscores the need for accurate risk profiling.

The search for accurate risk stratification methods to predict SCD is ongoing. Reduced left ventricular ejection fraction is universally accepted as a marker of the risk of SCD as is more severe symptoms of heart failure. Historically, Holter monitoring has been an important clinical diagnostic test for the recording of cardiac tachy and brady arrhythmias and it has evolved over the last three decades. It can now provide additional information including ST segment changes (to assess ischaemia providing the ECG is not significantly abnormal under non-ischaemic conditions), R-R interval

changes (to assess heart rate variability, as a marker of autonomic function), QRS measurements and signal averaged ECG (for late potentials).

10.2 HOLTER MONITORING IN HEART FAILURE

In patients with heart failure, Holter monitoring is useful in four situations; diagnosis and assessment of symptoms (such as palpitations or dizziness), evaluate chronotropic competence, prognostic assessment and risk stratification and evaluation of therapeutic interventions (such as changes in drug therapy, assessment of paroxysmal AF or ventricular rate control etc.).

Trials such as ESVEM (Electro physiologic Study Versus Electro cardiographic Monitoring) compared Holter monitoring with invasive methods such as electro physiologic studies to assess drug efficacy in patients with ventricular arrhythmias.[231] This trial demonstrated that Holter monitoring yielded more information at a much smaller cost. Later studies showed that variables obtained from Holter such as heart rate, heart rate variability, heart rate turbulence and presence of arrhythmias such as atrial fibrillation, ventricular premature beats, non-sustained ventricular tachycardia have prognostic value in heart failure.[34, 37]

And yet Holter monitoring is not routinely recommended in professional guidelines (such as National Institute of Clinical Excellence – NICE, in the UK) as part of routine management of heart failure (except for risk stratification for ICD therapy) which is logically inconsistent.

It should be noted that these studies on Holter monitoring were done some years ago and great progress has been made in treatment of heart failure since then. At present Holter monitoring is not widely performed as a routine investigation in patients with

heart failure. Hence I have attempted in this study to answer the question of usefulness of Holter monitoring in the contemporary era in providing prognostic information in patients with heart failure.

10.3 AIMS

1. To study the prevalence of arrhythmias in patients with chronic heart failure.
2. To study the relation between the abnormalities on Holter monitoring and mortality.

10.4 STUDY POPULATION AND METHODS

Patients being regularly followed up in a community heart failure clinic with stable heart failure symptoms and on optimal medical therapy were invited to participate. Patients were recruited after written informed consent.

Data were collected on history, NYHA status, clinical examination, medication, ECG, routine blood tests, echocardiogram. Holter monitoring was performed for 24 hours with Life Card CF digital Holter recorder (Del Mar Reynolds Medical Inc.) and data were analysed with Reynolds Pathfinder II program (Del Mar Reynolds Medical Inc.). Heart Rate Variability (HRV) parameters were also recorded. Vital status was recorded for all patients at the end of the follow up period.

The predominant Holter rhythm was recorded. All arrhythmias were captured. For patients in sinus rhythm, heart rate variability index of SDNN (standard deviation of the average R – R intervals) was recorded. Frequent ventricular ectopics (VE's) was defined as > 10 VE's /hour.[232] Non sustained ventricular tachycardia (NSVT) was

defined as 3 VE's or more in succession, but less than 30 seconds in duration. Sustained VT was defined as occurring more than 30 seconds in duration.

10.5 STATISTICAL METHODS

Both clinical variables and Holter variables were subjected to univariate analysis predicting mortality by binary logistic regression. A p value of < 0.05 was considered statistically significant. Those variables which were significant on univariate analysis were then included in a multivariable logistic regression model to predict mortality. Statistical analysis was done with SPSS v16 software.

10.6 RESULTS

194 patients were recruited over a 2 year period. The patient characteristics are given in table 10.1. On echocardiography, 67 (34%) had mild LVSD, 63 (33%) had moderate LVSD and 18 (9%) had severe LVSD.

The mean follow up period was 32 (9) months and 27 (14%) patients died during this period. 11 (41%) had sudden cardiac death, 11 (41%) died due to worsening heart failure and 5 (18%) died due to mainly non cardiac causes. The prevalence of arrhythmias is given in table 10.2. Six patients received an ICD in this period and were censored for analysis. Of those that received an ICD none died during the follow up period.

Of the 27 patients who died, 20 had moderate or severe LVSD and 12 had NSVT on Holter. Patients who died were older, had a longer QRS duration, more likely to have severe LV impairment or renal impairment, and had higher prevalence of AF, DM, frequent VEs and NSVT (table 10.3). Patients who died suddenly were more likely to

Table 10.1. Patient characteristics and LV function

Characteristic	**All** (n = 194)	**LVSD (n)**		
		None (n=46)	**Mild** (n=67)	**Mod/Severe** (n=81)
Age (yrs) - Median (IQR)	69 (13)	67 (17)	72 (11)	72 (14)
Male Sex (%)	138 (71)	26	50	62
Ischaemic Heart Disease (%)	138 (71)	29	44	65
Dilated Cardiomyopathy (%)	15 (8)	1	7	7
Hypertension (%)	89 (46)	24	32	33
Diabetes Mellitus (%)	31 (16)	5	12	14
Persistent Atrial Fibrillation (AF) at Assessment	40 (21)	3	18	19
Never smoked	50 (26)	15	11	24
Ex smoker	108 (56)	22	44	42
Current	29 (15)	7	11	11
Renal Impairment (%)(serum creatinine of > 127 µmol/l in men or > 107 µmol/l in women)	27 (14)	3	10	14
Medication (%)				
Aspirin	113 (58)	26	41	46
Warfarin	36 (19)	4	11	21
Beta blocker	140 (72)	24	52	64
Amiodarone	14 (7)	1	2	11
Digoxin	31(16)	4	9	18
ACEI or ARB	157 (81)	22	56	79
Thiazide	9 (5)	7	1	1
Loop diuretic	95(49)	12	32	51
Spironolactone	29 (15)	3	3	23
Statin	106 (55)	26	33	47

Table 10.2. Prevalence of arrhythmias on holter monitoring.

Arrhythmias	Overall No (%)	LVSD		
		None	Mild	Mod/Severe
Atrial fibrillation	40 (21)	3 (7)	18 (27)	19 (23)
Frequent VE's	47 (24)	3 (7)	16 (24)	28 (35)
NSVT	35 (18)	3(7)	11 (16)	21 (26)
Sustained VT	6 (3)	0	3 (4)	3 (4)

have had significant arrhythmias on Holter monitoring; frequent VE's in 73%, NSVT in 73%and AF in 64%. On univariate analysis, the same factors (except age and QRS duration) predicted higher mortality (table 10.4). On multivariable analysis, presence of NSVT on Holter monitoring predicted increased mortality along with the clinical factors such as AF, diabetes, renal impairment and severe left ventricular dysfunction (table 10.5). SDNN, the measure of heart rate variability did not predict outcome.

Table 10.3: Differences in clinical characteristics between patients who survived or died at 2 years

Variable	Alive	Dead	P value
Age in years (median)	68	75	0.014
QRS duration in ms (median)	98	126	0.089
VE count (median)	98	1789	0.008
Couplet count (median)	0	13	0.001
Frequent VE's (%)	20	48	0.002
NSVT (%)	14	44	< 0.001
Renal impairment (%)	10	37	< 0.001
AF (%)	16	52	< 0.001
No LVSD (%)	28	0	0.002
Mild LVSD (%)	36	26	0.311
Moderate LVSD (%)	30	48	0.061
Severe LVSD (%)	7	26	0.001
Diabetes (%)	13	30	0.008

Table 10.4. Univariate predictors of mortality

Variable	OR	95% CI	P value
Frequent VE's	3.6	1.6 – 8.5	0.003
VE count	> 1.0		0.013
NSVT	5.0	2.1 – 12.0	< 0.0001
Couplet count	>1.0		0.031
Renal impairment	5.1	2.1 -13.1	0.001
AF	5.8	2.5 -13.8	< 0.0001
Severe LVSD	5.0	1.7 – 14.3	0.003
DM	3.3	1.3 – 8.3	0.011

Table 10.5. Multivariable predictors of mortality

Variable	OR	95% CI	P value
NSVT	3.3	1.1 – 10.0	0.032
Renal impairment	6.8	2.2 – 20.9	0.001
AF	5.3	1.9 – 15.1	0.002
Severe LVSD	4.3	1.2 – 15.4	0.025
Diabetes	3.2	1.1 – 9.8	0.039

10.7 DISCUSSION

This analysis of Holter monitoring shows that arrhythmias remain extremely common in patients with chronic heart failure despite modern pharmacological therapy and that NSVT remains an important predictor of prognosis. This suggests that NICE guidelines should be made consistent and perhaps all patients with heart failure, unless they are clearly not a candidate for an ICD due to frailty and co-morbidity, should undergo Holter monitoring. The current NICE guidelines mention Holter monitoring only in the context of patient selection for an ICD. This analysis suggest that Holter monitoring may provide additional prognostic information. The duration of monitoring and how often this should be repeated are unknown.

