

HEART

Introduction

β Blockade in congestive heart failure

During the past decade heart failure has become one of the most important areas in cardiovascular disease (if not the most important) in terms of prevalence, morbidity, health care consumption and cost, and mortality. As heart failure is typically a disease of the elderly, and as average life expectancy is increasing steadily, so is the incidence and prevalence of heart failure, particularly in the very old in whom incidence and prevalence of heart failure may easily reach 10–15%. Morbidity, expressed as hospitalisation frequency for worsening heart failure is particularly prominent in this age group. As the health care budget for heart failure is dominated by hospitalisation costs, it is obvious that much of the available resources go to the elderly. Another factor that explains the continuous rise in heart failure cases relates to aetiology. Ischaemic cardiomyopathy is the underlying cause in approximately 70% of patients. The treatment of ischaemic heart disease has improved significantly over the past few decades. As a result, fewer patients die of ischaemic events such as myocardial infarction; however, they often survive at the cost of diminished cardiac function, the setting stage of heart failure.

In addition to the economic costs, which are linked to frequent and often long hospitalisations, heart failure is an emotionally and socially destabilising disorder. Patients are unable to function properly in terms of vocational and social behaviour; isolation is a clear danger. The burden on those who are close to the heart failure patient is often overlooked, but is nevertheless an important aspect of this syndrome. Moreover, the prognosis for the heart failure patient is poor. Depending on the severity of the syndrome, one year survival may be as low as 40–50%, which compares badly with most cancers. As such, heart failure may rightfully be called a malignant disease.

Do we have the potential to halt the occurrence of heart failure or to change this bleak outlook on quality and duration of life? In previous decades the emphasis on heart failure treatment has been to alleviate signs of worsening failure, by reversing fluid overload with diuretics and by trying to improve cardiac pump function with vasodilator treatment and with digitalis glycosides or other forms of inotropic treatment. Although such symptomatic treatment is important as it may provide (temporary) relief to the patient, it is questionable whether it is able to stop or even retard the process of worsening heart failure. Diuretics, with or without digitalis glycosides have figured in large controlled trials as background treatment in “placebo” groups. Digitalis glycosides may reduce hospitalisations for heart failure, but this is offset by inducing more hospitalisations for other reasons. Combinations of hydralazine nitrates may afford better exercise capacity; however, improvement of survival is not as good as with ACE inhibitors. Regarding positive inotropes, orally active

agents thus far evaluated clinically have resulted in increased mortality rates with doubtful or negative effects on long term clinical well being. It is fair to state that there is little evidence that prevention of worsening heart failure is to be expected from these treatments.

More recently, different therapeutic regimens have emerged. These do not focus solely on symptomatic treatment, but aim at preventing or delaying progressive cardiac dysfunction and subsequent maladaptive cardiac and extracardiac processes, which lead to the clinical syndrome of heart failure and its ultimate outcome, terminal heart disease. In this respect, the scene has undoubtedly been set by the introduction of ACE inhibition in the treatment of heart failure. Although initially considered as vasodilators, ACE inhibitors exert far more extensive effects, modulating neurohormonal activation, cardiac growth, fibrosis and remodelling, and possibly reducing myocardial ischaemia. In large controlled trials in cardiac dysfunction, postmyocardial infarction, and in heart failure, ACE inhibition has resulted in significant reductions in hospitalisation for heart failure and, in most trials, a reduction in mortality. Overall, symptomatic improvement occurs in approximately 70% of heart failure patients. Moreover, ACE inhibition decreases the incidence of myocardial ischaemic events, such as unstable angina or myocardial infarction, in patients with left ventricular dysfunction or heart failure. Consequently, ACE inhibition is considered obligatory in the treatment of heart failure and, in recent treatment guidelines, proclaimed first line treatment. Is it sufficient? The answer is clearly “no”.

Mortality is still high, despite treatment with ACE inhibitors, as is hospitalisation for worsening heart failure, and the incidence and prevalence of heart failure is still increasing. Clearly, additional or alternative forms of treatment are needed. As our insight into the pathophysiology of heart failure increases so, hopefully, does the development of novel therapeutic interventions beyond ACE inhibition.

Of these, β blockade has, much to the surprise of many sceptics, proven to be of significant value. Not long ago β blockade was considered contraindicated in the treatment of heart failure based on its intrinsic negative inotropic activities and the fact that it inhibits the sympathetic stimulation widely believed necessary for supporting reduced cardiac function in heart failure. However, there is now accumulating evidence from both small and large controlled trials that certain β blocking agents can prevent worsening of heart failure and reduce mortality. These clinically evident effects are supported by observations that β blockade results in long term improvement in clinical wellbeing, a significant reduction in hospitalisation for heart failure, and a reduction in mortality in patients with

ischaemic and non-ischaemic heart failure. As such, it differs from available experience with selective β_1 blocking drugs, which have shown either no effect on survival or a positive effect in selected groups only.

Although this difference in survival may be explained by the fact that the latter studies were too underpowered to observe an effect on mortality, it may also be explained by the different pharmacological profile of carvedilol. In addition to non-selective β blockade, carvedilol has α blocking properties and antioxidant effects. The ability to attack free radicals, reduction of ischaemia reperfusion injury, reduction of circulating endothelin concentrations, and the possibility that it may affect apoptosis are some other effects of this molecule. This complex pharmacological profile potentially opens up a much larger area in which to intervene during the process of developing or worsening heart failure than β blockade alone.

This supplement aims to provide insight in the development of β blockade and carvedilol treatment in heart failure against the background of current knowledge of the epidemiology, pathophysiology, diagnosis, and other avail-

able drug treatments. The pivotal role of neurohormonal activation in the heart failure process is highlighted, emphasising the deleterious effects of sympathetic activation and providing the basis for the beneficial effects of β blockade. This form of treatment has been accepted as an essential part of our management of heart failure in recent guidelines, although several questions remain unanswered. These concern the need for data in severe heart failure, the question of whether certain β blocking drugs may be more efficacious than others, and whether β blockade, in particular with carvedilol with its complex pharmacological profile, may compare favourably with ACE inhibition. These questions are currently being addressed in large controlled trials, such as COPERNICUS (carvedilol prospective randomised cumulative survival trial), COMET (carvedilol or metoprolol European trial), and CARMEN (carvedilol ACE inhibitor remodelling mild heart failure evaluation).

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