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Scientific Update™

Heart Failure: Are We Optimizing Patient Management?

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The past two decades will be remembered as the era in medical history when the importance of evidence-based medicine grew dramatically and came to occupy a central role in medical education and clinical research. Arguably, no other field is a more outstanding example of evidence-based medicine than cardiology. Large clinical trials have established the importance of ß-blockers in secondary prevention of post-myocardial infarction, heparin and Aspirin® in unstable angina, thrombolysis in acute myocardial infarction (MI), angiotensin converting enzyme (ACE) inhibitors in congestive heart failure (CHF), and lipid-lowering therapy in the primary and secondary prevention of coronary artery disease (CAD).

However, it would be inappropriate to assume that all of these landmark studies have made the desired impact on clinical practice. In other words, it seems prudent to ask whether the considerable amount of resources – money, effort, and time – invested in clinical trials has had a major influence in clinical practice. Perhaps this question could be subdivided to reflect two major concerns:

1. **Do clinical trials influence <u>which</u> drug is used?**
2. **Do clinical trials influence <u>how</u> drugs are used in clinical practice?**

The use of ACE inhibitors in heart failure represents an ideal example for the analysis of these important issues.

Do clinical trials change clinical practice?

In the domain of cardiovascular medicine, data from demographic analyses suggest that clinical trials clearly showing a benefit or harm have influenced how physicians practice. Indeed, the analysis of background medications in the Survival and Ventricular Enlargement (SAVE)[1] trial supports this contention. When benefits of Aspirin® were demonstrated in acute coronary syndromes, the use of Aspirin® increased, but the overall effect on clinical practice was modest. When studies showed a detrimental effect of calcium channel blockers (CCBs) in patients with left ventricular dysfunction (LVH), a decline in the use of this medication occurred.

The answer to the question of whether or not clinical trials influence how drugs are used in clinical practice is more difficult. The prescription of ACE inhibitors represents one of the most important and informative examples of what physicians do with the results of clinical trials. It is clear from SAVE[1] and other clinical trials that relatively high dosages of ACE inhibitors are associated with substantial clinical benefit, including longer survival. However, when dosages in clinical trials are compared with dosages in clinical practice, a rather disturbing picture emerges. In clinical practice, only about 15 to 25% of dosages that are known to benefit survival in clinical trials are prescribed (Table 1).

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Table 1: Dosages in clinical trials vs clinical practice

ACE inhibitor	Dosage in clinical trials (mg daily)	Dosage in clinical practice (mg daily)
captopril	150	12.5-25
enalapril	20-40	2.5-5
lisinopril	5-20	2.5-5

Adapted from M. Packer, 1996[4]

What are the reasons for the underdosing of ACE inhibitors? It appears that most physicians assume that there is a linear relationship between how much drug is used and the therapeutic effect. Although reasonable, this relatively basic assumption is not necessarily true. In reality, drug response is not necessarily linear and dosages that affect the patient's symptoms may differ from those that affect his or her survival. In light of clinical knowledge, is this good clinical practice?

A recent study by Wollert[2] examined the left coronary ligation model of heart failure in rats that were randomized to no treatment or low or high doses of lisinopril. Investigators found that only the high dose of lisinopril achieving an inhibition of tissue ACE, was associated with improvement in left ventricular mass and survival benefits. Similar data has been reported from single-centre trials, suggesting that this type of dose relationship may be true in patients. Importantly, in every dose-response study of ACE inhibitors in heart failure, the frequency of adverse reactions at high and low doses has not differed, suggesting that toxicity is relatively flat while efficacy is curvilinear. If this is true, the importance of using appropriately high doses of ACE inhibitors needs to be emphasized. The strategy of prescribing low-dose ACE inhibitors in patients with heart failure may expose them to the risk of drug-related adverse events but limit potential benefits, including survival.