Although arrhythmias are common, their prevalence may be lower than previously reported, when more than 85% of patients with heart failure were reported to have frequent VEs.[233] This may reflect improvement in treatment of heart failure such as widespread use of beta blockers but could also reflect differences in case selection, since previous studies tended to focus on patients with severe LVSD.

Those patients who had arrhythmias such as atrial fibrillation and non sustained ventricular tachycardia had a poorer prognosis, independent of other traditional risk factors such as diabetes, renal impairment and severity of left ventricular systolic dysfunction. This is in line with previous studies and a recent meta-analysis of 16 studies involving 53 969 patients suggesting that the presence of AF is associated with an adverse prognosis in CHF irrespective of LV systolic function.[234] My study supports this observation.

Previous studies have suggested that non sustained VT in patients after myocardial infarction was associated with a higher mortality,[37] but it was inferior to other

markers such as left ventricular dysfunction in its predictive value. On the other hand an epidemiological study of heart failure conducted before the widespread use of beta-blockers (UK-HEART) suggested that presence of symptomatic non sustained VT on Holter monitoring was associated with higher risk of sudden death.[34] A recent analysis of DYNAMIT trial found that patients with non sustained VT experienced higher rates of both arrhythmic and non arrhythmic death.[235] A meta analysis which included 11 prognostic studies with > 100 patients with good quality data and multivariate analysis of predictors of sudden cardiac death found that absence of NSVT was associated with a low probability of sudden cardiac death in patients with left ventricular impairment.[236] It is possible that higher prevalence of arrhythmias reflect sicker ventricles and therefore imply higher risk of both arrhythmic and non arrhythmic death.

Severe left ventricular dysfunction, diabetes and renal impairment are well established markers of high risk in patients with heart failure and several studies have demonstrated their association with poor prognosis. However, these are generally non modifiable risk factors and their presence simply imply a worse prognosis since any therapeutic interventions are unlikely to modify these risk factors in the majority of the patients. Obviously, more accurate assessment of risk is unlikely to be useful in the absence of effective therapeutic interventions to target these adverse prognostic factors. In contrast, the arrhythmic markers revealed by Holter monitoring can be modified by intense medical therapy with maximum tolerated dose of beta blockers and ACE inhibitors which may reduce both incidence and prevalence of arrhythmias, thereby altering the risk profile favourably. Patients with silent paroxysmal AF may benefit from anticoagulation with warfarin and patients with poorly controlled AF may

benefit from amiodarone therapy or newer treatments such as AF ablation, thereby preventing tachycardia mediated deterioration in LV function.

Although not demonstrated in this study, a small proportion of elderly heart failure patients would be of high risk of sudden death due to silent bradyarrhythmias that may be unmasked by Holter monitoring. Those patients with heart failure and relatively few symptoms but high risk arrhythmias on routine Holter monitoring could be considered for device therapy with ICDs (or CRT-D). Thus Holter monitoring can identify additional prognostic indicators that can be modified by effective therapeutic interventions.

10.8 LIMITATIONS

The patient numbers are small in this analysis, as I had included only those patients for whom I was responsible for arranging the Holter monitor.

10.9 CONCLUSIONS

In summary, Holter monitoring is useful in the management of patients with heart failure as it can provide prognostic information in addition to its value in evaluating arrhythmias. Hence it should be considered routinely in all patients with heart failure, even in the absence of symptoms suggestive of arrhythmias and it may aid selection for ICD as suggested by the NICE guidelines.

11. PREDICTORS OF SHOCKS AND MORTALITY IN HEART FAILURE PATIENTS WITH IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS (ICDS) – ALL INDICATIONS

11.1 INTRODUCTION

The incidence of sudden cardiac death is 100,000 / year in the UK.[237] Implantable Cardioverter Defibrillators (ICD) represent a major advance over the last decade in the fight against sudden cardiac death.[238] ICDs are used for both primary and secondary prevention of sudden cardiac death in high risk populations such as those with heart failure or inherited cardiomyopathies and as a bridge to heart transplant.[239-241] ICDs have been shown in many clinical trials to be effective in aborting sudden arrhythmic death.[242] [60, 166]

Only limited data exist about the determinants of long term outcome after ICD implantation.[243] A proportion of patients do not benefit and experience adverse effects such as infection, unnecessary shocks, potential for pro-arrhythmia, device malfunction, highly publicized manufacturer advisories, and procedural complications, which can adversely affect morbidity and quality of life.[244-251] Patients get no benefit in terms of heart failure symptoms or quality of life with an ICD and indeed there is some evidence that they make symptoms worse.[252] ICDs do reduce the risk of dying from a lethal arrhythmia but may reprogram the mode of death from sudden arrhythmic death into death due to worsening heart failure. In the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), seven more people were alive after 5 years for every 100 devices implanted, but 29 had died despite an ICD implant.[54] In a meta-analysis that showed a significant difference in mortality in favour of ICD with a combined follow-up period of 6 years, patients with defibrillators lived only 4.4 months longer than those treated with anti-arrhythmic therapy, and all statistically significant

differences were non-sustained, narrowing at 4 years towards negligible after 6 years.[253] ICDs are expensive (total cost probably in excess of 30,000 euros for purchase, implantation and programming). A critical appraisal by an expert group considering all the published evidence concluded that the major clinical trials have overestimated the clinical benefits and underestimated the risks and cost effectiveness.[254] Hence patient selection is a major issue in the absence of reliable risk stratification methods for primary prevention.[255] I believe that longitudinal follow up data from those patients who had ICDs implanted will help in better patient selection and to find out those interventions which will minimise the risk of adverse events due to the ICD.

11.2 AIMS

1. To identify predictors of mortality after ICD implantation.
2. To identify predictors of appropriate shocks due to malignant ventricular arrhythmias.
3. To estimate the incidence of adverse effects and inappropriate shocks.

11.3 STUDY POPULATION

I invited 211 patients who were being seen in a tertiary centre ICD clinic to participate in the Heart Care (comprehensive heart failure assessment and follow up) programme of the academic department of cardiology at the University of Hull. 165 patients agreed to participate and they were included in the study after written consent.

11.4 METHODS

Patients were seen at regular intervals (at least twice a year) and a comprehensive assessment was done at each visit. In addition to detailed history and clinical

examination, investigations included 12 lead ECG, signal averaged ECG, 2D echocardiogram, routine blood tests, NT pro BNP, six minute walking test, regular ICD interrogation and review of medical therapy. ICD interrogation was done by expert technicians and all arrhythmia episodes were reviewed by attending physicians. All therapies by the device were reviewed by the attending physician and deemed appropriate or inappropriate.

The relationship between the likelihood of experiencing an appropriate shock, mortality and the predictor variables was investigated by binary univariate and multivariable logistic regression and odds ratios calculated. The relation between the number of inappropriate shocks and the predictor variables was examined by Poisson regression from which incidence rate ratios (IRR) were estimated.

11.5 RESULTS

165 patients were enrolled in this study. Mean age was 67 $\pm$ 10 (range 31 – 84) years and 83% were men. Most (76%) had history of coronary artery disease and 72% had history of previous myocardial infarction. Among patients with CAD, 56% had previous coronary revascularisation (percutaneous in 11%, bypass surgery in 41% and 3% had both). The indications for ICD and the type of ICD in this study population are given in table 11.1. The most frequent indication was ischemic heart disease with impaired left ventricular function (75%). 89% of ICDs were implanted for secondary prevention. The baseline characteristics are given in table 11.2.

The mean follow up period was 68 (34) months. A significant complication related to implant and necessitating extended hospital stay or re-admission, occurred in 26 patients (16%). 45 patients (28%) were readmitted due to an arrhythmia.

Table 11.1 Indications for ICD

Indication	**No (%)**
Coronary artery disease and impaired LV function – primary prevention	8 (5)
Coronary artery disease and impaired LV function – secondary prevention	115 (70)
Dilated cardiomyopathy – primary prevention	7 (4)
Dilated cardiomyopathy – secondary prevention	32 (19)
Heart failure due to hypertrophic cardiomyopathy	3 (2)
ICD device type	
Single chamber	96 (58)
Dual chamber	52 (32)
Bi ventricular	11 (7)

Device interrogation showed episodes of supra ventricular tachycardia in 36 (22%) patients, non-sustained ventricular tachycardia in 61 (37%) and frequent ventricular ectopics in 28 (17%) patients. 51 (31%) patients had a generator or lead change during the follow up period (5 ½ years). Sustained ventricular arrhythmias occurred in 59 patients (36%) during this period. Anti tachycardia pacing was activated in 63 (38%) patients and was successful in terminating the arrhythmia in 38 (60%) patients on at least one occasion. 27 patients (16%) died. 46% had shocks from the ICD, appropriate in 32%, inappropriate in 22%. 9% had both appropriate and inappropriate shocks. The time to first shock was 20 (23) months. Those who had appropriate shocks were alive for a median period of 34 months after the first shock and those who had inappropriate shocks were alive for a median of 26 months after the first shock.

