Hotline Editorials

The merit of beta₁-blockade in heart failure

Twenty-five years ago, it was known that heart failure was associated with an increase in sympathetic nervous activity, but the prevailing opinion was that this was a compensatory increase, in order to counteract depressed myocardial function, and that beta-blocker treatment might cause worsening heart failure[^1]. Consequently, beta-blockade was regarded as contraindicated in the treatment of patients with heart failure. In 1975, Finn Waagstein, Åke Hjalmarson and their colleagues at Sahlgrenska Hospital in Göteborg, Sweden, published an article reporting surprising effects of beta-blocker treatment in patients with congestive cardiomyopathy and severe heart failure[^2]. There was a clear alleviation of symptoms, and the working capacity and a number of non-invasive measures of cardiac function improved. This observation was the first pioneering step in a long process that has been no less than a paradigm shift as beta-blockade has become established treatment in chronic heart failure.

The circle closed when the Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF) was published in June 1999, with Hjalmarson and Waagstein as co-authors[^3]. The study was designed and powered to examine whether the beta₁-selective antagonist metoprolol CR/XL, in comparison with placebo treatment, was associated with a reduction in all-cause mortality. Three thousand nine hundred and ninety-one patients with chronic heart failure in NYHA functional classes II–IV and an ejection fraction of ≤0.40 stabilized with optimal standard therapy were enrolled in a double-blind randomized study. Ninety-five percent of the patients were treated with an ACE inhibitor or an angiotensin-II blocker. The study medication was up-titrated for 6–8 weeks, starting with 12.5 mg (NYHA functional classes III-IV) or 25 mg once daily (NYHA II) and the target dose was 200 mg once daily. The study, performed in 13 European countries and in the U.S.A., was stopped early on the recommendation of the independent safety committee, because the second, pre-planned, interim analysis showed that the pre-defined criterion for termination of the study, because of benefit, had been met and exceeded. Treatment with metoprolol CR/XL conferred a 34% reduction in all-cause mortality (95% CI 19 to 47%), the annual mortality being reduced from 11.0 to 7.2%. This means that 27 patients have to be treated for 1 year to prevent one death, indicating a high cost-effectiveness. The incidence of sudden death was reduced by 41% (95% CI 22 to 55%) and death from worsening heart failure by 49% (95% CI 21 to 67%). Sudden death was the most common mode of death, occurring in 64% of the patients in NYHA functional class II and decreasing to 59% in NYHA III and 33% in NYHA IV. Conversely, the proportion of patients who died from worsening heart failure increased with increasing severity of heart failure. Further results regarding the effects on combined end-points, hospitalizations, changes in NYHA functional class and quality of life, should have been reported on by the end of 1999. A long-acting, once daily preparation of metoprolol succinate was used as it has been shown to give a more sustained and effective beta₁-blockade than conventional–immediate release metoprolol tartrate given three times daily[^4]. There were no safety concerns, as metoprolol CR/XL was well tolerated in terms of mortality in pre-defined subgroups, such as elderly vs younger patients, and those with low ejection fractions or in different NYHA classes.

In the longer term there is now very firm evidence that beta₁-blockers should be added to conventional therapy with ACE inhibitors and diuretics in patients with symptomatic heart failure and decreased ejection fraction, in order to improve the prognosis. Earlier this year, the CIBIS II study was published, reporting data on the effect of the beta₁-selective antagonist bisoprolol[^5]. The MERIT-HF and CIBIS-II studies are the only studies published so far which have been adequately designed and powered to examine the survival benefit of beta-blockade in patients with heart failure. Together, these two studies encompass 6638 patients and 746 deaths during follow-up, to be compared with the 7105 patients who were included in a meta-analysis of the benefit of ACE inhibitors in cases of heart failure[^6]. The data that can be extracted from these two large beta₁-blocker studies are very consistent and also complementary. The most common aetiology of heart failure was
ischaemic heart disease and 90% or more of the patients were also treated with an ACE inhibitor. The CIBIS II study did not include patients in NYHA class II as was the case in the MERIT-HF study. In contrast to many previous studies there were no run-in periods with active treatment in the MERIT-HF and CIBIS-II studies, examining tolerance to beta-blockade prior to randomization. The results of these two studies are virtually identical. Data on hospital admissions for worsening heart failure have so far been published only for the latter study and were reduced by 36% in the beta-blocker group. The tolerability of beta-blockade was excellent, with a withdrawal rate that did not differ from that of placebo treatment, even seeming to be lower than placebo treatment in the MERIT-HF study.

The message from these two studies is clear. Sudden death, the most common mode of death from chronic heart failure, is reduced by more than 40% by beta1-blockade, thereby being complementary to ACE-inhibitor therapy, which has no proven effect on sudden death among such patients[8,9]. This effect of beta1-blockade is in line with the general concept of the anti-arrhythmic property of beta-blockers. However, together the CIBIS-II and MERIT-HF studies also demonstrated a reduction in death from worsening heart failure and a decreased need of hospitalization due to progressive heart failure, indicating that other mechanisms are operative. These underlying mechanisms have not been clarified, although it is known that beta1-blockers are anti-ischaemic and have favourable effects on left ventricular geometry and function, improve myocardial metabolism and increase physical work capacity[7].

The MERIT-HF study indicated that total mortality was as effectively reduced in patients with an ejection fraction above 0.25 as below 0.26, an effect that contrasts with that of ACE-inhibitors, which seem to have no or only a limited survival benefit in patients with an ejection fraction above 0.30[8,9]. Although the combined results of the MERIT-HF and CIBIS-II studies indicated that beta1-blockers have similar beneficial effects on patients in NYHA functional classes II to IV, it is important to keep in mind that the patients in NYHA class IV were relatively few and were not representative of the category of bedridden patients with severe, chronic, heart failure.

There are also other data which have accumulated during the last 15 years supporting the concept of a beneficial effect of beta-blockade treatment in cases of chronic heart failure. A meta-analysis of 24 smaller, randomized trials of treatment with various beta-blockers in patients with chronic heart failure encompassing 3141 patients and 297 deaths, indicated a 31% reduction in the odds of death in patients assigned such therapy[10]. The efforts made in examining the effects of carvedilol on heart failure patients have been important in raising the interest in beta-blockade treatment for this condition. This non-selective beta-receptor antagonist also blocks alpha1-receptors and has anti-oxidant effects. The US carvedilol trial, consisting of four studies, included in total 1094 patients and found that there was an impressive survival benefit, although there were only 53 deaths in total[11]. This trial was not designed and powered to examine mortality as the predefined efficacy variable. However, the need of more data on the effect of carvedilol on mortality in heart failure seems to be met by several ongoing studies. The findings in the US carvedilol studies were also supported by the Australia/New Zealand Heart Failure Research Collaborative Group Trial, which consisted of 415 patients, as the rate of death or hospital admissions was 26% lower in the carvedilol than in the placebo group[12].

The available documentation indicates that the prominent effect of treatment with beta-blockers, which also have a number of additional effects, is most probably to be attributed to beta-blockade and in particular to beta1-antagonism. In this respect, the recent news that the beta-blocker evaluation survival trial (BEST) has been terminated early because there was no likelihood of observing an effect of treatment on mortality, is confusing. Bucindolol, which was used in the BEST study, is a potent non-selective beta-blocker with sympathomimetic activity, a possible alpha-blocking effect and a weak vasodilatory effect. We have to await the presentation of the results and the realization of this study, which may explain the unexpected outcome.

Although the value of beta1-blockers in chronic heart failure has been proved, it should be kept in mind that these studies have been carried out in selected populations which do not represent the entire population of patients with heart failure. Thus, the studies discussed above have uniformly recruited groups of patients with heart failure due to systolic dysfunction, the majority of the patients have been 50 to 70 years old and predominantly of male sex. In addition, a number of criteria have been used which have led to the exclusion of patients with co-morbidity in other diseases. In the community setting, the typical patient is older than 70 years, the sex distribution is more equal and co-morbidity frequent[13]. Often there are diagnostic difficulties, as multiple aetiological and precipitating factors may interact and diastolic dysfunction may be more important. In this patient category, symptom alleviation, improved quality of life and a reduced need of
hospital care may be more important aspects of treatment than increased survival.

Today we have firm evidence that the symptomatic patient with a decreased ejection fraction stabilized on standard therapy benefits from treatment with a beta$_1$-selective antagonist. In clinical practice, such a patient should always be considered for treatment with one of the beta-blockers which have shown documented effects. It is important to observe contraindications and to start treatment with low doses which have to be gradually increased, keeping in mind that a few patients may have a transient period of worsening symptoms, necessitating an increased dose of diuretics or a lower beta-blocker dose. Metoprolol CR/XL and bisoprolol, in the doses which have been applied in the MERIT-HF and CIBIS-II studies, can be used in clinical practice when treating patients with chronic heart failure with beta$_1$-blockers. In a few cases beta-blockade has to be permanently withdrawn due to adverse side effects.

Considering the difficulties in obtaining an optimal use of ACE-inhibitors in patients with chronic heart failure and beta-blockers in post-myocardial infarction patients, the effective use of beta-blockers in the treatment of chronic heart failure patients may take time to be accepted in clinical practice. Therefore it will be important to promote such treatment actively, keeping in mind that for many experienced doctors the use of beta-blockers in heart failure patients conflicts with their early training, and that this is the practical consequence of a paradigm shift.

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References