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Treatment of Chronic Cardiac Insufficiency with Betablockers: Results of the Cardiac Insufficiency Bisoprolol Study II (CIBIS II)

U. Schotten, P. Hanrath

Despite basic therapy consisting of digitalis, diuretics and ACE inhibitors, severe cardiac insufficiency based on ischaemic or dilatory cardiomyopathy still has a high morbidity and mortality. Based on recent pathophysiological findings related to cardiac insufficiency with an activation of the sympathoadrenergic system, and the results of numerous clinical trials, adjuvant therapy with betablockers has become an integral part of the treatment of cardiac insufficiency, provided there are no contra-indications. In addition to an improvement of the symptoms and the systolic pump function of the left ventricle, the advantage of this additional medication lies primarily in the beneficial influence on morbidity and mortality. The improved prognosis has been demonstrated by the US Carvedilol Study, as well as the two more recent major randomized studies CIBIS II and MERIT-HF. Both studies were able to show that this additive therapeutic measure can be implemented with a very high level of safety, even in non-specialized clinics, if the initial dose is low, the patient is monitored carefully, and the dosage is gradually increased at weekly intervals. It may be hoped that these studies will reinforce the physicians' confidence in betablocker therapy for cardiac insufficiency, and that more and more patients will have the benefit of receiving this treatment as a result.

A clear answer to the question of whether there are any substance-specific differences between the betablockers and which patient populations (aetiology, severity of cardiac insufficiency) can profit most from this therapy is expected to result from the on-going multicenter studies (COPERNICUS, CAPRICORN, CARMEN, COMET) with several thousands of patients. *J Clin Basic Cardiol 2000; 3: 11-3.*

Key words: CIBIS II, bisoprolol, betablockers, cardiac insufficiency

Cardiac insufficiency syndrome is one of the greatest health challenges of our day. In the western industrialized nations, between 1 and 4% of the population are affected, and with increased aging of the population this share will continue to rise in future. Even today, cardiac insufficiency is one of the main reasons for the admission of people aged over 60 to hospital, and a major cause of sick-leave in the labour force. Moreover, the prognosis of cardiac insufficiency NYHA class III and IV is associated with a 5-year mortality rate of about 50% and thus comparable with malignant diseases. The increased efforts to treat cardiac insufficiency more effectively must be viewed in the light of these facts.

New findings on the pathophysiology of cardiac insufficiency

In recent years, the pathophysiological research of cardiac insufficiency has made great progress and led to an improved prognosis with the development of new substances. A classical example of this is the development of ACE inhibitors and their beneficial effect on the symptoms, haemodynamics and mortality of cardiac insufficiency. In particular, this was favourably influenced by the explanation of characteristic neurohumoral changes. Not only is the renin-angiotensin-aldosterone system activated and the release of vasopressin and endothelin increased in cardiac insufficiency, but the sympathoadrenergic system is also activated. These activation processes would appear useful in the first, acute stage, because they help to maintain the cardiac output and blood circulation to the peripheral organs through compensation. However, it is now known that in the long term this mechanism has destructive effects on the diseased heart and contributes towards chronic progression of the disease. Based on these pathophysiological findings, the interest of research into cardiac insufficiency is now focused less on the development of new positive inotropic substances and more on the search

for new modulators of this humoral dysfunction. Therefore, it is not surprising that sympatholytic agents are also being considered, despite the old textbook opinion that betablockers are contra-indicated in cardiac insufficiency because of their negative inotropic effect.

Results of clinical research into betablocker therapy for chronic cardiac insufficiency to date

Based on the described pathophysiological findings and the experience made in post-infarction therapy that patients with severe left-ventricular dysfunction usually profit most from additive betablocker therapy, betablockers have experienced a renaissance in the treatment of chronic cardiac insufficiency of diverse aetiology in recent years. After the initial report by Waagstein [1], a beneficial effect of betablockers on the symptoms and haemodynamics has been described in several smaller, uncontrolled and controlled studies. These were followed by a series of major, prospective randomized studies to investigate the influence of betablockers on morbidity and mortality. In addition to metoprolol [2] and carvedilol [3, 4], the β_1 -selective betablocker bisoprolol has also been studied. In this study published in 1994 (Cardiac Insufficiency Bisoprolol Study, CIBIS I) [5] with a follow-up period of about two years, 641 patients with cardiac insufficiency (95% NYHA III, 5% NYHA IV) of various aetiology received bisoprolol or placebo in addition to standard therapy with diuretics and ACE inhibitors. This study also showed a significantly beneficial effect of the betablocker on the clinical symptoms and readmission rate. However, it was not possible to prove a reduced mortality rate as a result of betablocker therapy, the 20% decrease in mortality in the verum group was not statistically significant. In a retrospective subgroup analysis for idiopathic dilated cardiomyopathy and ischaemic cardiomyopathy without prior infarction, however, a statistically significant decrease in mortality could be shown. In patients with ischaemic car-

diomyopathy after infarction, on the other hand, no significant effect was found compared with the placebo. This result is contrary to the results of secondary prophylaxis in patients after infarction, who all show a clear reduction in mortality with betablocker treatment. Whether the deviating observation in the CIBIS trial was due to concurrent anti-arrhythmia therapy with amiodaron in 20 % of the patients remains speculation. In order to clarify these issues, the study was repeated in 1997 (CIBIS II), whereby the influence of additive bisoprolol therapy on morbidity and mortality of cardiac insufficiency was to be investigated with a greater number of patients. The results of this study were published in January 1999 [6].

CIBIS II – Results

2,647 patients with chronic cardiac insufficiency based on an ischaemic (confirmed in 50 % of all patients) or dilated (confirmed in 12 % of all patients) cardiomyopathy NYHA class III (83 %) or IV (17 %) were recruited in 247 European centers. All patients received basic therapy with diuretics and ACE inhibitors unless contra-indicated. The use of digitalis and vasodilators was optional. All patients were stable on this therapy, the ejection fraction measured by means of echocardiography was less than 35 %, mean 27.5 %.

The patients received 1.25 mg bisoprolol daily ($n = 1,327$) or placebo ($n = 1,320$), without an evaluation of the tolerability of bisoprolol in the initial run-in phase. The bisoprolol dose was increased to 2.5 mg, 3.75 mg and 5.0 mg at weekly intervals, then to 7.5 mg and 10 mg every 4 weeks, provided the patients tolerated the dose increase. Most patients reached the target dose of 10 mg ($n = 564$), 152 patients tolerated 7.5 mg, and 176 patients were able to complete the therapy with a dose of 5.0 mg.

The patients were to be observed for a period of 2 years, but after a mean treatment duration of 1.3 years the study was discontinued by the Safety Committee. At this point, the overall mortality, the primary outcome variable of the study, had already been reduced by 32 % in the bisoprolol group. In this group, 156 patients (11.8 %) died compared with 228 (17.3 %) in the placebo group. The estimated annual mortality rate was thus reduced from 13.2 % in the placebo group to 8.8 % in the verum group.

With regard to the secondary outcome variable (hospitalization, cardiovascular deaths or one of these events), there was also a significant decrease in the bisoprolol group. The aetiology (ischaemic or dilated) and severity of the disease had no influence on morbidity or mortality. However, patients with NYHA class III or ischaemic cardiomyopathy tended to profit most from this therapy.

The effect of bisoprolol on sudden deaths was particularly impressive, with incidence reduced by 42 %. The incidence of deaths due to pump failure, on the other hand, was only slightly reduced, but there was a decrease in the number of admissions to hospital because of progressive cardiac insufficiency.

The therapy dropout rate of 3.1 % in the bisoprolol group was low and hardly differed from the placebo group (2.1 %).