Table 11.2. Baseline patient characteristics (n = 165)

Age (yr)	
Median	68
Interquartile range	62 - 72
Male Sex (%)	137 (83)
NYHA (%)	
I	12 (7)
II	49 (30)
III	84 (51)
IV	7 (4)
Ischaemic Heart Disease (%)	123 (75)
MI pre implant	118 (72)
MI post implant	3 (2)
Coronary revascularisation (%)	
PCI	14 (9)
CABG	51 (31)
Both PCI & CABG	4 (2)
Dilated cardiomyopathy (%)	39 (24)
Hypertension (%)	56 (34)
Diabetes (%)	27 (16)
Smoking (%)	
Never smoked	56 (34)
Ex smoker (> 12 m)	89 (54)
Current	18 (11)
ECG Rhythm (%)	
Sinus	117 (71)
Paced	37 (22)
Atrial Fibrillation (all types)	59 (36)

QRS duration (ms)	
Median	118
Interquartile range	100 - 152
Left ventricular ejection fraction (%)	
Median	30
Interquartile range	20 – 40
Hyponatraemia (%) (Na < 135 mmol/l)	15 (9)
Hyperkalaemia (%) (K > 5 mmol/l)	26 (16)
Renal Impairment (%) (serum creatinine of > 127 µmol/l in men or > 107 µmol/l in women)	67 (41)
Anaemia (%) (Hb < 13 g/dl in men or Hb < 12 g/dl in women)	46 (28)
Medication (%)	
Anti platelet drugs	100 (61)
Warfarin	52 (32)
Beta blocker	150 (91)
Amiodarone	77 (47)
Digoxin	13 (8)
ACEI	116 (70)
ARB	19 (12)
Thiazide	5 (3)
Loop diuretic	110 (67)
Spironolactone	43 (26)
Statin	111 (67)
Nitrate	21 (13)
Nicorandil	11 (7)

The overall rate of adverse events, including implant or device complications and inappropriate shocks, was 32%. 20% of patients did not derive an explicit benefit from ICD (i.e. appropriate shocks or ATP), but experienced an adverse event related to the ICD. 43% received no explicit benefit but had no adverse event (table 11.3).

Table 11.3: Details of benefit and harm from ICD

Neither Benefit nor Harm 71 (43%)	Benefit Only (Appropriate shock or successful ATP) 38 (23%)
Harm Only: 26 (16%) Inappropriate Shock: 14 (9%) Other complications: 12 (7%)	Benefit & Harm 28 (17%)

11.5.1 Shocks

11.5.1.1 Appropriate shocks

The univariate predictors of appropriate shocks are given in table 11.4. When examined as continuous variables, increasing QRS duration and lower ejection fraction were both associated with increased risk of appropriate shocks. When examined as categorical variables, presence of bundle branch block on ECG, paced rhythm on ECG and severe left ventricular impairment on echocardiography were both associated with increased risk of appropriate shocks. Prevalence of arrhythmias such as frequent ventricular ectopics, non sustained ventricular tachycardia and supraventricular

tachycardia (SVT) were also associated with appropriate shocks. Patients with more severe symptoms, as those in NYHA class 3 or on Spironolactone were also more likely to experience an appropriate shock.

On multivariable analysis, three variables were independently associated with an increased risk of experiencing an appropriate shock; severe LVSD (OR 2.2; 95% CI 1.1 – 4.8; p = 0.035), paced rhythm on ECG (OR 2.5; 95% CI 1.1 – 5.9; p = 0.032) and SVT (OR 2.7; 95% CI 1.2 – 6.3; p = 0.019).

11.5.1.2 Inappropriate shocks

The factors associated with inappropriate shocks are given in table 11.5. The IRRs derived from Poisson regression indicate the association with not only the risk but also the number of inappropriate shocks. Atrial fibrillation and supraventricular tachycardia were the strongest predictors. The paucity of variables did not allow a multivariable analysis. Patients who had dual chamber ICDs had lower incidence of inappropriate shocks when compared to those with single chamber ICDs (18% vs 25%), but this did not reach statistical significance.

11.5.1.3 NYHA class and outcome

84 (51%) patients were in NYHA class 3 status at the time of ICD implantation. Among this group, 19 (23%) died, 46 (56%) experienced shocks, 32 (39%) appropriate and 21 (26%) inappropriate. NYHA class 3 was significantly associated with increased risk of shocks (OR 2.3; 95%CI 1.2-4.3; p = 0.01). When analysed separately for appropriate and inappropriate shocks, there was a tendency for increased risk of both types of shocks (tables 11.4 and 11.5).

Table 11.4 Univariate predictors of appropriate shocks

Variable	OR	95% CI	P
QRS			0.048
BBB	2.2	1.1 – 4.4	0.019
Paced rhythm on ECG	3.0	1.2 – 7.1	0.015
Severe LVSD	2.7	1.3 – 5.6	0.010
EF	0.97	0.94 – 0.99	0.017
VEs	3.1	1.3 – 7.0	0.009
SVT	2.5	1.2 – 5.5	0.019
NSVT	2.5	1.3 – 5.0	0.007
Spironolactone	2.2	1.1 -4.6	0.033
NHYA class III	2.0	1.0 – 3.8	0.05

Table 11.5. Univariate predictors of inappropriate shocks (Poisson regression models)

Variable	OR	95% CI	P value
Atrial fibrillation	3.5	1.5 – 8.2	0.004
Supra ventricular tachycardia	5.8	2.8 – 11.9	< 0.0001
Non sustained VT	1.9	1.0 – 4.0	0.08
NYHA 3 at implantation	2.3	1.0 – 5.4	0.06
BMI	0.9	0.86 – 0.99	0.03

11.5.2 Mortality

Univariate associations for all-cause mortality are presented in Table 11.6. Increasing age, body mass index and QRS duration were associated with increased risk of death. Patients in paced rhythm, those with diabetes, anaemia, renal impairment, hyponatremia, hyperkalemia and patients with severe LVSD were more likely to die. Patients in sinus rhythm and those on beta blocker treatment were less likely to die. There was a significant relationship between death and appropriate shocks. NYHA class 3 was again associated with adverse prognosis. In a multivariable model, adjusted for age, three variables were significantly associated with all-cause mortality. Two variables were associated with a favourable prognosis; sinus rhythm (OR 0.1; 95%CI 0.1-0.6; p = 0.015) and beta blocker treatment (OR 0.1; 95%CI 0.1-0.6; p = 0.020). Patients who had renal impairment were more likely to die (OR 8.4; 95%CI 1.2-60.6; p = 0.034).

11.6 DISCUSSION

This study suggests that presence of non sustained arrhythmias, increased QRS duration and lower left ventricular ejection fraction increased the risk of having an appropriate shock. SVT and atrial fibrillation predicted the rate and number of inappropriate shocks. Renal impairment increased the risk of all-cause mortality in patients who have received an ICD. ECG rhythm was a major factor affecting the outcome and beta blocker treatment was beneficial.

Severe LV impairment and non sustained VT have previously been shown to be associated with higher risk of death in heart failure patients.[256-258] In the TOVA study, an EF < 20% was associated with higher risk of appropriate shocks (OR 3.9; 95%CI 1.3 – 11.2).[258]

Table 11.6. Univariate predictors of mortality

Variable	OR	95% CI	P value
Age (years)	1.1	1.0 – 1.4	0.038
BMI	1.1	1.0 – 1.1	0.025
NYHA class III	2.7	1.1 – 6.5	0.031
Diabetes	2.6	1.0 – 6.8	0.05
Sinus rhythm	0.4	0.2 – 0.9	0.02
Paced rhythm	3.0	1.2 – 7.1	0.015
Filtered QRS on SAECG	1.01	1.0 – 1.02	0.014
Broad QRS (> 120 ms) on 12 lead ECG	2.4	1.0 – 6.0	0.049
Severe LVSD	3.3	1.4 – 7.8	0.006
Renal impairment	7.0	2.6 – 18.5	< 0.001
Hyperkalaemia	2.8	1.1 – 7.4	0.036
Hyponatraemia	4.1	1.3 – 12.7	0.015
Anaemia	2.4	1.0 – 5.7	0.04
Spironolactone	2.8	1.2 – 6.5	0.02
Beta blocker	0.2	0.1 – 0.5	0.002
Appropriate shocks	2.8	1.2 – 6.5	0.018

In this study NSVT was associated with higher risk of appropriate shocks and severe LV impairment was associated with death. However, NSVT did not predict death suggesting that ICDs do indeed manage this mortality risk factor effectively. This was also shown in the previous analysis of Holter monitoring in which NSVT predicted death but none of the ICD recipients died during the follow up period.

QRS duration is a marker of cardiac dyssynchrony and in my study increased QRS duration was associated with worse prognosis. This supports the argument that patients with heart failure needing an ICD should be considered for more aggressive management with a CRT-D device, if they have a broad QRS duration since CRT has been shown to reduce mortality in patients with symptomatic heart failure and broad QRS duration.[52, 259] However, it should also be noted that those patients in paced rhythm did not do well.