Definitive studies, such as large-scale clinical trials with definitive endpoints, are needed to address these important issues. At least one ongoing trial, the Assessment of Treatment with Lisinopril and Survival (ATLAS),[3] fulfills these criteria. A multicentre trial which began in 1992, ATLAS has enrolled more than 3,200 patients with chronic CHF. Participants have an ejection fraction of ≤30% and New York Heart Association Functional Class II-IV rating.

In ATLAS, patients were randomized to a low dose (2.5-5 mg daily) or high dose (32.5-35 mg daily) of lisinopril. The duration of follow-up is five years. The primary endpoint is all-cause mortality. Follow-up will end in the fall of 1997 and preliminary study results will be presented at the American College of Cardiology meeting in the spring of 1998.

CHF in Europe and the USA

Given the fact that CHF is a common condition, it seems surprising that no clear, universally accepted definition of heart failure or therapeutic guidelines exist. It is unknown whether physicians in different countries are treating the same clinical entity with appropriate medications. This question is particularly relevant, because landmark studies in heart failure therapy were conducted predominantly in North America and Scandinavia and ischemic heart disease was the main etiology of their heart failure.

Industry-based data (Cardiomonitor study[5]) has evaluated the clinical therapy of CHF in the USA, Germany, Italy, France, Spain, and the United Kingdom. In 1992, the main differences in clinical practice were the low use of diuretics in Germany and high use of these agents in the United Kingdom. The use of ACE inhibitors was limited to 25% of the overall population. Large numbers of patients were on calcium channel blockers, while a few were on ß-blockers and oral anticoagulants.

By 1996, significant changes in clinical practice had occurred. The use of diuretics was still high in the United Kingdom. The use of digoxin had declined in Germany and the United Kingdom. The use of ACE inhibitors had risen from 25 to 60%. Calcium channel blockers were still prescribed more often than ß-blockers and the use of anticoagulants was still at 4 to 5%.

As previously mentioned, the beneficial effect of ACE inhibitors on the survival of patients with CHF has clearly been established in a series of landmark trials. Unfortunately, the Cardiomonitor data confirmed that, in clinical practice, ACE inhibitors were still administered in doses much lower than those shown to benefit survival. This realization highlights the importance of the ATLAS study.

Important differences in the etiology of CHF and major differences in drug treatment exist among countries. Fortunately, some evidence indicates that clinical practice may be converging to reflect the impact of evidence-based medicine from large, landmark clinical trials.

Diagnoses and detection of CHF

The explanation of why so many patients with CHF are not receiving adequate and proven therapy may be partly due to problems in diagnosis. A workable and universally accepted definition of CHF may be a prerequisite to its correct diagnosis and treatment. CHF has a different meaning for general practitioners, cardiologists, and cardiovascular physiologists. It would appear, therefore, that a diagnostic scheme is necessary to bring uniformity to the detection and management of this important condition.

In reality, two diagnoses must be made. The first confirms that the heart is indeed failing; the second searches for the underlying etiology that explains this failure.

The European Society of Cardiology has developed pragmatic guidelines for the diagnosis of CHF. Their essential message is simple and self-evident. Heart failure is the presence of appropriate symptoms, at rest or exercise, in the setting of documented evidence of significant cardiac dysfunction at rest. Arguably, this definition may lack some specificity, but the European Society of Cardiology believes that it is sensitive enough to include the majority of patients who will most likely benefit from treatment or further investigation, without subjecting patients without heart failure to unnecessary diagnostic procedures or treatment.

Despite their simplicity, implementation of these guidelines will not necessarily be easy. As a basic minimum, any definition of CHF would have to consider the patient's clinical picture. The problem with clinical presentation is that differential diagnoses can confound the definition of CHF. For example, most patients with dyspnea have no evidence of systolic or diastolic left ventricular (LV) dysfunction. Therefore, patients who present with breathlessness usually do not have CHF.[6]

While the importance of symptoms, physical examinations and laboratory testing should not be underestimated, the limitations of these diagnostic techniques need to be clearly understood. For example, jugular venous pressure is quite specific but not very sensitive in diagnosing CHF. Other laboratory tests, such as chest x-rays, provide much information but are not an objective measurement of cardiac function. Indeed, many patients who would benefit from ACE-inhibitor therapy have normal chest x-rays. The electrocardiogram (ECG) may contribute in a limited way to the diagnosis. In the presence of a normal ECG, the chances of significant LV dysfunction have been reported to be as low as 1%. However, only 10% of patients with an abnormal ECG have significant LV dysfunction.[7]

