Risk stratification in chronic heart failure

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Introduction

Despite advances in medical and surgical management, the prognosis of chronic heart failure remains poor. Few patients with chronic heart failure can be considered to have a good prognosis, but different trials have indicated a 6 month mortality between 5% and 60% depending on the severity of heart failure; identifying patients at truly low risk is difficult. A host of factors have been identified that predict outcome, at least in univariate analyses. Cohn[1] wrote an article entitled 'Poverty Amidst a Wealth of Variables' some years ago, describing the difficulties in choosing which prognostic variables to use for clinical purposes in heart failure. This article reviews in a systematic fashion those peer-reviewed papers that have assessed the utility of prognostic variables in heart failure. This summary of existing knowledge should determine those prognostic factors that have proved most reliable so far, indicate which of the many new potential factors are most promising for further research and suggests ways in which the interpretation and reporting of such information might be improved.

Methods

Medline and Current Contents databases, and reference lists of relevant papers were reviewed to identify studies of chronic heart failure. Medline was interrogated using the key words 'death' or 'deaths' or 'survival' or 'mortality' or 'prognosis' or 'risk' and combined with 'heart failure' or 'cardiac failure' or 'ventricular dysfunction'. The abstract of each publication was read to identify original studies. All relevant papers were then read in full to identify if they should be included. The references of each paper were then scrutinized to identify any additional papers. Studies reported up to June 1997 have been included. This search was supplemented by published abstracts from landmark trials where no appropriate full publication was available. Only studies of patients with chronic heart failure or left ventricular dysfunction have been included in the present overview. Studies of new-onset heart failure, defined as heart failure of less than one month’s duration, such as in the AIRE trial[2,3], have not been included.

Results

Gender

The Framingham study[4] suggested that women had a better prognosis than men with 5-year survival rates of 25% and 38% for men and women with chronic heart failure, respectively. The age-adjusted mortality rates from chronic heart failure are also reported to be higher amongst men than women[5–7]. This difference may reflect the greater inaccuracy of diagnosis of chronic heart failure in women[8] (those with a false-positive diagnosis are likely to have a good prognosis) or less marked impairment of ventricular function in women for a given level of symptoms[9]. The Studies of Left Ventricular Dysfunction (SOLVD), that excluded those with an ejection fraction >35%, suggested that women had a worse outcome than men[6], although this was not confirmed in the SOLVD-registry [10] which did not require a low ejection fraction for entry. When heart failure is due to ischaemic heart disease, gender has been reported to have little effect on prognosis[7,11]. The better prognosis of women with heart failure due to causes other than ischaemic heart disease may be due, in part, to less severe left ventricular systolic dysfunction[12]. In summary, once confounding factors have been taken into account, gender may have little independent role in determining prognosis.

Race

Black patients may have a worse prognosis than whites[4]. However, there are significant differences in
the aetiology of chronic heart failure, and therefore potentially prognosis, between blacks and whites. In the SOLVD registry, 73% of white patients had ischaemic heart disease compared to only 36% of black patients; 4% of whites had chronic heart failure due to hypertension vs 32% of black patients[39]. In the SOLVD registry, the cardiovascular and total mortality was not different between blacks and whites, but as blacks were younger than whites and as a higher proportion of blacks were women and the aetiology of heart failure was different, this information is difficult to interpret. Any difference in the prognosis between whites and blacks could also reflect socio-economic differences.

Age

The incidence and prevalence of chronic heart failure increase with age and elderly patients with chronic heart failure have generally been shown to have a poor prognosis[5–7,11–17]. However, in the Vasodilator in Heart Failure Trials (V-HeFT) [18], from which patients >75 years had been excluded, age was not an independent predictor of survival. Studies of the very elderly[19,20] indicate that patients over the age of 75 years with chronic heart failure have a very high mortality and morbidity. The risk of death or readmission within 6–12 months is in excess of 40%[12,21,22]. The high excess mortality is mainly observed in the first year after diagnosis and subsequent prognosis may be more akin to the elderly population without heart failure[20]. This may reflect, in part, inaccurate diagnosis in a group of patients who are probably under-investigated.

Symptoms of heart failure

Even crude evaluations of symptomatic severity, such as the New York Heart Association (NYHA) class, consistently predict mortality in chronic heart failure[7,11,22–32]. Other measures of symptomatic severity, including quality of life score[33], daily activity[34] and activity assessed by footfall pedometer also provide independent prognostic information[34]. Patients who present with peripheral or pulmonary oedema also have a worse prognosis[35].

A long duration of symptoms also predicts a higher mortality, possibly reflecting more advanced disease[36,37] and a low likelihood of spontaneous recovery from conditions such as dilated cardiomyopathy. However, Steimle et al. described some patients with a long history of dilated cardiomyopathy who later showed marked improvement in ventricular function despite having been referred for consideration of transplantation[38]. To what extent this can be attributed to treatment with ACE inhibitors[39] and beta-blockers[40] is not clear.

