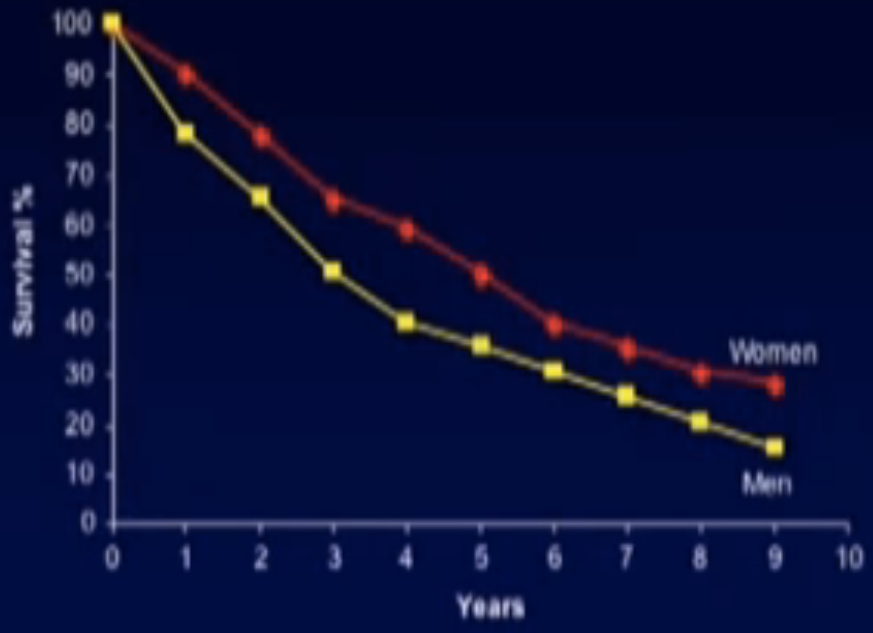
Prognosis With Heart Failure

Overall
5-year mortality 50%

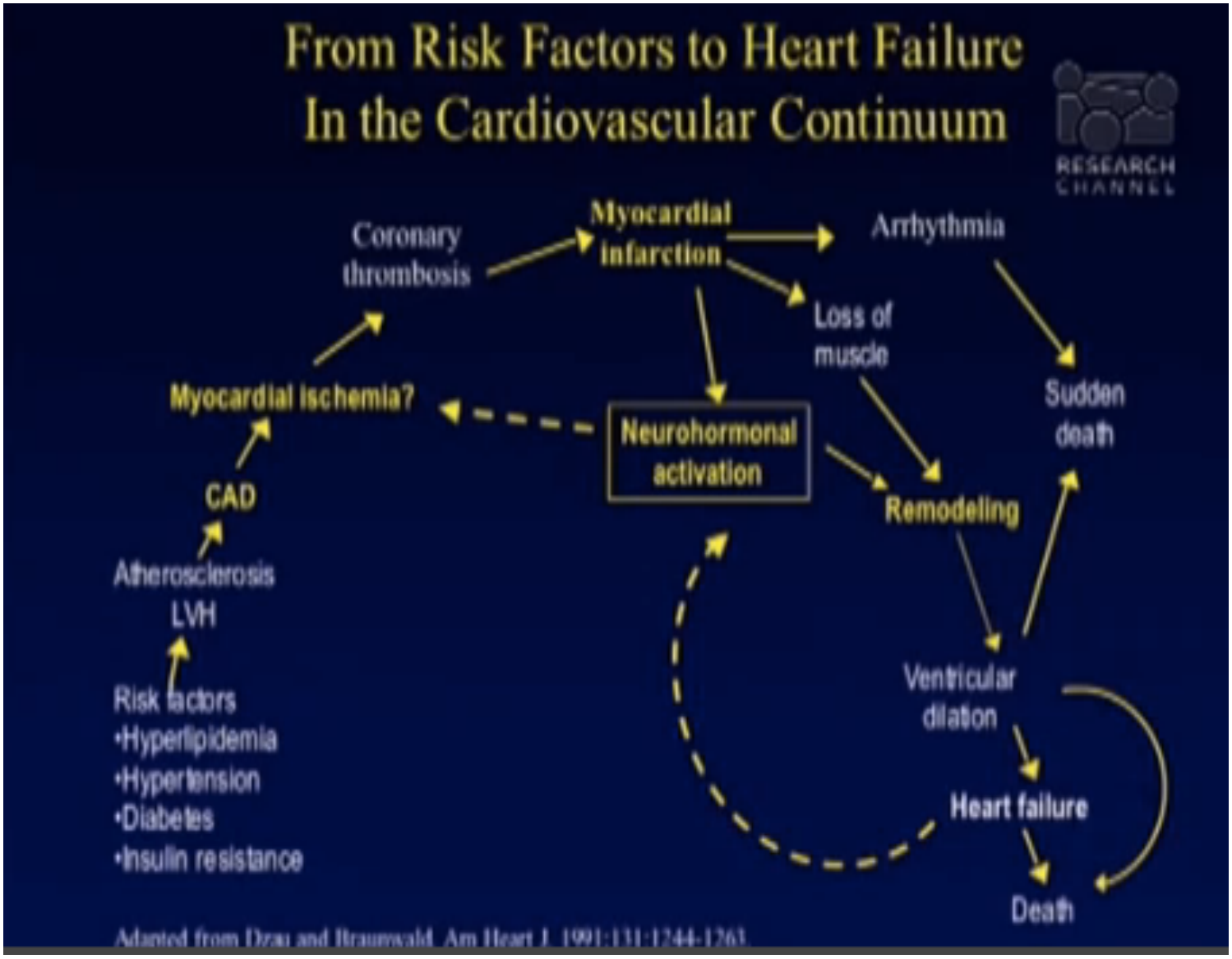
Hospitalized Patients
1-year mortality:

Mild to Moderate Symptoms
10-20%

Severe Symptoms
40-60%



AHA, 1998 Heart and Statistical Update
NCHS, National Center for Health Statistics
Survival after the onset of congestive heart failure in Framingham Heart Study subjects


From Risk Factors to Heart Failure
In the Cardiovascular Continuum
RESEARCH CHANNEL
Coronary thrombosis
Myocardial infarction
Arrhythmia
Loss of muscle
Sudden death
Myocardial ischemia?
Neurohormonal activation
Remodeling
CAD
Atherosclerosis
LVH
Risk factors
•Hyperlipidemia
•Hypertension
•Diabetes
•Insulin resistance
Ventricular dilation
Heart failure
Death
Adapted from Dzau and Braunwald. Am Heart J. 1991;131:1244-1263.

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Point of View

Life-saving or life-prolonging? Interpreting trial data and survival curves for patients with congestive heart failure

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Abstract

Chronic heart failure is responsible for considerable suffering and mortality throughout the world. Clinical trials have consistently demonstrated the benefits of pharmacological therapies such as angiotensin-converting enzyme inhibitors and beta-adrenoceptor blockers. These drugs are often quoted as reducing mortality from heart failure, yet all patients with heart failure deteriorate and most will die because of their disease. Therapies in heart failure are not truly life saving; they modify the natural history of the disease and delay the time to deterioration. The time benefit in survival is not usually reported in clinical trials, which are conducted over fixed time points and report risk reductions during this period only. In this paper, we discuss the use of prolongation of life statistics as an outcome measure in clinical trials and review simple techniques for calculating the lifetime benefit of pharmacological intervention in heart failure using data from a number of major studies.

Keywords: Outcomes; Relative risk; Clinical trials; Survival; Heart failure

1. Introduction

Cardiologists are fortunate to have a large evidence base to justify the treatments they offer to patients. The best evidence stems from randomised placebo-controlled trials, which have become the standard by which treatments are judged. However, clinical trials are conducted over finite time periods and differences between treatments may change with time. Researchers, and especially those with vested interests (for example, the pharmaceutical industry), present results in the most positive way, which is best achieved by focusing on the maximum effect and using relative risk reductions instead of absolute differences. Doctors are also guilty of exaggerating benefit and are understandably enthusiastic about novel and interesting treatments. However, in reality in overall terms of health gain, benefits are often surprisingly small.