Atrial fibrillation and SVT were strong predictors of inappropriate shocks. As most of the ICDs were programmed to detect VT by rate algorithm, any supraventricular rhythm with a high rate above the VT threshold is likely to be misinterpreted by the device. Atrial fibrillation has been shown previously to be associated with an increased risk of mortality or appropriate device therapy and increased the risk of inappropriate device therapy by three fold.[260, 261]

It is known that patients in NYHA class 3 are likely to get more shocks than those in NYHA class 2.[262] This study supports this observation as those in this group were at a significantly higher risk of death or experiencing a shock. It is also known that patients with NYHA class 4 are more likely to get appropriate shocks very soon after implant.[263] Some cardiologists believe that patients with severe heart failure should not have ICDs implanted as benefit vs risk ratio is likely to be small. But a recent

analysis of published literature has found no evidence for this argument, as no attenuation of benefit of ICD implantation was found in patients with higher NYHA class or lower LVEF.[264] This study also supports this observation as patients in NYHA class 3 had a higher incidence of death and appropriate shocks. Patients on spironolactone in this study were more likely to get an appropriate shock as spironolactone is usually prescribed for those patients in NYHA class 3 or worse symptoms.

In the MADIT II study and SCD-HeFT, inappropriate shock occurrence was associated with increased probability of mortality in follow-up. Coupled with potential effects on quality of life, this association with increased mortality heightens the importance of efforts to reduce the occurrence of inappropriate shocks. The main strategy to avoid inappropriate shocks has been to implant a dual chamber ICD (DC-ICD), but the extent to which DC-ICD devices confer advantage is controversial. Some studies found no benefit whereas others have shown a modest reduction.[265, 266] In my study there was trend towards lower incidence of inappropriate shocks with DC-ICDs.

Advanced age was a predictor of death as expected. This is an important observation as there are no clear criteria for ICD implantation in very elderly, since this group was excluded in trials. Despite this, approximately one fifth of devices are implanted in this age group. This was demonstrated in a recent multivariate analysis of data from a large registry of 26,887 patients (73% male with a median age of 70). The in-hospital mortality increased from 0.7% among patients younger than 80 years to 1.2% among those aged 80 to 85 years and 2.2% among those older than 85 years ($P < .001$).[267] Hence more studies should address the benefit of ICD in very elderly.

Higher body mass index was associated with increased risk of death in this study. In MADIT II, BMI $\geq$ 30 was associated with increased risk for appropriate ICD therapy for VT, VF, or death.[268] In this trial obese patients who comprised 25% of the study population had appropriate ICD therapy in 39% as compared to 24% in non obese patients at 2 years of follow up. However in some heart failure studies, increased BMI was in fact associated with better prognosis.[92, 170] This is thought to be a part of "reverse epidemiology" whereby traditional risk factors such as high blood pressure, high cholesterol and obesity are associated with a better survival in advanced HF. My findings are however in line with MADIT II analysis with regards to BMI. This may be due to a selection bias, as thin cachectic patients with advanced heart failure are less likely to have received an ICD on the basis that their prognosis is so poor that an ICD is unlikely to alter it favourably.

Renal impairment has been consistently associated with adverse outcome in both acute and chronic heart failure. In this study population renal impairment was the strongest predictor of death. This questions the value of ICD implantation in those with established renal impairment, as ICD may not prevent premature death in this high risk population.

Beta blocker therapy has been proven to be the most valuable pharmacological treatment along with ACE inhibitors in heart failure. Hence it is not surprising that it's beneficial effects extend to those who have had ICD therapy. This also proves that pharmacological and device therapy in heart failure are complimentary to each other with incremental benefit.

Over a quarter of all ICD recipients needed rehospitalisation following the implant for reasons including arrhythmias, inappropriate shocks and device related factors. This

highlights the significant morbidity associated with the device, the need for long term medical intervention and the associated cost. This situation is unlikely to change as evident from recent manufacturer recalls of defective ICD generator and leads. [269-271]

11.7 LIMITATIONS

ICD therapies may not be a surrogate for sudden cardiac death, as many episodes may have been non-sustained non-fatal events. Hence all appropriate shocks might not be "necessary" shocks. This study population included patients from pre "Care-HF" period and hence had a low rate of BiV –ICD implants.

11.8 CONCLUSIONS

In summary, ICDs may prevent arrhythmic death by delivering appropriate shocks in a significant proportion of patients and the rest may be benefitting indirectly by the reassurance of having ICD protection. However, this comes with a price of significant adverse events and inappropriate shocks. Renal impairment is associated with a high risk of death in ICD recipients and beta blocker treatment favourably affects the outcome.

CHAPTER 12. ICDS FOR PRIMARY PREVENTION – FACTORS ASSOCIATED WITH SHOCKS AND MORTALITY IN CONTEMPORARY HEART FAILURE POPULATION.

12.1 INTRODUCTION

Increasing numbers of ICDs have been implanted over the last few years for primary prevention of sudden cardiac death in patients with heart failure after publication of MADIT II and SCD-HeFT trials. With increasing survival after myocardial infarction the population eligible for ICD for primary prevention is large.[272, 273] With limited health resources, it is not possible for most economies to afford an ICD to everyone who is eligible based on these trial data. Currently less than 10% of eligible patients (based on trial data) receive an ICD in the USA.[274] Thus it is necessary to understand the factors which influence the clinical outcome after ICD implantation and establish that risk benefit ratio in these patients is favourable in order to justify the enormous cost involved. Hence I undertook this study examining those patients who have heart failure and received the ICD for primary prevention of sudden cardiac death.

12.2 STUDY POPULATION

Consecutive patients who had received an ICD for primary prevention indications in heart failure, at a large tertiary centre in the UK (Liverpool Heart and Chest Hospital, Liverpool) during 2007-2008.

12.3 AIMS

1. To describe the incidence of shocks and mortality.

2. To identify factors that predicted shocks and mortality.

3. To describe the device related complications.

12.4 METHODS

Approval for this study was obtained from the R&D department of the Liverpool Heart & Chest Hospital. Patients who had an ICD for primary prevention in heart failure during 2007 – 2008 were identified by the clinical audit department. I then retrieved the patients' clinical records, ICD implantation details, follow up clinical and ICD interrogation data. Those who had a primary prevention ICD for non heart failure related indications such as channelopathies or adult congenital heart disease were excluded. The vital status (alive or dead) was determined from the case records and this was cross checked with the patient administration system linked to national deaths database.

Patients' baseline clinical characteristics, NYHA functional status, left ventricular ejection fraction, details of medication, QRS duration on ECG, urea, creatinine and haemoglobin were recorded. The type of ICD, device complications and any system change during follow up were also recorded. The incidence of appropriate shocks and inappropriate shocks were obtained from the ICD follow up records. The prevalence of any non sustained arrhythmias detected during ICD interrogation was also recorded.

12.5 RESULTS

105 patients were enrolled in this study. All of them had objective evidence of left ventricular systolic dysfunction and had ICD implantation for primary prevention. The baseline clinical characteristics are given in table 12.1. More than 90% were men and 88% were in NHYA class II/III. 75% had suffered previous myocardial infarction. Approximately one-fourth of them had diabetes. 94% of patients were treated with ACE inhibitors and 71% with beta blockers.

Biv-ICD was the most common type of device implanted (56%). 21 (20%) had a device related complication, 11 (10%) of which needed a reoperation (table 12.2). Others were managed conservatively (table 12.3). Two patients needed a device enhancement at a later date (table 12.2).

The median follow-up was 25 months (inter-quartile range 18 – 30 months). During this period 21 (20%) patients died, 6 (6%) patients experienced at least 1 appropriate shock and 7 (7%) experienced inappropriate shocks. The relation between ECG rhythm (prior to ICD implantation), beta blocker therapy and outcome is shown in table 12.4.

There was a trend for better survival in patients who were in sinus rhythm when compared to those in atrial fibrillation, but this was not statistically significant ($p = 0.134$). There was also trend for better survival in those on beta blocker therapy, again not statistically significant ($p = 0.134$). Patients with diabetes had a higher rate of death (26% vs 18%), but the difference was not statistically significant ($p = 0.409$).

Only one patient experienced appropriate shocks on four occasions and another patient experienced three inappropriate shocks before death. The only variable associated with increased risk of death was elevated serum creatinine; > 127 µmol/l in men or > 107 µmol/l in women (OR 4.1; 95%CI 1.4 – 11.7; $p=0.008$). The relationship between serum creatinine level (in quartiles) and mortality is shown in table 12.5. Patients who had their creatinine in the lowest or highest quartiles had worse outcome than those who had creatinine in the mid two quartiles (figure 12.1).

No specific variables predicting appropriate shocks were identified. The causes of inappropriate shocks were given in table 12.6.