Concomitant symptoms

Syncope is an ominous symptom[35,41,42] whether or not it is associated with an identified arrhythmia. These patients are at a high risk of sudden death[42]. As may be expected, a documented history of severe ventricular arrhythmias carries an adverse prognosis[37].

Angina suggests that there may be viable myocardium at risk and indicates that prognosis may be worse[11]. Angina symptoms and possibly prognosis may be improved following revascularization[43]. A recent history of unstable angina or myocardial infarction has a marked adverse impact on prognosis[44]. Patients with angina should be considered for detailed investigation.

Aetiology of chronic heart failure

Most studies have suggested that the prognosis of patients with ischaemic heart disease is worse than for patients with dilated cardiomyopathy[7,11,30,45–49] although exceptions exist[5,25,50]. The SOLVD trial[51] showed no difference in prognosis in patients with or without ischaemic heart disease as the aetiology of chronic heart failure. However, as many patients who supposedly did not have ischaemic heart disease as the cause of chronic heart failure subsequently had a myocardial infarction[44], a lack of diagnosis of ischaemic heart disease should not necessarily be equated with an absence of coronary disease in this study. Peripheral vascular disease is also associated with a worse prognosis[11].

Diabetes was an independent predictor of morbidity and mortality in patients in the SOLVD trial and registry[52] and in other studies[5,11,48].

Alcohol abuse has been reported to be an independent and powerful predictor of mortality[48], but a recent study suggested an improved outcome for patients with alcoholic, as opposed to idiopathic dilated cardiomyopathy[48,53]. Genetic markers may help determine prognosis in the future[54].

There is little evidence that a history of hypertension is an independent predictor of risk, although the PRAISE study[30] indicated that a history of hypertension was associated with a somewhat better prognosis. A large observational series has suggested the converse[11]. Arterial pressure measured at examination is discussed below.

Clinical examination

Weight

Severe weight loss appears to predict reduced survival[55], independent of symptom severity or exercise capacity, as does low body weight[30].

Pulse

Faster heart rates appear to be associated with a worse prognosis[49,56] although heart rate is infrequently cited as an independent predictor of outcome.

Atrial fibrillation has been associated with increased mortality in most reports[6,57–62], although

V-HeFT demonstrated no increase in major morbidity or mortality for patients with atrial fibrillation\textsuperscript{63}. Recent reports suggest that atrial fibrillation may no longer be an important predictor of prognosis, at least in advanced heart failure\textsuperscript{64}. It is not clear if this represents a wider use of anticoagulants or amiodarone for this indication or a reduced use of class I anti-arrhythmic drugs.

Low systemic arterial pressure consistently indicates a poorer prognosis\textsuperscript{18,28,30,32,33,46,49,65–67} with, possibly, further information being added by the pulse pressure\textsuperscript{30} and failure of systolic blood pressure to rise on exercise\textsuperscript{15}. Low arterial pressure is probably an intrinsically bad sign, but also limits the use of effective doses of beta-blockers and ACE inhibitors and is often accompanied by declining renal function.

Although hypertension persisting after the development of heart failure has not been shown to have an adverse effect on mortality it is associated with more frequent adverse outcomes such as hospitalization\textsuperscript{6}.

A third heart sound is associated with increased mortality\textsuperscript{29,32,68,69}. However, the interobserver reproducibility of the third heart sound and many other signs of chronic heart failure is sufficiently low\textsuperscript{70,71} that it probably renders them of limited value in the evaluation of prognosis.

**Medication**

As would be expected, use of ACE inhibitors\textsuperscript{39} and beta-blockers\textsuperscript{40} is associated with a lower mortality\textsuperscript{16}. Greater diuretic doses are associated with a worse outcome\textsuperscript{72}, probably reflecting the fact that diuretic dose is good marker of the severity of heart failure. However, diuretics could also drive the progression of heart failure by activating neuroendocrine systems\textsuperscript{73}. Observational studies have suggested a higher mortality with digoxin use\textsuperscript{14}, but a large trial of digoxin has suggested no impact on mortality\textsuperscript{74}. In randomized trials, subsets of patients with heart failure after myocardial infarction, have not benefited from aspirin\textsuperscript{75}. Observational experience suggests that aspirin use is associated with a better outcome\textsuperscript{14,16,76–78}. However, warfarin may be reserved for use in more advanced chronic heart failure and these patients would tend not to get aspirin. Aspirin therefore may be a marker of milder heart failure rather than of real benefit\textsuperscript{75}. The trial data indicating a mortality benefit from warfarin are inadequate\textsuperscript{79} but observational experience suggests benefit in some\textsuperscript{14,16,30} but not all studies\textsuperscript{78}. Data for amiodarone on mortality are also inconclusive\textsuperscript{81,82}.

**Biochemistry and Haematology**

Serum sodium concentration has a strong inverse correlation to plasma renin activity and is a powerful predictor of cardiovascular mortality\textsuperscript{30,31,49,58,65,83–85} even when haemodynamic variables are considered\textsuperscript{31,49,83}. Hypokalaemia has also been associated with a poor prognosis on univariate analysis\textsuperscript{86}. Patients with hypomagnesaemia had more ventricular arrhythmias and a worse prognosis than patients with normal magnesium levels during long-term follow up, despite a similar severity of chronic heart failure and neurohumeral activation in one study\textsuperscript{87}, but patients with high magnesium levels had an even worse prognosis, associated with more severe symptoms, greater neurohumeral activation and worse renal function.