2. Natural history of heart failure

Heart failure is a common cause of morbidity and mortality, especially in the elderly population [1,2]. It is a consequence of damage to the heart from all insults and has a poor prognosis [3]. The drive to develop treatments for heart failure has produced a number of therapeutic options and these may be used in combination. Clinicians and their patients are presented with treatment choices on a daily basis. The clinician has the patients' best interests at heart but is subject to various external pressures. Authors, drug companies and commentators claim that treatment 'saves lives' and the National Service Framework guidelines for heart failure in the UK recommend treatment with a combination of drugs at maximal doses. Medical compliance with these guidelines is subject to ongoing audit. Clinicians may feel pressured to offer "life-saving" treatment based on research results and fear litigation if they fail to do so. Patients understandably want the best treatment and access to these 'life-saving' therapies but they also want quality of life, absence of drug side effects and in most cases a perception of prognosis.

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Interpreting clinical trials for patients correctly demands knowledge of the natural history of the disease. For those physicians faced with explaining the benefits or risks of treatments to patients, relative and even absolute differences in percentage terms are of limited value. What the patient wants to know is how much better will I feel with this treatment, or how much longer will I live set against the side effects it will give me? Patients know that drugs cause side effects—they know that treatments may result in benefit as well as harm. Results of randomised controlled trials against placebo are especially useful in informing decision making, but the doctor must be able to present the information to the patient in an understandable format.

It is misleading to tell a patient with heart failure that a drug will save his or her life. Heart failure of any aetiology is progressive, irreversible and inevitably fatal—only the rate of progression is variable. Patients with a persistent underlying disease like ischaemic heart disease, die more rapidly than the patients whose hearts have been damaged by a single insult, e.g. myocarditis or cardiomyopathy [4]. The prognosis is also related to the degree of left ventricular damage. Untreated congestive heart failure has approximately 50% survival at 12 months [5], the overall prognosis of all patients with heart failure on treatment is around 50% at 5 years and this has changed little in the past 20 years [3]. Data from clinical trials in heart failure demonstrate that the majority of patients diagnosed with heart failure ultimately die of the condition despite treatment. In the V-Heft 2 study for example, of the 403 patients on Enalapril treatment 132 had died after 2.5 years, 107 of these were due to complications of congestive heart failure (including sudden deaths) [6]. Furthermore, there is objective evidence of symptomatic decline, since despite angiotensin converting enzyme inhibitor (ACE-I) therapy the VO_2 max in the treatment group was significantly reduced at follow-up. The progressive decline in function was reinforced by the SOLVD prevention study. In this trial, patients with asymptomatic left ventricular dysfunction were treated with ACE-I or placebo [7]. After 3 years, 30% of these initially asymptomatic patients had developed manifest heart failure and of the 313 deaths nearly 60% had died due to complications of heart failure. Given that heart failure is progressive with or without treatment, patients with mild heart failure eventually become severely affected and patients with severe heart failure die. This outcome is worse than many cancers, and in this sense, heart failure is a malignant disease. The comparison with cancer is useful to a point but there is one difference, some cancers can be cured, whereas congestive heart failure cannot. This phenomenon was demonstrated by the landmark CONSENSUS Trial, which was the first major mortality study in severe heart failure. It demonstrated that severe heart failure carries a very poor prognosis but showed that Angiotensin-converting enzyme inhibitors improved survival [8]. The initial reports showed a relative reduction of mortality of 40% at 6 months and 20% at 12 months, and the Kaplan–Meier survival curves were initially divergent. However, the long-term follow-up of this study showed the reality, the Kaplan–Meier survival curves began to converge after 2 years and all the patients had died by 10 years—the survival curves eventually met [9]. Thus, the mortality reduction that positioned ACE-I inhibitors as life-saving treatment was temporary.

If heart failure progresses despite treatment and patients inevitably die from it, then treatments cannot be claimed to save lives. In fact, the treatments are changing the natural history of progression and prolonging the time to death or intractable symptoms.