CIBIS II – Conclusions

Until the publication of the MERIT-HF study in June 1999, CIBIS II was the largest prospective randomized study to demonstrate reduced mortality in patients with chronic cardiac insufficiency as the result of therapy with betablockers, regardless of the initial tolerability. A reduction in mortality

through the additive administration of a betablocker could already be shown for carvedilol in the US Carvedilol Heart Failure Study [4] in 1996, which consisted of several substudies. However, compared with the major ACE inhibitor studies, this study was relatively small (1,100 patients). Moreover, the patients had a run-in phase that may well have resulted in a certain pre-selection of the patient population. The design of the CIBIS II study does not provide for a run-in phase and the patients were treated at 247 centers, some of which were not specialized clinics. Therefore, the therapy situation in this study is better suited than previous studies for conclusions to be drawn with regard to feasibility in general clinical practice. All randomized clinical trials counted, more than 6,000 patients had been treated with betablockers on conclusion of the CIBIS II study. In accordance with a meta-analysis of all studies to date [7], the reduction in mortality was slightly over 30 %, even in CIBIS II. Thus, the treatment of cardiac insufficiency with betablockers has finally concluded the experimental phase.

The particularly marked reduction in the incidence of sudden cardiac death as a result of bisoprolol (–42 %) underlines the anti-arrhythmic potential of betablocker therapy in cardiac insufficiency. This effect has also been shown for carvedilol [4] and metoprolol [8]. The anti-arrhythmic action of bisoprolol is also supported by the observation in CIBIS II that the number of admissions to hospital due to ventricular tachycardia or ventricular fibrillation was reduced significantly. Effects on cellular electrophysiology, the balance of the autonomous nervous system and the cardiac energy balance could be involved in this process. On the other hand, there was only a slight tendency towards reduced incidence of death due to pump failure in CIBIS II. Because of the strict definition criteria, however, the cause of death must be regarded as unclear in 19 % of all deaths. It may be assumed, that numerous cardiac deaths are concealed by these events, especially since the number of such cases was only half as high in the bisoprolol group. According to the CIBIS II authors, these deliberations underline the importance of overall mortality as a primary outcome variable in similar studies.

The observation that patients with ischaemic cardiomyopathy clearly benefited from the therapy is very interesting. CIBIS I had raised a number of questions in this context. In a subgroup analysis, it had not been possible to demonstrate a decrease in mortality rate in patients with previous myocardial infarction. 50 % of the 2,647 patients recruited for CIBIS II suffered from ischaemic cardiomyopathy, and the benefit of bisoprolol in these patients was slightly higher than in other patient groups. Therefore, the mild effect of bisoprolol on the mortality of post-infarction patients in CIBIS I is most likely due to the low number of cases. It must also be taken into account that the bisoprolol dose administered in CIBIS II (more than 5 mg in 50 % of the patients) was clearly higher than in CIBIS I, where 51 % of the patients received the maximum dose of 5 mg.

The CIBIS II study also makes a major contribution to the issue of which betablockers to recommend for the treatment of cardiac insufficiency. The results of the US Carvedilol Heart Failure Study [4] suggest the possibility that carvedilol might offer patients a greater benefit than other betablockers, especially since no reduction in mortality could be shown for any other betablockers at the time. This assumption is supported by the theoretical consideration that carvedilol has superior cardioprotective potential due to its α -blocking and antioxidant properties. The results of the CIBIS II study and the recently published MERIT-HF study [8], in which metoprolol reduced the mortality of patients with chronic cardiac insuf-

iciency to a very similar degree, clearly show that β_1 -selective betablockers certainly can improve the prognosis of cardiac insufficiency considerably, even without additional substance properties. The benefit of betablockers, therefore, is probably due to a substance class effect, and bisoprolol, metoprolol and carvedilol can be recommended equally for the treatment of cardiac insufficiency. A reduction of mortality has been demonstrated for all of these substances, and they have all demonstrated good tolerability and safety with low dropout rates.

Despite the considerable gain of information through CIBIS II, some issues still remain unanswered. Only few patients with cardiac insufficiency NYHA class IV (17%) were recruited in CIBIS II, for example. Therefore, the benefit for patients with most severe cardiac insufficiency has not been absolutely shown yet. The same goes for older patients (age > 70) with asymptomatic or primarily diastolic left-ventricular dysfunction.

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