A raised serum urea or creatinine predict a worse outcome in chronic heart failure\textsuperscript{22,83–85,88–90} possibly because of the association with electrolyte disturbances, lower arterial pressure or more intense neuro-endocrine activation. Abnormal liver function tests may also be a strong predictor of mortality\textsuperscript{72,83,88}. Aspartate transaminase\textsuperscript{72} and bilirubin\textsuperscript{72,83} and serum urate\textsuperscript{72} have all been found to be powerful predictors of mortality in multi-variate analyses of simple clinical and laboratory variables.

Chronic heart failure patients with low (\(<11\) mm) or normal (\(<25\) mm) erythrocyte sedimentation rates have been found to have more severe haemodynamic abnormalities and a worse one year survival than patients with elevated rates\textsuperscript{72,88}.

**Neuro-endocrine activation**

Consistent with the adverse prognostic significance of hyponatraemia several studies have reported that renin-angiotensin-aldosterone system activation is associated with a worse prognosis\textsuperscript{63,91,92} in the absence but not the presence of an ACE inhibitor. However, renin–angiotensin–aldosterone system activation, unlike hyponatraemia, has not been shown to be an independent predictor of mortality once measures of cardiac function are included\textsuperscript{82,90}. This may reflect the fact that concentrations of plasma renin, like many other neuro-endocrine indices, can fluctuate markedly during the day, making single measurements an inadequate assessment of activation.

Plasma norepinephrine has predicted prognosis in several multivariate analyses\textsuperscript{80–84} but not all\textsuperscript{82}. However, when exercise capacity and radionuclide left ventricular ejection fraction are added to the analysis the predictive value of norepinephrine appears to be lost.

High plasma concentrations of C-terminal\textsuperscript{92,95} and N-terminal\textsuperscript{96,97} atrial natriuretic peptide and brain natriuretic peptide indicate a poor prognosis in chronic heart failure\textsuperscript{98}. Natriuretic peptides have also been shown to predict outcome after myocardial infarction\textsuperscript{99–101}, although it is not yet clear if they add predictive value to measurements of ventricular function\textsuperscript{90,101,102}.

Plasma endothelin-1 is a strong independent prognostic marker in chronic heart failure\textsuperscript{103}, possibly reflecting its relationship with pulmonary hypertension\textsuperscript{104}, another marker of poor prognosis. Big
endothelin-1, the biologically inactive precursor of endothelin-1, has also been shown to predict 1 year mortality better than haemodynamic variables and levels of atrial natriuretic peptide and peak oxygen consumption. Endothelin-1 and soluble intercellular adhesion molecule-1 both provided independent prognostic information that was, in turn, independent of biochemical and clinical variables in one study of patients with chronic heart failure.

Cytokines

Circulating levels of the cytokine, tumour necrosis factor, are increased in cachectic patients with chronic heart failure. Receptors for tumour necrosis factor can be detected as soluble forms in blood and urine and increased receptor levels have been shown to predict a poor short-term prognosis.

Electrocardiography

Atrial fibrillation is discussed above.

ECG evidence of left ventricular hypertrophy predicted a worse outcome in women but not in men in the Framingham study. First or second degree atrio-ventricular block appears to be an independent risk factor for cardiac death in dilated cardiomyopathy. Intra-ventricular conduction delay or left bundle branch block has also been shown to be associated with increased risk in patients with dilated cardiomyopathy, although not when chronic heart failure is due to ischaemic heart disease.

However, implantation of a pacemaker is itself associated with an adverse prognosis in severe heart failure. This may reflect an intrinsically higher risk among these patients or that incoordinate ventricular activation causes further deterioration of cardiac performance.

Whether abnormalities of the signal-averaged electrocardiogram indicate an increased risk of sustained ventricular arrhythmias and/or death, particularly sudden death, in patients with dilated cardiomyopathy or chronic heart failure due to ischaemic heart disease is disputed. Some studies have noted a high specificity of some indices but sensitivity remains low.

Some studies suggest that an abnormal signal averaged ECG predicts sustained ventricular tachycardia but not prognosis while others have suggested it predicts an increased risk of worsening heart failure. The presence of bundle branch block appears to detract from the little prognostic value that late potentials have in chronic heart failure.

QT dispersion is another proposed method of stratifying risk in chronic heart failure, although this cannot be evaluated properly in atrial fibrillation or bundle branch block. Studies supporting and refuting the usefulness of this measure exist. A recent report suggested that the dispersion of the heart rate corrected QT interval (JTc-d) had over a 90% sensitivity and specificity for predicting sudden death or serious ventricular arrhythmias. Only arterial pressure added to the predictive value of JTc-d for all cause mortality.