3. Explaining statistics to patients using Kaplan–Meier survival curves

A useful method for treatments with an immediate effect—such as thrombolysis for myocardial infarction is to describe benefit is in terms of lives saved per 1000 patients treated. However, for chronic progressive conditions like heart failure, the statistic is artificial because it varies widely at different time points. At any given point in time, more patients given placebo may have died compared with those given the active drug but eventually all the patients will die. Thus, the time where there is the biggest separation of the Kaplan–Meier survival curves will produce the biggest risk reduction both relative and absolute. Fig. 1 demonstrates this phenomenon; this survival curve shows the probability of survival in subjects with congestive heart failure treated with an ACE-I (Trandalopril) or placebo. The annotated percentage numbers report the absolute risk benefit of the ACE-I at each time point, the statistical benefit varies and the perceived benefit of Trandaloril depends on the time of data sampling. For example there is an 8.7% risk benefit at 3 years, whereas the benefit is only 6.4% at 5 years. We could use this

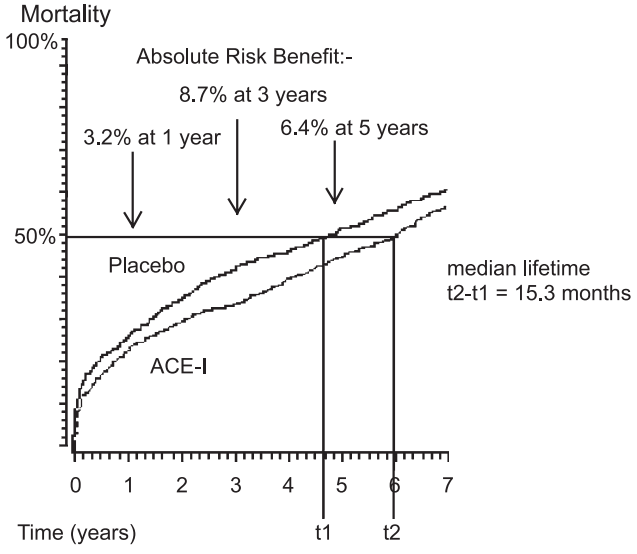

Fig. 1. Survival data from the TRACE study. Reprinted with permission from Ref. [11] Elsevier.

information for patients but it is artificial and does not tell the whole story. A better way of describing the effect of the drug therapy on the natural history of heart failure is to use the extension to life statistic. A patient might understand this value far better than more abstract concepts such as relative or absolute risk reduction. Unfortunately, most published trials do not use extension of life statistics even though these values are relatively easily calculated [10]. It is possible to make an estimate of life extension by analysis of Kaplan–Meier survival curves.

There are three common shapes to Kaplan–Meier survival curves in medicine.

1. Divergent–convergent. Here the curves initially separate but eventually join up. In the context of heart failure, therapy delays the natural progression of the underlying disease but does not prevent deterioration. Survival is prolonged temporarily. (e.g. ACE I in heart failure TRACE trial, Fig. 1) [11].
2. Divergent–parallel. The curves rapidly separate and remain apart but generally parallel, indicating that treatment immediately improves survival and that this is maintained into follow-up. Curves of this type reflect an intervention that has an immediate effect on the case fatality rate such as thrombolysis for acute myocardial infarction—ISIS 2, Fig. 2) [12]. If thrombolysis is given appropriately there is an immediate 25% improvement in survival. There are no drug therapies in heart failure that acutely reduce the case fatality rate.
3. Increasingly divergent. Here the survival curves continue to separate over time. The treatment has ongoing, cumulative benefit during the observation period. This curve is misleading in heart failure since follow-up time is often limited; there is no treatment that stops the progression of heart failure. (e.g. B-blockers in heart failure. COPERNICUS study, Fig. 3) [13].

Fig. 2. Survival data from the ISIS-2 study. Reproduced with permission from Ref. [12].

