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Heart Failure Treatments

Issues of Safety Versus Issues of Quality of Life

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Abstract

Congestive heart failure is an important cause of morbidity and mortality in western countries. The profound impact that congestive heart failure has on life expectancy and quality of life has been a continuous stimulus for the development of new drugs for the treatment of this condition. Despite favourable effects on (aspects of) quality of life in short term studies, several of these new agents have been shown to reduce survival in mortality trials.

However, patients with severe congestive heart failure may experience such incapacitating symptoms that the question should be raised as to whether an improvement in quality of life makes the increased risk of mortality associated with these new agents acceptable. Drugs which improve quality of life at the expense of an increased risk of mortality can be of value in the treatment of patients with severe congestive heart failure. However, this is only the case if the probability of improvement in quality of life and prolongation of life expectancy for those using the drug exceeds the probability of improvement in quality of life and prolongation of life expectancy for those not using the drug. Unfortunately, most clinical trials in which both mortality and quality of life are evaluated fail to provide information on this composite probability.

Despite disappointing results of some recent mortality trials on new pharmacological treatments of congestive heart failure, sound and well designed clinical trials on innovative heart failure treatments in which these composite probabilities are also assessed should be carried out.

Congestive heart failure has a profound impact on quality of life and life expectancy. Dyspnoea and exercise intolerance pose major limitations to the daily activities of patients with congestive heart failure. In the management of congestive heart failure, loop diuretics and ACE inhibitors are the mainstays of therapy. Depending on the characteristics of the disease for the individual patient, a beneficial effect may also be obtained by adding digoxin and vasodilators to the treatment regimen.

However, even with the most optimal treatment currently available, many patients experience incapacitating symptoms and their life expectancy is reduced significantly. Furthermore, epidemiological

Table I. Double-blind, randomised clinical trials on drugs associated with a statistically significantly increased risk of mortality in patients with congestive heart failure

Trial	Total number of patients in the trial	Drug (dosage)
Xamoterol[5]	516	Xamoterol (200mg twice daily)
Enoximone[6]	151	Enoximone (50-100mg 3 times daily)
PRIME-II[7]	1906	Ibopamine (100mg 3 times daily)
PROMISE[8]	1088	Milrinone (40 mg/day)
VEST[9]	3833	Vesnarinone (30 or 60 mg/day)
PROFILE[10]	2304	Flosequinan (75-100 mg/day)
FIRST[11]	471	Epoprostenol (median 4 ng/kg/min)

studies indicate a marked increase with age in both the incidence and the prevalence of congestive heart failure.[1-4]

Apart from the therapeutic progress made with the introduction of the ACE inhibitors, the expanding knowledge of the pathophysiology of congestive heart failure has failed to provide substantial progress to the usual pharmacotherapeutic treatment of this condition, and prognosis of patients with congestive heart failure has remained poor, both in terms of life expectancy and quality of life. Over the years, several promising new drugs developed for the treatment of congestive heart failure have been shown to decrease survival in double-blinded randomised clinical trials (table I).

Regardless of the pharmacological differences among agents such as xamoterol, milrinone, flosequinan and ibopamine, their ultimate effect on survival in patients with congestive heart failure can only be considered as unfavourable. Despite the inability of these drugs to exert favourable or even neutral effects on survival in patients with congestive heart failure, many of them may improve exercise tolerance and relieve symptoms. This raises the key question as to whether we are willing to accept improved quality of life at the expense of decreased survival, assuming that both the beneficial effect on quality of life and the unfavourable effect on survival of the drug involved have unequivocally been demonstrated.

1. Safety of Pharmacological Treatment of Heart Failure

Safety, effectiveness and efficacy are central issues in the development of new drugs. Safety can be regarded as a measure of the absence of adverse drug effects, but must always be considered in relation to effectiveness, that is, the wanted pharmacological effect of the drug. Efficacy of the pharmacological treatment of congestive heart failure is essentially characterised by 2 aspects: improvement of symptoms and prolongation of life expectancy. In the evaluation of congestive heart failure treatment, a strict distinction between efficacy and safety is of little relevance, as both concepts refer largely to similar effects. In congestive heart failure, prolongation of survival has been demonstrated with ACE inhibitors and the combination of hydralazine and isosorbide dinitrate.[12-14] Furthermore, results from recent trials with ß-blockers indicate favourable effects on mortality, although the effect may depend on the aetiology of congestive heart failure and on characteristics of the ß-blocker involved.[15-17]