A high frequency of ventricular ectopics, ventricular couplets or non-sustained ventricular tachycardia on Holter monitoring indicate worse prognosis in most but not all studies. Longer runs of ventricular tachycardia also indicate a worse outcome. Whether arrhythmias predict the mode of death is disputed and they may merely reflect the severity of ventricular dysfunction. In the PROMISE trial the presence of non-sustained or sustained (>10 beats) ventricular tachycardia predicted cardiovascular death but did not predict sudden death.

However, exacerbation of arrhythmias by milrinone did predict sudden death. The aetiology of heart failure may affect the predictive power of arrhythmias.

There is now growing evidence to suggest that heart rate variability, an index of cardiac autonomic balance, is an important marker of early mortality in chronic heart failure, although not all studies agree. Heart rate variability appears to add prognostic information to the left ventricular ejection fraction. A recent report suggested that on multivariate analysis that measures of heart rate variability were better predictors of the risk of rapid progression of heart failure than conventional measures of ventricular dysfunction.

Baro-reflex sensitivity may be of some prognostic significance but is of less predictive value on multivariate analysis. Formal electrophysiological studies have been disappointing as a means of stratifying risk in chronic heart failure patients. The presence of inducible ventricular tachycardia by programmed ventricular stimulation does not affect prognosis. One study suggested that an abnormal signal averaged ECG and inducible arrhythmias indicate an increased risk of serious arrhythmias or sudden death with a positive predictive value of 50%, but this was not supported by another.

Chest X-ray

Cardiothoracic ratio was an independent predictor of survival in the V-HeFT trials and others. There was a poor correlation between cardiothoracic ratio and left ventricular ejection fraction in V-HeFT, suggesting that the chest X-ray was not an adequate guide to the presence or severity of left ventricular dysfunction. However, cardiothoracic ratio correlated better with peak oxygen consumption, suggesting that enlargement of other structures (e.g. the atria and right ventricle) provide important information, independent of left...
ventricular function, on functional capacity in chronic heart failure. Congestion on the chest X-ray has also been an independent prognostic determinant of mortality in multivariate analysis.

Echocardiography

Echocardiographic variables measure many different aspects of cardiac function that may influence prognosis. Measures of systolic function including left ventricular fractional shortening and left ventricular end-diastolic end-systolic internal dimension, mitral E-point septal separation, end-systolic radius/wall thickness and a wall motion index, based on a nine-segment model have all been shown to contain prognostic information. It is not clear which measure will prove superior, although wall motion index is a relatively simple and robust measurement. Echocardiographic ejection fraction, with rare exceptions, has failed to predict prognosis in multivariate analysis, perhaps reflecting the inaccuracy of measuring ejection fraction by this technique.

Measures of diastolic function have also been shown to be of prognostic value. Shortened deceleration time has indicated a worse outcome in several studies among patients in sinus rhythm. Deceleration time, left ventricular ejection fraction and peak E velocity have been reported to be independently associated with symptoms in dilated cardiomyopathy. Traversi et al. suggested that changes in transmitral flow patterns after chronic optimized therapy predicted outcome, while Pozzoli et al. found that assessing deceleration time while varying pre-load improved the prognostic power of this measure.

Measurements of systolic and diastolic function may be additive. Patients with left ventricular ejection fraction $<0.25$ and deceleration time $<130$ ms had a 2-year survival of only 35%, as opposed to a 72% 2-year survival rate in the group with left ventricular ejection fraction $<0.25$ and Deceleration time $>130$ ms. Patients with a left ventricular ejection fraction $>0.25$ had 2-year survival of 95% regardless of deceleration time.

Doppler-derived estimates of pulmonary hypertension predict mortality and morbidity in patients with dilated cardiomyopathy. After 28 months of follow-up, 89% of patients with a high regurgitant flow velocity ($2.5 \text{ m.s}^{-1}$) had either died or been hospitalized, compared to 32% of the low velocity group; mortality was 57% and 17%, respectively.

Whether left ventricular thrombus identified at echocardiography is a marker of an increased risk of thrombo-embolism is a matter of controversy, but thrombus does appear to predict mortality. Increased mortality could reflect an increased risk of embolism, but thrombus may also be a marker of worse ventricular function. Patients with thrombus may also be managed differently and the increased mortality could be iatrogenic. Mitral regurgitation may protect against left ventricular thrombus formation, but nonetheless, mitral regurgitation is associated with a worse prognosis in dilated cardiomyopathy. Stress echocardiography has been used to assess contractile reserve and power output and myocardial viability in patients with left ventricular dysfunction, both of which have been shown to predict outcome, although in rather small studies (n=150).

Nuclear cardiology

Left ventricular ejection fraction measured by radionuclide ventriculography, rather than by echocardiography, has predicted mortality, when used, in almost all studies of chronic heart failure but exceptions exist. Left ventricular ejection fraction measured by radionuclide or echocardiographic techniques may be of limited prognostic value in the elderly. The change in ejection fraction from rest to exercise also appears to be a powerful predictor of prognosis in dilated cardiomyopathy and it is reasonable to expect the same in patients with ischaemic heart disease where a fall in ejection fraction during exercise may reflect ischaemia.