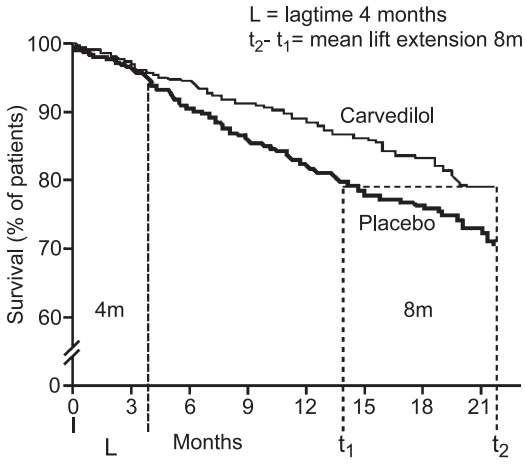

Fig. 3. Survival data from the COPERNICUS study. Reproduced with permission from Ref. [13]. Copyright 2001 Massachusetts Medical Society. All rights reserved.

In heart failure, survival curves should always of the type 1 (divergent–convergent) since heart failure cannot be cured and progression of morbidity and cumulative mortality only delayed. There are no type 2 (parallel) curves in chronic heart failure because there is no treatment for heart failure that immediately reduces the case fatality rate. The long-term follow-up studies of thrombolysis showed parallel survival curves for 10 years after myocardial infarction showing that the treatment had no other effect other than to reduce hospital mortality at the time of the event: streptokinase is truly life-saving. In fact, the most common curve observed in the literature is the type 3 curve (increasingly divergent). This curve is seen because many trials have short follow-up times. The curves diverge reflecting ongoing benefit compared to placebo, but this benefit is temporary and it can be assumed that the curve will eventually converge as demonstrated by the CONSENSUS-1 and TRACE long term follow-up studies [9,11].

If life extension is not calculated in a paper it can be estimated from the Kaplan–Meier curve. If there is adequate follow-up time to the death of the median patient, the difference in median lifetimes of placebo and treatment group can be quoted as the median life extension. This technique was first used by Torp-Pederson et al. with the TRACE data [11]. To calculate this value a line is drawn through the y-axis and curves at the point of the 50th centile patient. The time difference between the treatment and placebo curves on the x-axis is the difference in median lifetimes (Fig. 1). This term can be used for patients to explain that the treatment extends life by an average duration.

There are two limitations to this method. The first is that most heart failure studies do not continue follow-up to the death of the median patient. We believe that heart failure trials without follow-up to the death of the median patient should be discouraged since a continually diverging curve suggests persistent and permanent benefit, which does not occur in this population. It also difficult to give the accurate

assessment of the life extension benefit, in the absence of this precise statistical value, a life extension estimate can be made by recording the survival difference when the trial terminates. It is accepted that the curves may diverge further but will (eventually) converge; this extrapolation is not made (Fig. 3). This figure can be quoted to the patient as the 'proven lifetime benefit' or the best current estimate demonstrated by the study. The second limitation is the right hand tail of Kaplan–Meier curves are based on fewer data (because of cumulative patient deaths and withdrawals) and are consequently less reliable. There is therefore increasing error in estimates further down the curve [14]. As long as these limitations are understood and explained to patients during discussion, estimates of life extension are potentially a valuable resource.

This method of analysing survival curves can also be used for morbidity assessments. Many studies use re-admission, recurrent events or unremitting symptoms as secondary outcome measures. If the Kaplan–Meier curve is plotted for these outcomes the same technique can be used. This is invaluable information for the patient and the doctor, since in some cases patients may value improvements in morbidity over mortality. A final important measure may be made from analysis of the Kaplan–Meier curve, and this is the time to treatment effect. A treatment may confer survival benefit but there is a lag time before this benefit is realised. This can be calculated by recording the time taken for the Kaplan–Meier curve to diverge. An example of this is the COPERNICUS study (Fig. 3). Here it took 4 months for the treatment and placebo curves to diverge. Thus, there is a time delay of 4 months before the treatment affects survival.

We have calculated life extension values and morbidity extension values for all of the major randomised controlled trials of treatment for heart failure and heart failure following myocardial infarction (Table 1). In the table, lifetime extension, lag time and type of curves are listed. The type of Kaplan–Meier curve is recorded, divergent–convergent (D/C), increasingly divergent (Div) or parallel (P). Extension to survival is made by comparison of the difference in median lifetimes unless marked. In trials where the death of the 50th centile patient is not available, then maximum demonstrated survival extension the 'proven lifetime benefit' is used. For congestive cardiac failure, the morbidity outcome is a composite of time to re-admission or unremitting severe symptoms. Fields are left empty if no data is available for that statistic.