Table 12.1 Baseline clinical characteristics (n = 105)

Age (yr)	
Median	68
Inter-quartile range	61 – 73
Male Sex (%)	98 (93)
NYHA (%)	
I	9 (9)
II	35 (33)
III	58 (55)
IV	3 (3)
Ischaemic Heart Disease (%)	86 (82)
Previous MI	79 (75)
Coronary revascularisation (%)	
PCI	9 (9)
CABG	43 (41)
Both PCI & CABG	5 (5)
Dilated cardiomyopathy (%)	12 (11)
Hypertension (%)	50 (48)
Diabetes (%)	23 (22)
Smoking (%)	
Never smoked	17 (16)
Ex smoker (> 12 m)	73 (70)
Current	9 (9)
ECG Rhythm (%)	
Sinus	83 (79)
Paced	3(3)
Atrial Fibrillation	19 (18)

QRS duration (ms)	
Median	136
Inter-quartile range	112 – 162
Left ventricular ejection fraction (%)	
Median	27
Inter-quartile range	20 – 30
Renal Impairment (%) (serum creatinine of > 127 µmol/l in men or > 107 µmol/l in women)*	22 (21)
Anaemia (%) (Hb < 13 g/dl in men or Hb < 12 g/dl in women)*	27 (26)
Medication (%)	
Aspirin	52 (50)
Clopidogrel	23 (22)
Warfarin	47 (45)
Beta blocker	74 (71)
Amiodarone	25 (24)
Digoxin	17 (16)
ACEI /ARB	99 (94)
Loop diuretic	81 (77)
Spironolactone	49 (47)
Statin	89 (85)
Device Type (%)	
Single	26 (25)
Dual chamber	20 (19)
Bi ventricular	59 (56)

Table 12.2 Details of reoperation after ICD implantation

Intervention	**No**
Epicardial lead (as unable to position a endocardial LV lead)	5
Replacement of a faulty lead	1
Replacement of a faulty generator	1
Lead repositioning	4
Upgrade to a BiV device	1
Addition of SVC coil	1

Table 12.3 Complications managed conservatively

Complication	**No**
Severe anxiety	1
Muscle twitching	1
Wound sepsis	1
Wound discharge	1
Hematoma	1
Chronic pain over the site	1
RV lead malfunction (settings readjusted)	1
Lead fracture (device switched off)	1

Table 12.4 Relation between ECG rhythm (prior to ICD implantation), beta blocker therapy and outcome

	No BB	**BB**	**SR**	**AF**	**Paced**
Alive	22 (71%)	62 (84%)	67 (81%)	14 (74%)	3 (100%)
Dead	9 (29%)	12 (16%)	16 (19%)	5 (26%)	0 (0%)

Table 12.5 Relation between creatinine level (in quartiles) and mortality

Status	**Serum Creatinine** (µmol/l) **in quartiles**			
	Q1 ≤ 83 µmol/l	**Q2** 83.1 – 101.5 µmol/l	**Q3** 101.6 – 119.5 µmol/l	**Q4** > 119.5 µmol/l
Alive	20 (80%)	23 (92%)	23 (92%)	18 (72%)
Dead	5 (20%)	2 (8%)	2 (8%)	7 (28%)

Figure 12.1 Kaplan – Meier survival plot showing the relation between serum creatinine and survival after ICD implantation.

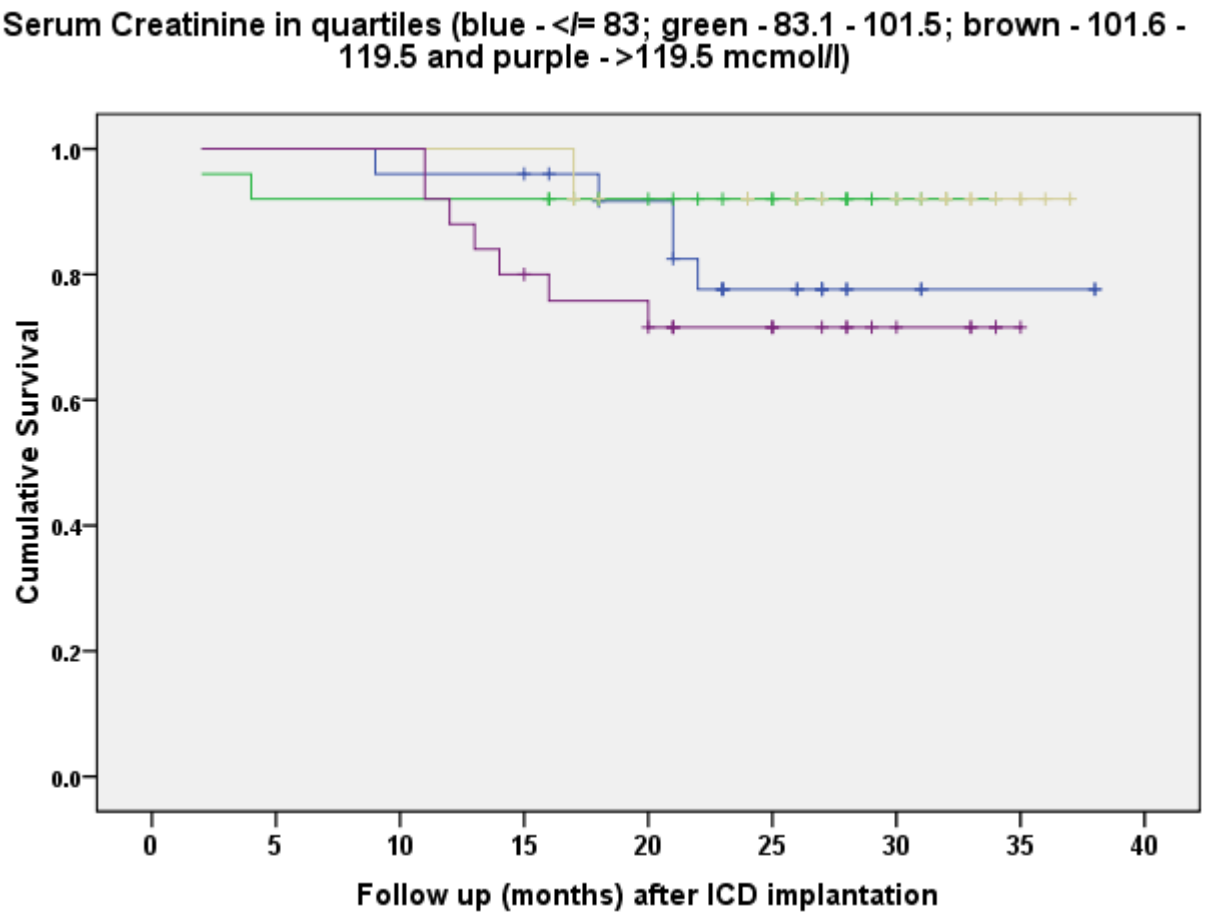


Table 12.6: Causes of inappropriate shocks

Cause of inappropriate shock	**No**
Atrial Fibrillation	2
Supra ventricular tachycardia	1
Non sustained ventricular tachycardia	1
"T" wave over sensing	2
Lead fracture (sprint fidelis)	1

12.6 DISCUSSION

This study was performed on contemporary patient population who were well treated with evidence proven therapies (ACE inhibitors and beta blockers). Despite ICD implantation a high annual rate of 10% death was observed and relatively few patients (6%) had a potentially life-saving defibrillation. This reiterates the fact that ICDs do not abolish the risk of premature death.

One fifth of the patients had a device related complication of which half of them needed a second procedure. This indicates that there is significant peri-operative morbidity. The commonest technical problem was inability to position the LV lead during BiV-ICD implantation, thus needing an epicardial lead. This was mainly due to unfavourable coronary venous anatomy.

This study shows that there is still a strong gender bias, as women get ICDs less frequently than men. However, women who do get an ICD may also gain less direct benefit from them. A meta-analysis by Santangeli et al showed that women enrolled in primary prevention ICD trials have the same mortality compared to men but experience significantly less appropriate ICD interventions.[275]

Renal impairment was a strong predictor of death. This was consistent with the findings of the previous chapter in which the study was done mainly in patients who had ICDs for secondary prevention. It is interesting to note that patients who had the serum creatinine in the lowest and highest quartiles had higher risk of death. As serum creatinine correlates with the lean body mass, it is likely that patients who had a low body mass index had worse outcome due the “reverse epidemiology” phenomenon in heart failure, in which traditional risk factors of poor clinical outcome and mortality in

the general population such as obesity, hypercholesterolemia, and high values of blood pressure have been associated with greater survival.[92, 170]

The association between renal impairment and poor outcome has been observed in many studies [67, 120]. The interaction between renal impairment and heart failure is complex.[276] Although there were earlier reports of benefit with adenosine receptor antagonists such as rolophylline in patients with heart failure and renal impairment, the PROTECT clinical trial failed to confirm this and there was no difference in death or readmission due to cardiovascular or renal causes at 60 days between rolophylline and placebo groups (31 vs 32%).[111] Hence the search for effective agents to treat patients hospitalised with heart failure and renal dysfunction is still ongoing.

Until a proven therapy emerges, this observation of increased mortality with renal impairment in heart failure raises the question whether renal impairment should be a contraindication for ICD implantation, since the ICD is unlikely to alter the prognosis in these high risk patients.

12.7 LIMITATIONS

This was a retrospective study. The body mass index was not recorded and hence the relationship between serum creatinine and death could not be explained in full.