Right ventricular EF, at rest and on exercise, may also be a strong predictor of survival in chronic heart failure, and was a more potent predictor of survival than peak VO$_2$ or % peak VO$_2$ in one study. Patients with a preserved right ventricular ejection fraction also achieved a significantly higher % peak VO$_2$. Right ventricular ejection fraction has also been studied using a thermodilution technique in patients with dilated cardiomyopathy and has been shown to add to the prognostic value of left ventricular ejection fraction on multivariate analysis.

The presence of numerous asynergic but viable segments on thallium scintigraphy has predicted prognosis in small studies in selected populations and improvement in global left ventricular function after surgery. Positron emission scanning has also been used to assess myocardial viability with evidence of hibernation indicating a poor prognosis with medical therapy. Revascularization in these patients was associated with improved survival and symptoms of chronic heart failure, although this was not a randomized comparison.

Heart failure with intact systolic function

Up to 50% of patients with heart failure do not have marked left ventricular systolic dysfunction. Among such patients clinical findings, ejection fraction or measures of diastolic dysfunction appear of little prognostic value. ‘Diastolic’ heart failure is predominantly found among elderly patients (>75 years), another group in whom ejection fraction appears to be of limited prognostic value.
Nuclear magnetic resonance (NMR) spectroscopy

One small study has suggested that a low myocardial phosphocreatinine/ATP ratio, indicating disturbed energy metabolism, carried adverse prognostic significance.[183]

Exercise testing

Numerous studies have reported the independent prognostic value of peak VO₂.[27,49,69,118,184–187] Discriminatory values between 10 and 16 ml·kg⁻¹·min⁻¹ have been used to try to distinguish high and low risk groups.[27,69,118,184–186] Although the use of any single arbitrary cut off value has been questioned[15,188] Peak VO₂ expressed as the percentage achieved of predicted peak VO₂ may be superior to measurement of VO₂ alone.[189] The actuarial 1- and 2-year survival of patients with a peak VO₂ ≤ 50% of predicted was 74% and 43%, respectively, compared with 98% and 90% in those with values >50%.

Left ventricular ejection fraction and distance walked in a 6 min walk test appear equally strong and independent predictors of mortality and hospitalisation for chronic heart failure.[190] However, the peak oxygen consumption may be superior to the 6 min walk.[191] Not all studies have found exercise capacity to be of independent prognostic value.[25]

Impaired ventilatory efficiency has also been associated with a poor prognosis carrying additional information to peak oxygen consumption alone.[189,192,193]

Failure of heart rate to increase during exercise also indicates a worse prognosis, probably reflecting a mixture of chronotropic incompetence and low exercise capacity.[190]

Central haemodynamic indices at rest

Assessing risk by resting haemodynamic profile has been disappointing. No individual variable consistently predicts outcome and, indeed, some have found no resting central haemodynamic variable to have prognostic significance in patients referred for transplantation[49,60,66.

Despite studying similar populations, different investigators have found, variably, only right atrial[38,61,167], pulmonary artery diastolic[118], pulmonary artery systolic pressure[35,36], pulmonary capillary wedge pressure[24,32,49,58,88,148,194], stroke volume[37] or resting cardiac output[12,195] to predict mortality in multivariate analysis. Patients with a resting cardiac index <2.0 and a peak oxygen consumption <12 ml·kg⁻¹·min⁻¹ had a particularly poor prognosis in one study.[195]

The haemodynamic response to therapy may have prognostic value. In one study, patients who achieved a pulmonary artery wedge pressure ≤16 mmHg on vasodilator therapy had a 1 year survival rate of 83% vs 38% among those who did not.[196] In another study[197] patients with a pulmonary vascular resistance >2.5 units were vasodilated with sodium nitroprusside. Those whose pulmonary vascular resistance fell to ≤2.5 units with a stable systolic blood pressure had a 3 month mortality of 3.8%. In contrast, those patients whose pulmonary vascular resistance did not fall below 2.5 units had a 3 month mortality of 40.6%.

Central haemodynamic indices during exercise

Cardiac output response to exercise has been shown to be an independent predictor of survival[186,198] but exercise cardiac output and VO₂ are closely related and exercise haemodynamic measurements may add little to the prognostic power of peak VO₂.[199] Griffin et al. studied central haemodynamics at rest and on exercise.[194] Multivariate analysis identified pulmonary wedge pressure at rest and peak exercise stroke work index as the only independent predictors of mortality.

Coronary arteriography

Patients with extensive coronary vascular disease and poor left ventricular function have a worse outcome than those with less extensive disease.[200] Patients with impaired left ventricular function and three-vessel disease were also most likely to benefit from surgery in one randomized study of coronary bypass surgery.[201] However, the randomized controlled trials of coronary bypass surgery excluded patients with an ejection fraction <35%, effectively excluding patients with heart failure. The mortality from coronary bypass surgery in patients with poor left ventricular function and chronic heart failure remains high, especially in patients over the age of 70 years who constitute the majority of patients with chronic heart failure. Operative mortalities between 3.8 and 11.0% have been quoted[202–204] for patients with an left ventricular ejection fraction around 20%.