4. Prolonging life in heart failure

The natural history of heart failure is of progressive decline. All heart failure patients will deteriorate symptomatically and eventually die. In this sense, these patients can be considered to be on a survival curve, the rate of attrition and thus the gradient of the curve can never be restored to that of a non-heart failure population. The task of clinicians is to reduce the gradient of decline. Most treatments take 1–2 months of treatment to have an effect. Moreover, treatment benefit does not persist indefinitely so survival curves are divergent–convergent. The curves that do not show convergence (e.g. CIBIS-2, RALES) [20,21], have short follow-up times and will eventually converge. Survival time in heart failure is poor and current treatments in severe heart failure give an average extension to survival of around 20 months. Treatment with an ACE-I prolongs life by 9 months, the addition of a beta-blocker confers a further 7 months and adding spironolactone gives up to 12 months more. Angiotensin II receptor inhibitors improve time to morbidity in groups either on an ACE Inhibitors or beta-blockers but not both. Digoxin has no effect on

Table 1
Life extension values and morbidity extension values for all major treatment trials for heart failure and heart failure following myocardial infarction (time is in months)

Drug	Lag time (months)	Survival extension (months)	Morbidity extension (months)	Trial	Curve
ACE-1 post MI (no CHF)	0	12	11	SAVE [15]	Div[a]
ACE-1 post MI (NYHA 1–2)	0	15.3	22	TRACE [11]	D/C
ACE-1 post MI (NYHA 3–4)	0.5	1		ISIS-4 [16]	Div[a]
ACE-1 (NYHA 1–2)	1.5	0	14	SOLVD prevention [7]	Div[a]
ACE-1 (NYHA 2–3)	1	6	15	SOLVD treatment [17]	D/C
ACE-1 (NYHA 3–4)	0	9		CONSENSUS [9]	D/C
B-Blocker (NYHA 2–3)	2	6	6	MDC [18]	D/C
B-Blocker (NYHA 2–3)	3	6	9	Merit-HF [19]	D/C
B-blocker (NYHA 2–3)	3	9		CIBIS-2 [20]	Div[a]
B-Blocker (NYHA 3–4)	4	8		COPERNICUS [13]	Div[a]
Spironolactone	3	12		RALES [21]	Div[a]
AT-2 antagonists	5	0	4	Val-HeFT [22]	Div[a]
Digoxin	0	0	16	DIG [23]	P[a]
Amiodarone	6	6		GESICA [24]	D/C
Amiodarone	0	0	0	StatiCHF [25]	P[a]
Cardiac transplant	1	8		COCPIT [26]	D/C

D/C=divergent–convergent; Div=increasingly divergent; P=parallel.

mortality, but has an instant effect on morbidity (producing an unusual type 2 parallel curve). If atrial fibrillation is present warfarin treatment reduces the morbidity associated with stroke [27], and a meta-analysis suggests a survival benefit but the extension to life has not been calculated [28].

5. Compliance

Drug treatment in cardiovascular disease is increasing and most patients with ischaemic disease will be asked to take three or more medications. The same is true in heart failure but in this situation there is clear evidence of synergism from combination therapy. Interpreting clinical evidence in a meaningful way to patients is important since many are reluctant to take several medications and compliance with poly-pharmacy is poor [29]. It is equally important to explain that treatment may take time to work, which again has important consequences for compliance. If a patient is told that a medication has to be taken for several months before any beneficial effects are realised there is a greater incentive to keep taking it. Transitory adverse side effects, common with beta-blocker dose-titration for example may be better tolerated if the patient understands that a therapy may take some months to deliver its effect.

Given that prognosis remains poor despite recommended treatments, quality of life becomes even more important. For example, in patients with severely symptomatic heart failure, the beneficial morbidity of effects of oral inotropes may be attractive despite the increased risk to life [30].

6. Conclusion

The irreversible progression of heart failure makes the comparison and power of treatments difficult to assess. A useful way of explaining the benefits of treatments to patients is to focus on the lifetime extension to survival afforded by individual therapies. However, information on treatment effects on morbidity may mean even more to patients than plain survival statistics. We hope that this technique and the values provided in the table give clinicians and patients useful understandable statistics to guide therapy.

References

[1] Haldeman GA, Croft JB, Giles WH, Rashidee A. Hospitalization of patients with heart failure: National Hospital Discharge Survey, 1985 to 1995. Am Heart J 1999;137(2):352–60.
[2] McMurray JJ, Stewart S. Epidemiology, aetiology, and prognosis of heart failure. Heart 2000;83(5):596–602.
[3] Levy D, Kenchaiah S, Larson MG, et al. Long-term trends in the incidence of and survival with heart failure. N Engl J Med 2002;347(18):1397–402.
[4] Steeds RP, Channer KS. Selective treatment for heart failure: the future beckons? Congest Heart Fail 1999;5(2):74–6.
[5] Ho KK, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. Circulation 1993;88(1):107–15.
[6] Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 1991;325(5):303–10.
[7] Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The SOLVD Investigators. N Engl J Med 1992;327(10):685–91.
[8] Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. N Engl J Med 1987;316(23):1429–35.
[9] Swedberg K, Kjekshus J, Snapinn S. Long-term survival in severe heart failure in patients treated with enalapril. Ten year follow-up of CONSENSUS I. Eur Heart J 1999;20(2):136–9.
[10] Yusuf S, Zucker D, Peduzzi P, et al. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. Lancet 1994;344(8922):563–70.
[11] Torp-Pedersen C, Kober L. Effect of ACE inhibitor trandolapril on life expectancy of patients with reduced left-ventricular function after acute myocardial infarction. TRACE Study Group. Trandolapril Cardiac Evaluation. Lancet 1999;354(9172):9–12.
[12] Baigent C, Collins R, Appleby P, Parish S, Sleight P, Peto R. ISIS-2: 10 year survival among patients with suspected acute myocardial infarction in randomised comparison of intravenous streptokinase, oral aspirin, both, or neither. The ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Bmj 1998;316(7141): 1337–43.
[13] Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344(22):1651–8.
[14] Pocock SJ, Clayton TC, Altman DG. Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. Lancet 2002;359(9318):1686–9.
[15] Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med 1992;327(10):669–77.
[16] ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. Lancet 1995;345(8951):669–85.
[17] Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. N Engl J Med 1991;325(5):293–302.
[18] Waagstein F, Bristow MR, Swedberg K, et al. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. Metoprolol in Dilated Cardiomyopathy (MDC) Trial Study Group. Lancet 1993;342(8885):1441–6.
[19] Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999;353(9169):2001–7.
[20] The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999;353(9146):9–13.
[21] Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341(10):709–17.
[22] Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001;345(23):1667–75.

[23] The effect of digoxin on mortality and morbidity in patients with heart failure. The Digitalis Investigation Group. N Engl J Med 1997;336(8):525–33.
[24] Doval HC, Nul DR, Grancelli HO, Perrone SV, Bortman GR, Curiel R. Randomised trial of low-dose amiodarone in severe congestive heart failure. Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA). Lancet 1994;344(8921):493–8.
[25] Singh SN, Fletcher RD, Fisher SG, et al. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. N Engl J Med 1995;333(2):77–82.
[26] Deng MC, De Meester JM, Smits JM, Heinecke J, Scheld HH. Effect of receiving a heart transplant: analysis of a national cohort entered on to a waiting list, stratified by heart failure severity. Comparative Outcome and Clinical Profiles in Transplantation (COCPIT) Study Group. BMJ 2000;321(7260):540–5.
[27] Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. Lancet 1989;1(8631):175–9.
[28] Cleland JG, Cowburn PJ, Falk RH. Should all patients with atrial fibrillation receive warfarin? Evidence from randomized clinical trials. Eur J Heart 1996;17(5):674–81.
[29] Morgan TO, Nowson C, Murphy J, Snowden R. Compliance and the elderly hypertensive. Drugs 1986;31(Suppl. 4):174–83.
[30] Cowley AJ, Skene AM. Treatment of severe heart failure: quantity or quality of life? A trial of enoximone. Enoximone Investigators. Br J Heart 1994;72(3):226–30.