12.8 CONCLUSIONS

Patients who have received an ICD for primary prevention continue to experience high rates of mortality. Renal impairment is associated with poor outcome.

CHAPTER 13. IMPROVING PROGNOSIS IN HEART FAILURE – A REVIEW OF THE MULTI-DISCIPILINARY APPROACH TO REDUCE MORTALITY

13.1 BACKGROUND

Heart failure is a common medical condition with high mortality. One third or more of patients with heart failure will die within 6 months of diagnosis and the annual mortality amongst 6 month-survivors is 10-15%.[7] Most patients with heart failure will die either suddenly or from progressive heart failure. However, not all sudden deaths in patients with left ventricular systolic dysfunction (LVSD) and heart failure are due to cardiac problems and a few will die from non cardiac causes. The causes of sudden death are varied and include ventricular arrhythmias, cerebro-vascular events, pulmonary embolism and ruptured aortic aneurysms. Aortic aneurysms are common in patients with heart failure and deep venous thrombosis is a common complication in hospitalised patients. Thus sudden death may be neither arrhythmic nor cardiac even in patients at risk of arrhythmias.

13.2 POST-MORTEM STUDIES IN SUDDEN DEATH

Studies of patients with LVSD either in the setting of chronic heart failure or after myocardial infarction suggest that many sudden deaths are associated with pathological evidence of acute coronary occlusion and/or myocardial infarction (Fig. 13.1).[277, 278] A thorough post-mortem can exclude a pulmonary embolism, cerebrovascular accident and a ruptured aorta, but these do not seem common in clinical trials, although typically only 10–15% of deaths result in a post-mortem so there may be selective reporting. It is likely that many episodes of ventricular arrhythmias causing sudden death occur outside the setting of acute myocardial

infarction (scar related). Thus, it may not always be possible to establish an accurate cause in all cases.

13.3 HOSPITALISED PATIENTS WITH ACUTE DECOMPENSATION OF HEART FAILURE

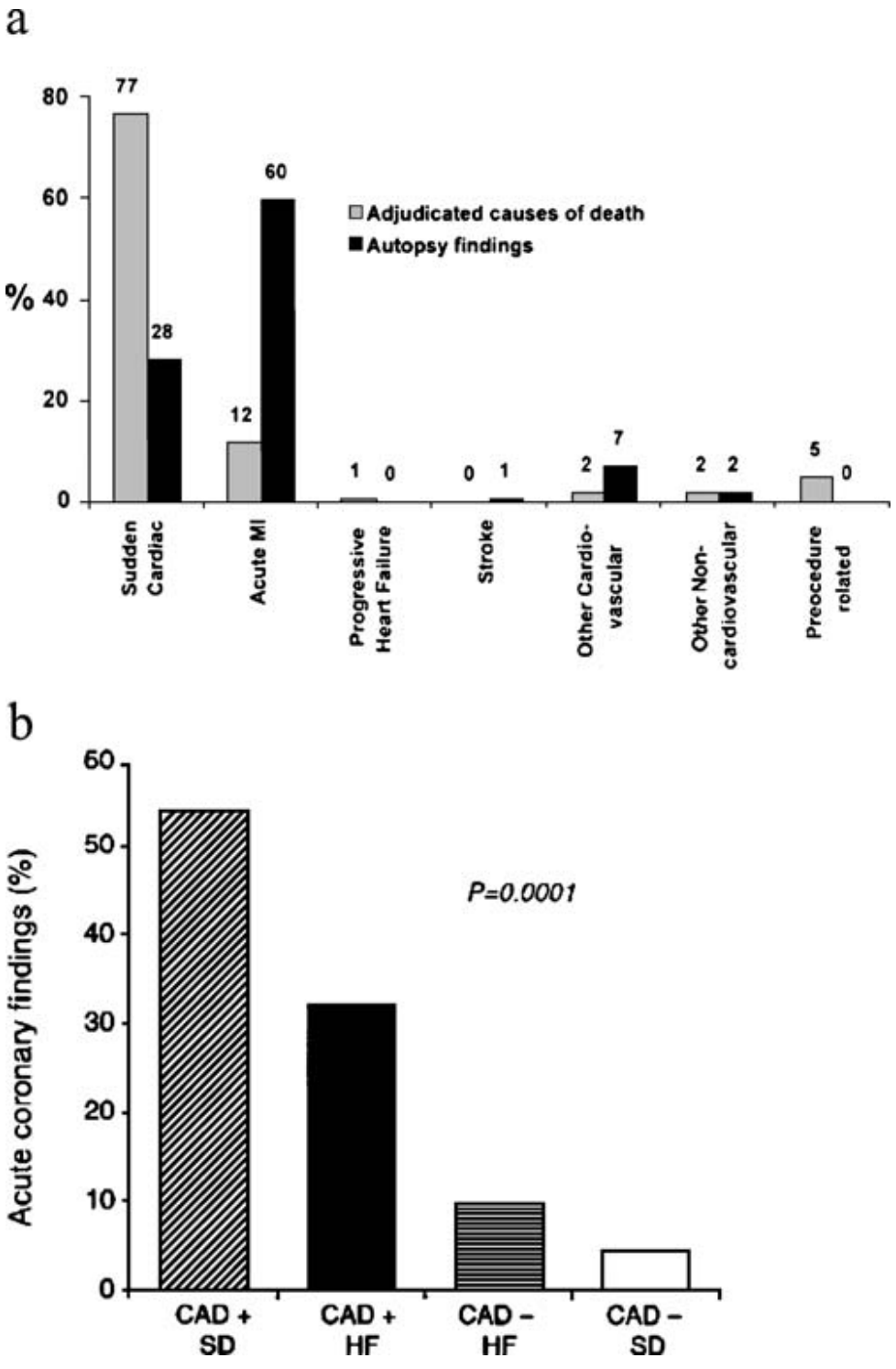
The mortality in hospitalised patients with acute decompensation of heart failure is high in the short term, as demonstrated in the Euro Heart Failure survey, in which 13% died within 12 weeks of hospital admission.[120] This is generally predictable, as most deaths in this group are likely to be due to progressive heart failure, rather than sudden and unexpected. The risk of dying from progressive heart failure is particularly high in the early period after diagnosis with over half of all progressive heart failure deaths in the first six months occurring within one month after diagnosis.[12] These patients are usually in NYHA class III or IV and hence at a higher risk of death due to progressive heart failure as demonstrated by the CONSENSUS-1 and RALES studies.[24, 25] Patients with advanced age, severe left ventricular impairment, renal impairment and those unable to tolerate optimal medical therapy are clearly at a very high risk of death.[120]

13.4 MECHANISTIC APPROACHES TO THE PREVENTION OF COMMON CAUSES OF SUDDEN DEATH

The most common causes of sudden death appear to be due to vascular events or arrhythmias. Both mechanisms of sudden death can be addressed. Vascular events might be prevented, either by stabilising plaque or preventing the propagation of occlusive thrombus, or the effects of the vascular event can be reduced.[279] Arrhythmias might be suppressed, their substrate may be corrected or they can be treated when they occur. It is unlikely that one strategy will be successful in all cases. The risks, benefits and, in the context of a public health service, the costs of each intervention needs to be weighed carefully.

Fig.13.1a Adjudicated causes of death in autopsied patients with a sudden mode of death (n=88) before and after autopsy was used to determine cause of death. [278]

13.1b Relation of acute coronary findings to mode of death and presence of CAD is shown (168 patients). + Indicates presence of; –, absence of. CAD patients with sudden death had highest prevalence of acute coronary findings [14]



(Reproduced with permission from Cleland J, et al[280])

13.4.1 Reducing sudden vascular death

ACE inhibitors, ARBs and beta-blockers are the mainstay of treatment for heart failure as they are proven therapies to prevent sudden death in heart failure. There is some evidence that intense statin therapy can cause plaque regression, as shown by the ASTEROID trial.[281] It is also possible that pharmacological therapy with these agents may prevent acute coronary events by altering plaque composition and reducing hemodynamic stress.

The other approach to the reduction in sudden death is revascularisation. There is no convincing evidence that percutaneous coronary intervention can reduce the risk of sudden death.[282, 283] This may reflect the fact that percutaneous coronary intervention deals with tight coronary lesions which are responsible for angina but not for sudden death. There is little evidence that CABG reduces the risk of a myocardial infarction but it may reduce its extent.[284] However, there is no good evidence that CABG reduces the risk of death in patients with LVSD.[285] Both HEART and STITCH trials failed to show any evidence of benefit from revascularisation in patients with LV systolic dysfunction.[286-288]

13.4.2 Reducing sudden arrhythmic death

Trials of agents primarily to suppress arrhythmias have generally met with failure. [289, 290] However beta-blockers and ACE inhibitors may also be considered anti-arrhythmic agents. These agents may reduce ventricular stress, protect from myocardial ischaemia, reduce general or episodic hypokalaemia, improve global ventricular function and reduce myocardial fibrosis. The same is also true of aldosterone antagonists. In addition beta blockers have direct anti-arrhythmic effects.

The decline in the use of digoxin and its use in lower doses (when used) may also reduce arrhythmogenic substrate.[291] Indeed, aldosterone antagonists and beta-

blockers appear to exert a greater reduction in mortality in the presence of digoxin.[292]

13.4.3 Cardiac Resynchronisation therapy (CRT)

Cardiac resynchronisation therapy reduces the risk of sudden death as demonstrated by the CARE-HF trial.[52] In this study, in patients with severe symptomatic HF from systolic dysfunction and left ventricular dyssynchrony in normal sinus rhythm, CRT decreased the incidence of both SCD and pump failure death.[293] The absolute percentage-point decrease in all-cause mortality for the CRT group was 7 at eight years of follow up. The predictors of SCD using multivariate analysis were limited to randomization to CRT and the severity of mitral regurgitation (MR) at 3 months. Thus by anatomical remodelling (thereby reducing the degree of MR) CRT could reduce the incidence of death. It has also been demonstrated that in CRT responders, anatomic remodelling leads to electrical remodelling resulting in significant reduction of premature ventricular beats and runs of non sustained ventricular tachycardia.[294]

13.4.4 Implantable Cardioverter-Defibrillators (ICD)

If there is reason to believe that the risk of sudden death remains high for an individual patient despite the above treatments, then consideration should be given to an implantable device that can treat the arrhythmia either using anti-tachycardia pacing or defibrillator therapy. Defibrillators are associated with substantial morbidity and are expensive. Current trials indicate that fewer than 10% of patients recommended for such treatment in existing guidelines will benefit from them directly (i.e. have their life saved) and a substantial proportion may be harmed (i.e. inappropriate shocks and worse heart failure). In addition, device discharge may not be an accurate surrogate for sudden death as randomised controlled trials suggest that the rate of sudden death in the control group of randomised trials may be much lower than the overall rate of

ICD device therapy. For instance, of the 720 patients with a defibrillator in MADIT-II, 169 (23.5%) received device treatment that was considered appropriate by the investigator including 138 patients (19.2%) who received a shock. [252, 295] This compares with 48 (9.8%) sudden deaths in the control group. In addition, about one third of ICD therapies in this study were considered inappropriate, indicating that the total therapy delivered by an ICD may be five times higher than is strictly necessary. Also, in SCD-HeFT, 259 patients received a shock from their device, 177 of them considered appropriate.[60] However, there were only 244 deaths in the control group of which, based on contemporary trials, only 30% or about 80 should have been sudden. Hence, a shock, whether considered appropriate or not cannot be equated with sudden death. Also, it is likely that a proportion of these shocks were delivered to patients who were dying for other reasons. Clearly, ICDs are a blunt instrument and careful patient selection is required to ensure that the benefit of this therapy exceeds the potential for harm and that the cost of this relatively expensive treatment is justified.

13.5 PREVENTION OF SUDDEN DEATH IN PATIENTS WITH ASYMPTOMATIC LVSD (ALSVD)

Most patients who have substantial LVSD will not have symptoms or signs of heart failure and will be recognised as a consequence of assessing LV function in the aftermath of a myocardial infarction or in patients with angina. Accordingly, studies of post-infarction LV systolic dysfunction are highly relevant. Long-term follow-up indicates that these patients have an adverse prognosis. More patients die suddenly without developing heart failure than develop heart failure and then die.[292, 296] Of course, many of the patients who do develop heart failure will also die suddenly.

Adequate evidence that ACE inhibitors reduce mortality in patients with ALVSD is provided by the SOLVD prevention and SOLVD-extension reports.[297] This is made robust by the repeated ability of ACE inhibitors to reduce overall mortality and sudden death in post-infarction studies, studies of patients at high risk of vascular events or with heart failure.[298] There is reasonable evidence that these benefits can be achieved or are replicated by angiotensin receptor blockers (ARBs) although no adequate evidence of an additive effect of these agents on overall mortality or sudden death in this setting.[299, 300]

Clinical trials on beta blockers (BB) had included patients with very mild heart failure and there are many reports of the effects of BB on post-infarction LVSD.[301, 302] In a subgroup analysis of the asymptomatic patients from CAPRICORN trial, the use of carvedilol resulted in a risk reduction of 31% in all-cause mortality. These provide adequate evidence of a beneficial effect on re-infarction and mortality. It is likely that this reflects a reduction in sudden death.[303]

The EPHESUS study provides evidence that the aldosterone receptor antagonist eplerenone reduces overall mortality and sudden death in patients with post-infarction LVSD.[18] There was 21 percent reduction in the rate of sudden death from cardiac causes in this trial. In addition, there was 15 percent reduction in the risk of hospitalization for heart failure and a 23 percent reduction in the number of episodes of hospitalization for heart failure. Most of these patients did not require long-term diuretic therapy and so the study may be considered predominantly one of asymptomatic LVSD post myocardial infarction.

Studies of ICDs suggest that patients with asymptomatic LVSD obtain as great or greater benefit in relative terms than patients with heart failure.[252, 295] However,

the absolute risk and risk reductions have not been reported and therefore no clear recommendation can yet be made.

The MADIT – CRT trial was published recently.[304] In this trial A total of 1,820 patients who were relatively asymptomatic (NYHA class I/II), were enrolled. The use of CRT-D was associated with a significant reduction (0.66; 95% CI, 0.52 to 0.84; P=0.001) in death or heart failure events when compared to traditional ICDs, during an average follow up of 2.4 years. The benefit was driven by a 41% reduction in the risk of heart-failure events and the benefit of CRT was seen in both ischemic and non ischemic cardiomyopathy. The death rate was however very low in both groups (3%) suggesting that this trial was done in highly selected low risk patients. This trial has provided strong evidence for advocating CRT-D implantation in patients with reduced LVEF, wide QRS and minimal or no symptoms. This is reinforced by the recently published RAFT trial in which, patients in NYHA class II or III with a wide QRS complex, and left ventricular systolic dysfunction experienced reduced rates of death and hospitalization for heart failure with the addition of CRT to an ICD.[305]

13.6 HEART FAILURE WITH A NORMAL LEFT VENTRICULAR EJECTION FRACTION

Few studies have focussed on heart failure with a normal LV ejection fraction. Data from the CHARM study showed that overall mortality rate and the rate of sudden death are lower than in patients with LVSD.[299] The proportion of deaths that are cardiovascular is also lower than in patients with LVSD. However, the proportion of cardiovascular deaths that are sudden deaths is similar in patients with or without LVSD.

13.7 REDUCING MORTALITY IN HOSPITALISED PATIENTS WITH ACUTE DECOMPENSATED HEART FAILURE

13.7.1 Medical therapy

These patients are clearly at extremely high risk and hence should be targeted for intense medical management. Symptomatic benefit is derived from diuretics and vasodilator therapy along with agents such as dopamine which helps to relieve the fluid overload. Prognostic benefit is obtained by initiation or continuation of beta blockers and ACEI during hospitalisation. As shown by the Euro heart failure survey data, patients not on beta blocker or ACE inhibitor for whatever reason are at a very high risk of death. [120]

Evidence for prognostic benefit from other medication such as antithrombotics and statin therapy had been conflicting and remains to be proven beyond doubt. Randomised trials of statin therapy in heart failure such as CORONA and GISSI-HF have been negative.[96, 97] However in a large registry of 54,960 Medicare beneficiaries who were hospitalised with a primary discharge diagnosis of heart failure, discharge statin therapy was associated with significant improvement in 1 year and 3 year mortality irrespective of cholesterol level or coronary artery disease status.[130]

Close follow up of these patients after discharge by nurse led heart failure teams have been shown to be effective in reducing repeat hospitalisation episodes and improving the quality of life.[306-308]

13.7.2 Other devices in heart failure management (excluding CRT/CRT-D)

A small group of patients with acute decompensated heart failure may benefit from non-conventional device therapy. Left ventricular assist devices (LVAD) have been

shown to benefit patients in refractory heart failure, not only as bridge to cardiac transplant but also as destination therapy. In future, miniaturization, increased durability, and complete implantability may render LVADs an option in earlier stages of heart failure, as a bridge to myocardial recovery or even as an alternative to transplantation.[309] Implant-based monitoring of intra-thoracic impedance to detect fluid overload early before clinical symptoms, is undergoing clinical evaluation.[310] Left atrial pressure sensors and pulmonary artery pressure sensors have been shown feasible to predict decompensation in small pilot studies.[311, 312] They help to prevent hospitalisations by physician directed self management therapy, guided by the pressure measurements, as demonstrated by the HOMEOSTASIS study.[313] However in the randomised COMPASS-HF trial, the implantable continuous hemodynamic monitor-guided care did not significantly reduce total heart failure related events compared with optimal medical management.[314]

13.8 DEVELOPING THE MOST EFFECTIVE STRATEGY TO REDUCE MORTALITY

Ultimately, a heart failure physician, leading a well-trained multi-disciplinary health-care team including specially trained nurses, pharmacists, experts in rehabilitation and geriatric medicine as well as device-electro physiologists, interventional cardiologists and cardiac surgeons, is most likely to deliver the optimum care for patients. Investment in this strategy, which can best judge which of the many treatments for sudden death are used and when, is more likely to be effective and cost-effective than a blunderbuss approach in which no patient is allowed to die without treatment, whether or not it is effective. Further research is required to help ensure that patients get the treatment they need and avoid the treatment they don’t.