Myocardial biopsy

A role for myocardial biopsy in predicting outcome is not widely accepted but has been suggested by small studies.[205–207] Multivariate analysis has suggested that haemodynamic indices are prognostically superior to myocardial biopsy findings in one early study.[67] One study suggested that detection of enteroviral RNA predicts a worse outcome[208] These results need to be reproduced in a prospective, blinded fashion.
## Table 1  Studies ranking the importance (on multivariate analysis) of >1 prognostic factor (where n>200)

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>Patient group</th>
<th>n=</th>
<th>Number of deaths</th>
<th>Rank 1</th>
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<tbody>
<tr>
<td>Lee[83]</td>
<td>Circulation 1986</td>
<td>Severe CHF (LVEF &lt;30%), IDCM and ischaemic</td>
<td>203</td>
<td>155</td>
<td>Serum sodium concentration</td>
<td>Left ventricular stroke work index</td>
<td>Serum creatinine concentration</td>
<td>Serum bilirubin concentration</td>
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<td>(P&lt;0.0001)</td>
<td>(P&lt;0.001)</td>
<td>(P=0.04)</td>
<td>(P=0.008)</td>
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<td>Likoff[69]</td>
<td>Am J Cardiol 1987</td>
<td>NYHA 2 or 3, IDCM and ischaemic</td>
<td>201</td>
<td>85</td>
<td>Ischaemic vs DCM</td>
<td>LVEF &gt; or ≤ 20% (P=0.004)</td>
<td>VO2 max &gt; or ≤13 ml. kg⁻¹.min⁻¹ (P&lt;0.05)</td>
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<td>Gradman[25]</td>
<td>J Am Coll Cardiol 1989</td>
<td>Mild/moderate CHF, IDCM and ischaemic</td>
<td>295</td>
<td>47</td>
<td>LVEF (P=0.006)</td>
<td>VT frequency (P&lt;0.008)</td>
<td>NYHA class (P=0.02)</td>
<td>DCM vs ischaemic</td>
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<tr>
<td>Rockman[62]</td>
<td>Am J Cardiol 1989</td>
<td>CAD</td>
<td>238</td>
<td>156</td>
<td>n.b. LVEF excluded from analysis</td>
<td>Plasma renin activity (P&lt;0.0001)</td>
<td>LV stroke work index (P&lt;0.001)</td>
<td>Serum creatinine (P&lt;0.004)</td>
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<td>Keogl[24]</td>
<td>Am J Cardiol 1990</td>
<td>DCM and ischaemic</td>
<td>232</td>
<td>76 died, 68</td>
<td>NYHA class (P&lt;0.0001)</td>
<td>PCWP (P&lt;0.008)</td>
<td>Plasma ANF (P&lt;0.002)</td>
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<tr>
<td>Komajda[35]</td>
<td>Eur Heart J 1990</td>
<td>DCM</td>
<td>201</td>
<td>56</td>
<td>LV end-systolic volume (P&lt;0.005)</td>
<td>Systolic PA pressure (P&lt;0.005)</td>
<td>LV end-diastolic volume (P&lt;0.01)</td>
<td>Symptom duration (P&lt;0.05)</td>
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<td>De Maria[13]</td>
<td>Am J Cardiol 1992</td>
<td>IDCM</td>
<td>218</td>
<td>27 died, 16</td>
<td>LV stroke work index (P&lt;0.001)</td>
<td>Severity ventricular arrhythmias (P&lt;0.01)</td>
<td>LV end-diastolic diameter (P&lt;0.01)</td>
<td>RV end-diastolic diameter (P&lt;0.01)</td>
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<td>Stevenson[58]</td>
<td>Am Heart J 1992</td>
<td>DCM and ischaemic</td>
<td>458</td>
<td>110 died, 131</td>
<td>Atrial fibrillation (P=0.001)</td>
<td>Sodium &lt;135 mEq. l⁻¹</td>
<td>PCWP &gt;15 mmHg (P=0.009)</td>
<td>LVEF &lt;0.21 (P=0.046)</td>
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<tr>
<td>Saxon[118]</td>
<td>Am J Cardiol 1993</td>
<td>DCM and ischaemic</td>
<td>528*</td>
<td>104 died, 147</td>
<td>LV diastolic dimension index &gt;44 mm. m⁻² (P&lt;0.001)</td>
<td>PA diastolic pressure &gt;19 mmHg (P=0.01)</td>
<td>Presence of permanent pacemaker (P=0.03)</td>
<td>Peak oxygen consumption &lt;11 ml. kg⁻¹.min⁻¹ (P=0.07)</td>
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<td></td>
<td></td>
<td>transplanted</td>
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<tr>
<td>Bourassa[6]</td>
<td>J Am Coll Cardiol 1993 SOLVD</td>
<td>Unselected (70% ischaemic)</td>
<td>6273</td>
<td>18% mortality</td>
<td>Atrial fibrillation odds ratio (OR)</td>