Significant variables confuse the objective tests of cardiac dysfunction, such as LV angiography, radionuclide angiography, magnetic resonance imaging, and echocardiography. The limitations of these modalities are evident from the fact that the LV ejection fraction of patients who are tested with different techniques may vary considerably, making it difficult to establish what is normal. The objective assessment of cardiac function needs to be clarified and standardized. The use of quality control in this area is long overdue.

More important is the issue of how to detect asymptomatic patients with CHF. It is clear that by the time that patients are symptomatic, therapy is still beneficial, but, at this late stage, the patient's prognosis is poorer. In other words, if physicians are to improve the outcome of patients with cardiac dysfunction, early diagnosis of this condition must improve and be extended to patients at the asymptomatic stage.

Epidemiologic studies have shown that most patients with definite CHF have a clinically discernible reason for this condition. Indeed, they have one or more of a group of well-defined cardiovascular risk factors, such as a previous history of CAD, angina, hypertension, diabetes, previous MI, or other vascular disease. Epidemiologically, cardiomyopathy is relatively rare in industrialized countries, although valvular heart disease remains a significant clinical problem. Therefore, a strategy designed to target high-risk populations to identify asymptomatic LV dysfunction may yield significant dividends.

It could be argued that the term "heart failure" has not served physicians well as it has focused them on treating patients who present at later stages of CHF instead of patients with asymptomatic cardiac dysfunction, which may be a precursor of CHF, and trying to prevent its progression.

Treatment strategies

Heart failure is a common syndrome that, even in its mildest forms, carries an unfavourable prognosis. Unlike other cardiovascular maladies, the prevalence of CHF is increasing. Therefore, it would be reasonable to assume that improved management strategies would benefit both patients and the health-care system.

Studies have shown that disease deterioration and readmission to hospital often relate to patients' lack of under-

standing of various factors related to their disease. Examples of these factors include a lack of compliance with drug or dietary treatment, the influence of environmental factors, and the impact of emotional stress on symptoms of cardiovascular disease.

Educational efforts need to be directed not only at patients and their families but to health-care providers, because CHF is a syndrome, particularly in its early stages, that may be difficult to diagnose. Its diagnosis is often based on insufficient information. In the future, it will be important to coordinate the efforts of hospital-based specialists and general practitioners to establish accurate methods for the diagnosis of CHF on the basis of particular etiologies in the population at risk.

In addition, the therapeutic strategy needs to be tailored to meet the needs of individual patients. The prevention of CAD, treatment of valvular heart disease, and more aggressive therapy of hypertension are some measures that may prevent the progression of LV dysfunction and the manifestations of CHF. As well, improvements in the pharmacologic therapy of CHF, as documented by large-scale clinical trials, need to be reflected in the desired level of modification of clinical practice.

Conclusion

Traditional, as well as contemporary, treatment of CHF includes the prevention of further coronary events or continuing damage to the myocardium, the relief of symptoms of pulmonary or peripheral edema with diuretics, and the use of effective medications that are known to reduce the risk of mortality.

Advances in the understanding of CHF will lead to new ideas about potential treatments. In the future, for example, physicians may intervene with drugs that inhibit cytokines or low-grade inflammation, agents that promote or inhibit cell growth to control and manipulate hypertrophy, and gene transfers to promote cell growth and angiogenesis. Other exciting possibilities such as gene therapy, the modification of apoptosis and the introduction of cellular transplantation with ex vivo-cultured myocytes may introduce a new era in CHF therapy.

As the therapeutic horizon widens, it seems obvious that not all treatments will be appropriate for all patients and that it will be necessary to identify different groups of patients according to the pathophysiology or pathogenesis of CHF to select the most appropriate intervention.

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