CHAPTER 14. CONCLUSIONS

Heart failure is a common clinical condition encountered in every day clinical practice for physicians. It causes high mortality and morbidity. The mode of death can be sudden and unexpected or preceded by progressive deterioration of heart failure symptoms. Some of the contributing clinical factors can be modified and some may just be markers of high risk patients. If identified early, some of the high risk patients can be protected from death by appropriate medical therapy with or without device therapy such as ICDs.

I have examined the data collected by the Euro Heart Failure Survey in patients hospitalised with or suspected heart failure to identify factors that predict short term mortality (within 12 weeks of hospital admission) using statistical models, as described in chapter 3. This analysis showed that advanced age, anemia, renal impairment, hyponatraemia, severe left ventricular impairment on echocardiography and the presence of atrial fibrillation were independently associated with an increased risk of death. Almost all of the standard medication used in these patients were independently associated with a better outcome. These included beta blocker, ACEI, ARB, calcium channel blockers, statins, warfarin and anti platelet therapy. However heparin and intravenous inotropes were associated with a worse outcome. I believe that this simply reflects the fact that patients on these medication were of high risk before the initiation of these medication due to acute coronary syndromes or cardiogenic shock.

I have proposed a risk scoring system based on few simple variables from these data. These variables were age, degree of LV systolic dysfunction on echocardiography, presence of elevated creatinine and treatment with beta blockers and ACEI/ARB. This

risk scoring system was able to identify patients with a risk of death ranging from 2% to 44%. This was comparable to other published risk scoring systems based on EFFECT, ADHERE and OPTIME-HF models, which were reviewed in chapter 2.

This risk score was validated in a contemporary in-patient population with heart failure in chapter 5. In this study, none of the patients with a risk score below 5 died. In patients with a risk score of $\geq$ 5, there was almost a linear relation between increasing score and increasing risk of death.

The relation between cholesterol and mortality in patients with heart failure was reviewed in detail. I have looked at the possible mechanisms explaining the so called "cholesterol paradox" – the association between low cholesterol and high mortality in heart failure. I have also reviewed the published literature with regard to the potential benefit of statin therapy in heart failure and the probable mechanisms. I found that although small non randomised studies have demonstrated benefit, the two large randomised trials (CORONA and GISSI-HF) failed to show any benefit of statin therapy in patients with heart failure.

The relation between cholesterol and risk of death in patients enrolled on the Euro Heart Failure Survey was examined in detail in chapter 7. This showed the well known pattern of "reverse epidemiology" as low cholesterol level was associated with a higher risk of death. Statin therapy was associated with a better prognosis. However it should be noted that this has not been confirmed by randomised trials.

Examination of the Euro Heart Failure Survey data has also revealed very interesting findings with regards to the utility of the simplest test in cardiology, the ECG, in predicting the presence and degree of LV systolic dysfunction. I found that QT interval in heart failure patients was prolonged and this was due to widening of QRS in interval.

The longer the QRS interval, the more likely that LV systolic dysfunction was present with a dose response effect. The patients with severe LVSD had longer QRS intervals than those with milder degree of LV systolic dysfunction. I also noted that patients on beta blockers tended to have shorter QRS intervals when compared with those with the same degree of LV systolic dysfunction but not on beta blocker therapy. The exact significance of this is not clear and merits further studies in the future.

The utility of Signal Averaged ECG, a special ECG technique which removes interference on the standard ECGs to reveal late potentials was examined in patients with heart failure. Late potentials had been believed to markers of predisposition to sudden arrhythmic death. I found no association between presence of late potentials on SAECG and all cause mortality in patients with heart failure. However SAECG was useful in predicting the presence of LV systolic dysfunction, as increasing prevalence of late potentials was noted with increasing severity of LV systolic dysfunction. This finding was similar to the observation from my earlier analysis done on the ECG data from Euro Heart Failure survey.

Holter monitoring is currently not routinely performed in all patients with chronic heart failure. I had assessed the utility of holter monitoring in a cohort of chronic heart failure patients attending a heart failure clinic. This showed that arrhythmias such as atrial fibrillation and non sustained ventricular tachycardia were very common, despite contemporary medical therapy and both were independently associated with a higher risk of mortality. Hence I believe holter monitoring should be considered as a routine investigation in all patients with heart failure to identify those at higher risk.

Implantable Cardioverter Defibrillators (ICD) have been used widely to reduce death in patients with heart failure based on the evidence from large randomised trials. The

factors associated with death after ICD implantation in patients with heart failure were examined in two cohorts. The first cohort comprised those who mainly received an ICD for secondary prevention indications. In this group, approximately one fourth of patients derived explicit benefit and one third had some benefit but also experienced an adverse event. 43% had no explicit benefit. Patients with renal impairment had a higher risk of death whereas patients in sinus rhythm and those on beta blocker therapy had a lower risk of death.

The second cohort comprised of ICD recipients for primary prevention in heart failure. The majority were men, indicating a strong gender bias. Although this cohort was well treated by beta blockers and ACE inhibitors, there was a 10% annual risk of death and only 6% received a life saving defibrillation from the device during the 2 year follow up. One fifth of patients experienced a complication. As in the previous study group, presence of renal impairment was strongly associated with an increased risk of death.

In summary, in this thesis, I have examined the various clinical factors which help to identify those patients with heart failure and at a higher risk of death. I believe that these analyses have provided some insights for better understanding of risk stratification in patients with heart failure and in those with Implantable Cardioverter Defibrillators.

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APPENDIX

NORTH AND EAST YORKSHIRE AND NORTHERN LINCOLNSHIRE STRATEGIC HEALTH AUTHORITY

SOUTH HUMBER LOCAL RESEARCH ETHICS COMMITTEE

Room C28
College House
Willerby Business Park
Willerby
HULL
HU10 6NS

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SH/KW/04.01.5
Please quote in all correspondence

11 February 2004

Professor J Cleland
Professor of Cardiology
Department of Cardiology
Castle Hill Hospital
Cottingham
HULL
HU6 7RX

Dear Professor Cleland

04.01.5 - Assessment of Markers of the Risk of Sudden Death in Patients with or at Risk of Heart Failure who may have Implantable Cardioverter Defibrillators (ICD)

I write to inform you that the above submission was considered by the Local Research Ethics Committee at its last meeting held on 6 February 2004 and confirm that a favourable opinion was given for the study to proceed.

Documents Reviewed:

Hull and East Riding LREC Application Form dated 31.01.04
Hull and East Riding Resource form dated 9.01.04
Protocol version 1.0 dated January 04
Patient Consent form
Patient Information Leaflet

You are required to notify this Committee, in advance of any significant proposed deviation from the original protocol. Reports to the Committee are required, once the research is underway, if there are any unusual or unexpected results which raise questions about the safety of the research. Reports on success (or difficulties) in recruiting subjects may also provide this Committee with useful feedback regarding the acceptability of the project among patients and volunteers.

Yours sincerely

DR S HERBER
CHAIRMAN
SOUTH HUMBER LOCAL RESEARCH ETHICS COMMITTEE

South Humber Local Research Ethics Committee Members
Dr S Herber (Chairman) Dr A Hill Mr S Richmond Mrs W Witter Mrs M Dickerson Mr P Isles Mr M Hockey
Rev J Fisher Mr T K Bagga Dr R Ezekwesili Mr O A Odukoya Mr J Hollingworth Mrs S Clark

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Our Ref: SB/JS/2971

22 March 2004

Prof. J Cleland
Dept. of Academic Cardiology
Castle Hill Hospital

Dear Professor Cleland

Re: Assessment of Markers of the Risk of Sudden Death in Patients with or at risk of Heart Failure who have Implantable Cardioverter Defibrillators (ICD). ELSY No. 2971

I am pleased to notify you formally that this study has been approved by the Trust and may now proceed.
Hull and East Yorkshire Hospitals NHS Trust manages all research in accordance with the requirements of the Research Governance Framework and the NHS Intellectual Property Guidance. In undertaking this study, you agree to comply with all reporting requirements, systems and duties of action put in place by the Trust to deliver research governance, and you must comply with Trust information management and data protection policies (see intranet Policies Nos: 134, 135, & 192). In addition, you agree to accept the responsibilities associated with your role that are outlined within the Research Governance Framework as follows:

- the study should follow the agreed protocol;
- participants should receive appropriate care while involved in the study;
- the integrity and confidentiality of clinical and other records and data generated by the study will be maintained;
- all adverse events must be reported forthwith;
- any suspected misconduct by anyone involved in the study must be reported

We would be very grateful if you would provide quarterly updates on the general progress of the study.
I would like to wish you every success with this project.

Yours sincerely

Sally Brown

Dr Sally Brown
Research & Development Facilitator

Cc:Mike Lammiman

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