<td>1.56</td>
<td>LVEF OR 1.56</td>
<td>Age OR 1.48</td>
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<tr>
<td></td>
<td>Registry</td>
<td>at 1 year</td>
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<td>Cohn[93]</td>
<td>Circulation 1993 V-HeFT 1 and 2</td>
<td>LV dysfunction as reqd for V-HeFT inclusion</td>
<td>V-HeFT 1:642</td>
<td>283</td>
<td>LVEF (P&lt;0.0001)</td>
<td>CTR (P&lt;0.003)</td>
<td>VO2 (P&lt;0.005)</td>
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<td>V-HeFT 2:804</td>
<td>285</td>
<td>VO2 (P&lt;0.0001)</td>
<td>LVEF (P&lt;0.0006)</td>
<td>CTR (P&lt;0.0002)</td>
<td>Ventricular arrhythmia (P&lt;0.01)</td>
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<tr>
<td>Bitner[90]</td>
<td>JAMA 1993; SOLVD substudy</td>
<td>LVEF ≤0.45, and/or pulmonary congestion on CXR</td>
<td>898</td>
<td>52</td>
<td>LVEF (OR) 1.74</td>
<td>NYHA III or IV v I OR 1.69</td>
<td>Distance walked (6 min) OR 1.5</td>
<td>NYHA II v I OR 1.33</td>
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<tr>
<td>Compana[32]</td>
<td>J Heart Lung Transplant 1993</td>
<td>Advanced heart failure</td>
<td>388</td>
<td>99 (166</td>
<td>PCWP (P&lt;0.001)</td>
<td>NYHA IV (P=0.002)</td>
<td>Third heart sound (P=0.005)</td>
<td>Cardiac output (P=0.007)</td>
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*continued*
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<tr>
<th>Author</th>
<th>Study</th>
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<th>n=</th>
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<th>Rank 1</th>
<th>Rank 2</th>
<th>Rank 3</th>
<th>Rank 4</th>
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<td>Batin[72]</td>
<td>Eur Heart J 1995</td>
<td>NYHA II-IV</td>
<td>552</td>
<td>218</td>
<td>LFTs</td>
<td>CTR</td>
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<td>Male gender</td>
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<td>Giannuzzi[29]</td>
<td>J Am Coll Cardiol 1996</td>
<td>LVEF ≤35%</td>
<td>557</td>
<td>201</td>
<td>Diuretic Dose</td>
<td>NYHA (P&lt;0.001)</td>
<td>NYHA (P&lt;0.001)</td>
<td>NYHA (P&lt;0.001)</td>
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<td>Adams[71]</td>
<td>J Am Coll Cardiol 1996</td>
<td>Clinical heart failure</td>
<td>557</td>
<td>201</td>
<td>Age</td>
<td>Male (RR1.2)</td>
<td>NYHA (P&lt;0.001)</td>
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<td>Pernetkil[22]</td>
<td>Am J Cardiol 1997</td>
<td>Age ≥70 years</td>
<td>288</td>
<td>38.2% at 1 year</td>
<td>LVEF</td>
<td>NYHA (P&lt;0.001)</td>
<td>NYHA (P&lt;0.001)</td>
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<td>Gomes[14]</td>
<td>Am J Cardiol 1997</td>
<td>IHD and DCM</td>
<td>369</td>
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<td>LVEF</td>
<td>NYHA (P&lt;0.001)</td>
<td>NYHA (P&lt;0.001)</td>
<td>NYHA (P&lt;0.001)</td>
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<td>Aaronson[9]</td>
<td>Circulation 1997</td>
<td>Age ≥70 years</td>
<td>268</td>
<td>31.2% at 5 years</td>
<td>LVEF</td>
<td>NYHA (P&lt;0.001)</td>
<td>NYHA (P&lt;0.001)</td>
<td>NYHA (P&lt;0.001)</td>
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<td>Nolan[85]</td>
<td>Heart Failure '97 Cologne</td>
<td>Advanced heart failure</td>
<td>471</td>
<td>6 min walk</td>
<td>Heart Failure</td>
<td>NYHA (P&lt;0.001)</td>
<td>NYHA (P&lt;0.001)</td>
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<td>Soifer[89]</td>
<td>J Am Coll Cardiol</td>
<td>Severe heart failure</td>
<td>516</td>
<td>193</td>
<td>Systolic blood</td>
<td>NYHA (P&lt;0.001)</td>
<td>NYHA (P&lt;0.001)</td>
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<td>O'Connor[30]</td>
<td>J Am Coll Cardiol</td>
<td>Advanced heart failure</td>
<td>433</td>
<td>52</td>
<td>Functional capacity</td>
<td>NYHA (P&lt;0.001)</td>
<td>NYHA (P&lt;0.001)</td>
<td>NYHA (P&lt;0.001)</td>
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</table>

*Rank based on analysis of 239 patients with complete data set.