Results from a recently published meta-analysis have confirmed the favourable effect of ß-blockade on all-cause mortality in patients with congestive heart failure, although their value in the treatment of congestive heart failure needs to be established in ongoing and future trials.[18]

The effect of diuretics on survival in patients with congestive heart failure has not been subject to randomised double-blind, placebo-controlled studies, as these drugs are the cornerstone of the treatment of fluid retention in patients with congestive heart failure and a placebo-controlled study would be unethical. Moreover, their beneficial effects are not seriously questioned.[19]

Results from a recent trial on the effect of digitalis on mortality and morbidity in patients with congestive heart failure indicated that digoxin did reduce the rate of hospitalisation both overall and for worsening heart failure, but did not affect mortality during 4 years of follow-up.[20]

In response to disappointing results of recent mortality trials on several new agents which were

assumed to have, at least theoretically, beneficial effects on the failing heart (table I), it has recently been suggested that it is now time for a moratorium on human studies that investigate drugs which stimulate the catecholamine receptor and their post-receptor pathways until convincing animal data endorse a beneficial effect on survival.[21]

In our opinion, however, the judgement of heart failure treatments deserves a more balanced approach. First, comparability between human and animal studies is subject to limitations. For instance, differences in catecholamine receptors among species may restrict any valid extrapolation from animal studies towards the human situation and is only one example why mortality in animals may differ from mortality in human beings.

Secondly, the establishment of such a moratorium may give rise to serious delays in the development of innovative pharmacological approaches to congestive heart failure. Since we face an important increase in the prevalence of congestive heart failure, such a delay in the development of new drugs is undesirable.

Thirdly, prolongation of survival should not be regarded as the only objective in the treatment of congestive heart failure. In particular, patients with severe congestive heart failure may experience such incapacitating symptoms that improvement in their clinical condition by a new pharmacological treatment may counterbalance the possibly unfavourable effect on survival. In some patients with severe congestive heart failure, the wish for relief of symptoms (quality of life) may even strongly dominate the wish to prolong life (quantity of life).

2. Quality of Life in Patients with Congestive Heart Failure

Quality of life is a broad concept which can be considered as the sum of all negatively and positively valued aspects of life. Although mental and physical health status are dominant determinants of quality of life, other aspects of life such as the socioeconomic situation, the presence of relatives and satisfying social contacts, and religious conviction may also contribute to quality of life. The appreciation of these aspects, however, can easily be influenced by changes in physical health status. Therefore, quality of life is generally considered as strongly physical health-related.

Improvement of quality of life is a very important aspect of congestive heart failure treatment. Several tests can be applied to measure (aspects of) quality of life in patients with congestive heart failure, such as the 6-minute walk test, the chronic heart failure questionnaire, and the Minnesota Living with Heart Failure Questionnaire.[22,23]

In the past, patient self-assessment of quality of life was considered to be of little relevance in clinical trials and emphasis was given to objective clinical outcomes. Nowadays, however, questionnaires on quality of life are increasingly included in the evaluation of the efficacy of congestive heart failure treatments. Symptomatic well-being of patients is much better reflected by quality-of-life questionnaires than by objective measurements of cardiac function, e.g. left ventricular ejection fraction. In a study on quality of life in patients with advanced heart failure (predominantly NYHA III-IV), no significant association could be found between left ventricular ejection fraction and measures of quality of life, such as functional status, physical symptoms, emotional state and psychosocial adaptation.[24] Among the numerous questionnaires available for the assessment of quality of life, the Minnesota Living with Heart Failure Questionnaire appears to provide the most suitable measurement of quality of life in patients with congestive heart failure.[22,23,25]

Effects on quality of life have been examined during treatment with ACE inhibitors, a class of drugs for which a favourable effect on survival in patients with congestive heart failure has unequivocally been established.[26,27] Valid comparisons among trials of the effect of ACE inhibitors on quality of life are almost impossible as a result of the various measures of quality of life. However, the overall impression is that ACE inhibitors exert a modest but consistent improvement of quality of life as compared with placebo. Beneficial effects

on quality of life, additional to the improvement of quality of life achieved by optimal treatment with ACE inhibitors, have also been reported with flosequinan and with enoximone. Unfortunately, both flosequinan and enoximone were associated with increased mortality.[6,28,29] As a matter of fact, the results of the large-scale mortality trial on flosequinan (Prospective Randomised Longevity Evaluation; PROFILE) have never even been properly published in an official medical journal, something which can only be regarded as regrettable. The recent results of the Second Prospective Randomised Study of Ibopamine on Mortality and Efficacy (PRIME-II) trial on mortality and efficacy of ibopamine in patients with congestive heart failure indicated that mortality increased by 26% in patients treated with ibopamine as compared to placebo.[7] These findings have once again demonstrated that most of the newer congestive heart failure treatments fail to combine short term improvement of quality of life with long term improvement of survival.

3. Safety versus Quality of Life

Improvement in quality of life and prolongation of life expectancy (quantity of life) are the main objectives in the treatment of patients with congestive heart failure. As pointed out before, some of the newer treatments of congestive heart failure have been shown to improve quality of life at the expense of increased mortality.

Table II. Intention-to-treat analysis of exercise capacity after 24 weeks of treatment with pimobendan 2.5 to 5mg or placebo. Data adapted from the Pimobendan in Congestive Heart Failure (PICO) trial[30]

Parameter	No. of patients (%)	
	placebo	pimobendan
Exercise capacity maintained or improved	64 (59)	132 (63)
Exercise capacity deteriorated	34 (31)	48 (23)
Too sick to exercise	4 (4)	5 (2)
Dead	6 (6)	24 (12)
Total	108 (100)	**209 (100)**

When treating an individual patient with congestive heart failure, physicians should decide on the primary aim of the treatment for that specific patient. This actually implies a translation of state-of-the-art knowledge on safety and quality of life issues into a therapeutic approach in which all the relevant patient characteristics are also taken into account. Of course, the patient must play an important role in this decision process.

Obviously, an increased risk of mortality in a clinical trial does not necessarily mean that an individual patient with congestive heart failure will die earlier. Likewise, an average improvement of quality of life in a clinical trial does not necessarily mean that every individual patient will experience relief of symptoms.

Use of drugs which have been demonstrated to decrease survival in patients with congestive heart failure can only be accepted, however, when the probability of improvement of quality of life and prolongation of life expectancy for those using the drug exceeds the probability of improvement of quality of life and prolongation of life expectancy for those not using the drug. In table II, the intention-to-treat analysis of exercise capacity data from the Pimobendan in Congestive Heart Failure (PICO) trial demonstrates that, despite a trend towards higher mortality in patients started on pimobendan, this probability is larger for those using the drug (63%) as compared to those not using the drug (59%). Unfortunately, only few clinical trials in which both survival and (aspects of) quality of life were evaluated offer the possibility for such a comparison.[30]

The adoption of an intention-to-treat approach to design and analysis instead of a per-protocol approach in the evaluation of repeated measurements of (aspects of) quality of life, e.g. exercise capacity, and the use of composite ranked end-points as in the PICO trial, may contribute to a joined evaluation of the actual drug effect.[31] It should be stressed that this analysis is only possible when all patients are followed until the planned end of the trial and, depending on clinical condition, the qual-

ity of life measures are obtained irrespective of study medication status.

Prescribing the most suitable treatment for patients with congestive heart failure implies a careful process of weighing the pros and cons of the therapeutic strategies against each other, in relation to the individual needs of the patient. In this process, there should be no *a priori* hierarchy between quality of life and prolongation of life expectancy in all patients with congestive heart failure. In order to combine the dimensions quality and quantity of life, the concept of quality-adjusted life-years has been introduced in the field of clinical decision analysis.

Quality-adjusted life-years reflect the number of years in full health that would be valued equivalently to the number of years of survival that are expected, including any morbidity during these years. This concept implies that the patient values the various health states on a scale of 1 to 0, where perfect health would be assigned the value 1 and a state as bad as death a value near 0. Multiplication of life expectancy in a certain health status with the appreciation of the health status as represented on the 1 to 0 scale, usually called the utility of the health state, leads to the number of quality-adjusted life-years (quality-adjusted life-years = expected number of years of survival $\times$ utility).

By using a method of health scale ranking with mutually exclusive categories, Olsson et al.[32] demonstrated that measures can be derived from clinical trials that allow direct adjustment of life expectancy for quality of life. The use of such measures may contribute to a clearer understanding of the actual effects on health status of the treatment studied. Furthermore, the number of hospitalisations for worsening congestive heart failure might also indirectly reflect aspects of both quality of life and life expectancy.

Despite the methodological limitations to measure quality of life in terms of reliability and validity, the concept of quality-adjusted life-years may offer additional support to a quantitative understanding of issues of life expectancy and quality of life in heart failure treatment. Obviously, these considerations will be particularly relevant in patients with severe congestive heart failure and debilitating symptoms. In patients with less severe congestive heart failure, prolongation of life expectancy should be the predominating aim of treatment.

In the absence of an established hierarchy between quality of life and prolongation of life expectancy in the treatment of patients with severe congestive heart failure, priority in the treatment of congestive heart failure may shift from improvement of survival towards improvement of symptoms. Patients with invalidating congestive heart failure may choose to use drugs which may improve their symptoms even if that leads to an increased risk of death.

In our opinion, this is acceptable provided that the patient is adequately informed of the risk-benefit profile of the drug involved. The patient should be regarded as the right person to judge whether the severity of symptoms is such that emphasis should be given to improvement of quality of life instead of prolongation of life expectancy. This does not mean that the patient's judgement is always well founded and that the clinician should agree with this judgement without any further comment. In most instances, however, patients and their clinicians will probably agree on the judgement of the severity of symptoms of congestive heart failure and its optimal treatment. Based on this judgement and the characteristics of the individual patient, the clinician should choose the most appropriate therapeutic strategy, bearing in mind these issues of safety and quality of life.

4. Conclusion

Improvement of life expectancy and quality of life are both mainstays of congestive heart failure treatment. In particular, in patients with severe congestive heart failure, however, the patient's wish for improving symptoms may prevail over any need for expanding life expectancy. Therefore, drugs which improve quality of life at the expense of an increased risk of mortality can be of value in the treatment of patients with severe congestive

heart failure, provided that the probability of improvement of quality of life and prolongation of life expectancy for those using the drug exceeds the probability of improvement of quality of life and prolongation of life expectancy for those not using the drug. Appropriate treatment in these patients may imply that relief of symptoms becomes the primary aim instead of prolongation of life expectancy.

The seriousness of congestive heart failure, both at the level of the individual patient as well as in epidemiological terms, justifies continuous research on new therapeutic strategies. Aspects of quality of life deserve major attention in the evaluation of new drugs, attention which is increasingly obtained in clinical trials. However, most clinical trials in which both survival and quality of life are evaluated fail to provide a risk assessment in which both aspects are properly included. Assessment of a balanced risk-benefit profile of new drugs implies careful consideration of aspects of safety and quality of life, because survival alone should not be considered synonymous to overall clinical effect. Only when both aspects are evaluated thoroughly, can a balanced assessment of the risk-benefit profile be made. Based on this risk-benefit profile, clinicians will be able, in dialogue with their patients, to choose the most appropriate treatment available.

References

1. Kannel WB, Ho K, Thom T. Changing epidemiological features of cardiac failure. Br Heart J 1994; 72 (2 Suppl.): S3-9
2. Cowie MR, Mosterd A, Wood DA, et al. The epidemiology of heart failure. Eur Heart J 1997; 18 (2): 208-25
3. Rich MW. Epidemiology, pathophysiology, and etiology of congestive heart failure in older adults. J Am Geriatr Soc 1997; 45 (8): 968-74
4. Croft JB, Giles WH, Pollard RA, et al. National trends in the initial hospitalization for heart failure. J Am Geriatr Soc 1997; 45 (3): 270-5
5. Anonymous. Xamoterol in severe heart failure: the Xamoterol in Severe Heart Failure Study Group. Lancet 1990; 336 (8706): 1-6
6. Cowley AJ, Skene AM. Treatment of severe heart failure: quantity or quality of life?: a trial of enoximone. Enoximone Investigators. Br Heart J 1994; 72 (3): 226-30
7. Hampton JR, van Veldhuisen DJ, Kleber FX, et al. Randomised study of effect of ibopamine on survival in patients with advanced severe heart failure: Second Prospective Randomised Study of Ibopamine on Mortality and Efficacy (PRIME II) Investigators. Lancet 1997; 349 (9057): 971-7
8. Packer M, Carver JR, Rodeheffer RJ, et al. Effect of oral milrinone on mortality in severe chronic heart failure: The PROMISE Study Research Group. N Engl J Med 1991; 325 (21): 1468-75
9. Important lessons from disappointing trial on vesnarinone in congestive heart failure. Reactions 1996; No. 630: 3-4
10. Packer M, Rouleau J, Swedberg K, et al. Effect of flosequinan on survival in chronic heart failure: preliminary results of the PROFILE study [abstract]. Circulation 1993; 88: I-301
11. Califf RM, Adams KF, McKenna WJ, et al. A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: the Flolan International Randomized Survival Trial (FIRST). Am Heart J 1997; 134 (1): 44-54
12. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure: results of a Veterans Administration Cooperative Study. N Engl J Med 1986; 314 (24): 1547-52
13. 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
14. Anonymous. 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
15. 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
16. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure: U.S. Carvedilol Heart Failure Study Group. N Engl J Med 1996; 334 (21): 1349-55
17. Anonymous. A randomized trial of beta-blockade in heart failure: the Cardiac Insufficiency Bisoprolol Study (CIBIS). CIBIS Investigators and Committees. Circulation 1994; 90 (4): 1765-73
18. Heidenreich PA, Lee TT, Massie BM. Effect of beta-blockade on mortality in patients with heart failure: a meta-analysis of randomized clinical trials. J Am Coll Cardiol 1997; 30 (1): 27-34
19. Hampton JR. Results of clinical trials with diuretics in heart failure. Br Heart J 1994; 72 (2 Suppl.): S68-72
20. Anonymous. 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
21. Niebauer J, Coats AJ. Treating chronic heart failure: time to take stock. Lancet 1997; 349 (9057): 966-7
22. Guyatt GH. Measurement of health-related quality of life in heart failure. J Am Coll Cardiol 1993; 22 (4 Suppl. A): 185A-191A
23. Guyatt GH, Nogradi S, Halcrow S, et al. Development and testing of a new measure of health status for clinical trials in heart failure. J Gen Intern Med 1989; 4 (2): 101-7
24. Dracup K, Walden JA, Stevenson LW, et al. Quality of life in patients with advanced heart failure. J Heart Lung Transplant 1992; 11 (2 Pt 1): 273-9
25. Rector TS, Kubo SH, Cohn JN. Validity of the Minnesota Living with Heart Failure questionnaire as a measure of therapeutic response to enalapril or placebo. Am J Cardiol 1993; 71 (12): 1106-7
26. Rogers WJ, Johnstone DE, Yusuf S, et al. Quality of life among 5,025 patients with left ventricular dysfunction randomized between placebo and enalapril: the Studies of Left Ventricular

Dysfunction: The SOLVD Investigators. J Am Coll Cardiol 1994; 23 (2): 393-400
27. Bulpitt CJ. Quality of life with ACE inhibitors in chronic heart failure. J Cardiovasc Pharmacol 1996; 27 Suppl. 2: S31-5
28. Massie BM, Berk MR, Brozena SC, et al. Can further benefit be achieved by adding flosequinan to patients with congestive heart failure who remain symptomatic on diuretic, digoxin, and an angiotensin converting enzyme inhibitor? Results of the flosequinan-ACE inhibitor trial (FACET). Circulation 1993; 88 (2): 492-501
29. 'Dear Doctor' letter. Boots Company, May 21, 1993
30. Lubsen J, Just H, Hjalmarsson AC, et al. Effect of pimobendan on exercise capacity in patients with heart failure: main results from the Pimobendan in Congestive Heart Failure (PICO) trial. Heart 1996; 76 (3): 223-31
31. Lubsen J. Exercise testing as outcome in congestive heart failure trials: design considerations when interpreting results. Drugs 1994; 47 Suppl. 4: 25-30
32. Olsson G, Lubsen J, van Es GA, et al. Quality of life after myocardial infarction: effect of long term metoprolol on mortality and morbidity. BMJ (Clin Res Ed) 1986; 292 (6534): 1491-3

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