#Multi-variate analysis using clinical variables only. CTR=cardio-thoracic ratio; ANF=atrial natriuretic factor; RV=right ventricular; HRV=heart rate variability.
**Multivariate analysis**

A tabular summary of reports with more than 200 patients with chronic heart failure in which a multivariate analysis of prognostic factors is shown.

**Discussion**

This systematic review identifies a variety of factors that predict prognosis but highlights the fact that few variables predict it consistently. This may reflect:

- the small size of some studies.
- selected patient populations with differing aetiology, severity of disease or age.
- selective acquisition of prognostic variables (i.e. only when exercise capacity is measured can it be of predictive value).
- many prognostic variables are inter-related. Closely related variables will compete in prognostic models and one or more predictive variable may be eliminated. (e.g. left ventricular ejection fraction by radionuclide ventriculography but not by echocardiography appears consistently to predict prognosis).
- the introduction of new therapies that may possibly alter the prognostic value of some tests (for example ACE inhibitors and serum sodium).
- the duration of follow-up, some factors may predict short- but not long-term prognosis.
- poor technical (i.e. laboratory test) or physiological reproducibility (e.g. diurnal variation, variation with posture or exercise) of some variables.
- problems with data handling (e.g. whether data is treated as a continuous variable where appropriate or an arbitrary cut-off value such as the median is used).

For routine clinical practice the severity of symptoms (NYHA class), measurement of ventricular function and the aetiology of disease are the variables that have been shown most consistently to have independent prognostic value. Simple biochemical markers including the serum sodium, creatinine and a measure of liver function may have added value although whether hyponaatraemia retains independent prognostic value in patients taking ACE inhibitors remains to be established. In a research setting markers of neuroendocrine activation may have additional prognostic information but this requires confirmation in further multi-variate analyses.

Symptoms have generally been assessed using NYHA class. It is likely that doctors take into account many factors in addition to symptoms when deciding on NYHA class. In addition a patient in NYHA class III on no furosemide probably has a better prognosis than a patient in NYHA class II requiring 200 mg·day⁻¹ of furosemide. Diuretic dose (furosemide ≥ 80 mg·day⁻¹) is a potentially powerful prognostic factor that has seldom been considered or reported.[22]

Echocardiographic left ventricular dimensions and radionuclide left ventricular ejection fraction are widely available, robust measures of cardiac function that predict outcome; echocardiographic indices of diastolic function may have additional value. However, echocardiographic left ventricular ejection fraction may be less useful, either because it is inaccurate or because other, more powerful prognostic indices are acquired at the same time. Cardiothoracic ratio may partially substitute for or complement information from the above imaging modalities.

Exercise capacity, in one form or another, has predicted outcome in many studies but, unfortunately, has frequently not been measured in the larger outcome studies shown in Table 1. It has yet to be convincingly demonstrated that measurements of exercise capacity add major prognostic information over and above more simple measures such as NYHA class.

The lack of consistency with which any one invasive haemodynamic variable has predicted prognosis is of concern. It is usually patients who already have severe CHF who undergo invasive studies and this may introduce selection bias.

The majority of studies reported above are from specialist centres which inevitably treat the severe end of the disease spectrum often in patients who have already had chronic heart failure for some time. These patients have selected themselves not only as survivors but also as patients at increased risk. The validity of extending prognostic variables from this population to the wider community with chronic heart failure has not been proved.

It is likely that different sets of variables will prove useful in different settings. In primary care it is important to be able to stratify risk on the basis of simple, readily available, clinical or laboratory variables, to identify patients who should be referred for specialist advice or intensive therapy. For the cardiologist prognostic variables are required to direct the intensity of therapy and the need for or urgency of surgery, including transplantation. There is very little information on the prediction of outcome in the large number of very elderly patients with chronic heart failure.

The use of a single arbitrary cut-off value is unlikely to show the true usefulness of a prognostic test that is continuously distributed. However, attaching prognostic importance to individual values also has problems as only the prognosis of cohorts of patients can really be described. An alternative is to grade continuous variables into a series of bands (for instances quartiles) to allow better separation of high and low risk groups. The use of a simple scoring system based on exercise performance, left ventricular ejection fraction and serum sodium has been suggested following a limited retrospective study.[209,210] This should be tested in a prospective study to determine whether these are the simplest measures to adequately predict outcome.

Several simple measurements may be more useful than one complex one. Measures such as the severity of symptoms, heart rate and blood pressure are obtained at no additional effort during the patients routine management. A hierarchy of prognostic testing that takes into account ease of measurement as well as the accuracy of the test is required. Identification of those prognostic variables that carry very similar information would lead the test is required. Identification of those prognostic account ease of measurement as well as the accuracy of ment. A hierarchy of prognostic testing that takes into than one complex one. Measures such as the severity of prognostic variable is overlooked[49,209,210].

References


[147] Ponikowski P, Anker SD, Chua PT et al. Depressed heart rate variability as an independent predictor of death in chronic congestive heart failure secondary to idiopathic or ischemic dilated cardiomyopathy. Am J Cardiol 1997; 79:


