REVIEW

Beta-blockers in heart failure

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Abstract

The problem of heart failure (HF) has become a topic of great interest. Until recently, the use of beta-blockers in patients with HF was considered as one of the contraindications which were taught to medical students as realities with a strict policy to avoid them in HF patients. Times have changed and the contraindicated drug is now an advised and prefered one to be used in HF patients with certain advised recommendations for its use in a safe and beneficial way.

Even though the use of beta-blockers in HF patients is an important and neccessary step towards an optimal treatment of these patients as most of the big studies have proved, still we need to emphasize these benefits in order to achieve more application of these agents in HF patients. Here we analyse the major studies which used beta-blockers in HF patients. It seems that beta-blockers have to be used in all patients with HF with reduced ejection fraction unless a real contraindication exists as they bring up a great benefit towards decreasing mortality and morbidity. ***(Ref. 44.)***

Key words: heart failure, beta-blockers, mortality, sudden death.

Medicine is an ever changing science with the facts being so until some time comes and proves something else. The story of beta blockers in heart failure (HF) is one of the best examples of that.

Until recently, the use of these agents in patients with HF was considered as one of the contraindications which were taught to medical students as realities with a strict policy to avoid them in HF patients. Time has changed and the contraindicated drug is now an advised and prefered one to be used in HF patients with certain advised recommendations for its use in a safe and beneficial way.

It was first discovered in Sweden during the early 1970s by Waagstein and coworkers (1) that administration of an intravenous β-blockers to patients with acute myocardial infarction, tachycardia, and pulmonary edema caused a dramatic improvement in their condition. Waagestein (2) published a paper in 1975 talking about the beneficial chronic use of β-blockers in patients with idiopathic dilated cardiomyopathy (CMP). Their report was based on their observations in 7 patients with congestive CMP who showed hemodynamic improvement after being treated with alprenolol or practolol for 5 months without showing adverse effects. This was the first report to be published in this field and was received with doubts. The Göteborg group reported their observations in the same subject in several reports (3, 4) in the period between 1979—1989. Several other reports helped in attracting attention to the promising role of β-blockers in the future treatment of HF patients. A lot of β-blockers (as carvedilol, metoprolol, bisoprolol, and sotalol) have been used in HF studies in the last 10 years the results of which were so encouraging. It is convenient here to mention that the interest in β-blockers and their benefits is old even that some β-blockers studies actually preceded the development of ACEIs the inability of which to modify the rate of sudden cardiac death (as it was thought at that time) emphasized the need for additional therapy to prevent arrhythmic death in HF (5).

In 1985 a double-blind design was used for the first time by Engelmeier and associates to show that the use of a β-blocker (metoprolol) in HF patients is associated with improvement in myocardial performance (6).

One paper appeared in 1992 summarizing the work done in the field of β-blockers in HF in the period between 1975—1991 (7). It concluded that during this period the results of researches stressed that β-blockers improve ventricular function and reduce neurohormonal activation in HF patients recommending their use as adjunctive therapy while treating such patients.

Here we will to present individual β-blockers with the major studies in which they were involved.

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Carvedilol in HF

The Australia/New Zealand study (8, 9) used carvedilol (non-selective β-blocker, α_1-receptor antagonist and antioxidant) in 415 patients with chronic stable HF due to ischemic heart disease. This study aimed to show the effects of β-blockers on HF patients with ischemic origin, the good effects of which were not proved at that time yet. The patients have been followed up clinically with repeated exercise test, radionuclide ventriculography and echocardiography at baseline, 6 and 12 months, with an average follow-up period of 19 months. Carvedilol was started at a dose of 3.125 mg b.i.d. and increased to 6.25 mg b.i.d. Those patients who tolerated such dose have been randomized to placebo or carvedilol group. The dose of carvedilol was increased gradually to 25 mg b.i.d. In 6 months period there was an increase in EF by 5.2 % in the carvedilol group compared with placebo. It was noticed that there was a decrease in both left ventricular end-diastolic diameter and left ventricular end-systolic diameter in the carvedilol group but there was no change in exercise tolerance or severity of symptoms in the majority of patients of both groups. However 28 % of the placebo vs 23 % of the carvedilol patients improved according to NYHA classification, while 5 % vs 12 % worsened. After 12 months of carvedilol therapy there was no noted new changes other than those mentioned above with the EF being increased by 5.2 % in the carvedilol group. However the rate of death or hospitalization was lower in the carvedilol group but without a significant change in mortality, exercise performace, symptoms, or episodes of worsening of HF. It is interesting that this study was the first to show such results in patients of HF with ischemic origin. The tolerability of this drug was reflected by the low number of patients withdrawn from the study (only 8 % more patients were withdrawn from the carvedilol than from the placebo group) (8). The benefit from this drug in increasing EF seems valuable since most of patients used it were already on ACEIs. The benefits from carvedilol could be explained by the improvement in diastolic function and reduced myocardial ischemia. This study has stressed the need for large trials to recommend or not the use of β-blockers in patients with HF as a routine treatment especially when the previous 8 studies which tested carvedilol have included only 1658 patients.

The PRECISE (10) trial was another trial of carvedilol in patients with moderate to severe HF. It included 278 patients already on ACEIs, digoxin, and diuretics. Only patients who were able to tolerate carvedilol 6.25 mg b.i.d. were included (target dose was 25 mg b.i.d.) and followed up for 6 months. The follow-up revealed improvement in NYHA class and EF in carvedilol group (8 % increase) with better exercise tolerance and reduction in the rate of cardiovascular hospitalization (p=0.06). There was also a reduction in death rate (p=0.26). It was also noticed that the effects of carvedilol were similar in patients with ischemic or nonischemic cardiomyopathy. This observation gave this study more importance being the first to show that the benefits of β-blockers can be utilized also in patients with ischemic CMP.

These benefits have not been proved in CIBIS I (11) and other studies (8) the thing which puts doubts about the adequacy of the total number of patients enrolled in such studies. Such positive results of clinical benefits were also proved in three single-centre trials while the reduction of risk of death was shown in a multicenter study (12, 13, 14, 15). In one of the studies (12) which again used carvedilol in patients with HF who were already on diuretics, digoxin and ACEIs, 5.6 % of patients did not tolerate this agent. The reduction in the risk of death with carvedilol was by 65 % regardless the etiology of HF, this was during a follow-up period averaged 6.5 months and extended to 15 months. There was also a reduction in the risk of sudden death in addition to the reduction in the risk of death from progressive HF. Hospitalization for cardiovascular causes was reduced by 27 %. Also this study is considered as one of the leaders in proving reduction in death risk in both ischemic and nonischemic CMP by the use of carvedilol.

It is worth noting that carvedilol blocks β_1, β_2, α_1-adrenergic receptors, reduces cardiac norepinephrine, and prevents up-regulation of cardiac β-receptors causing more sympathetic antagonism. These characters lead to the fact that carvedilol has less ability to improve exercise tolerance but can block the toxic effects of catecholamines on the failing heart. Carvedilol also has an anti-oxidant effect which prevents the loss of cardiac myocytes (9).

US carvedilol HF study (16) was one of the prominent studies which could shed new light on this issue. It was a randomized, double blind, placebo controlled, multicentre study on 336 patients with mild symptoms of HF with a follow-up period of 12 months. The results of this study showed a reduction in clinical progression of HF (death due to HF, hospitalization for HF, or the need for sustained increase in HF medications) in those patients receiving carvedilol (p=0.008). This reduction of total mortality risk which reached 63 % was not influenced by the etiology of HF. There was a subjective feeling of improvement in the carvedilol group with an improvement in NYHA class more than that in the placebo group (p=0.003). The drug was well tolerated with a significant improvement in EF in this group but the improvement in exercise tolerance was not significant.

MOCHA (17) is one of the studies which was interested in the effect of carvedilol dose on patients with HF. The patients who have been followed-up for 6 months showed a dose dependent improvement in EF and reductions in mortality and hospitalization rates with carvedilol whether they belonged to ischemic or nonischemic CMP.

Recently a paper appeared (18) talking about the cost effectiveness of carvedilol and depending to some extent on the data and results of the US carvedilol HF study. It stated that: the cost effectiveness of carvedilol for congestive HF compares favorably to that of other generally accepted medical interventions, even after conservative assumptions regarding the duration of therapeutic benefit.

The beneficial effects of carvedilol were also demonstrated (19) in patients after myocardial infarction even in those complicated by HF where carvedilol was well tolerated. It was observed that there was a reduction in total cardiac events in these patients when they were followed-up for a period of 6 months. The benefits from the use of carvedilol in patients with HF are well established but still stressing the fact that it can not alter submaximal or maximal exercise capacity in these patients as one Italian study (20) has demonstrated recently.It showed that carvedilol did not produce any significant improvement in total ventilation, respiratory rate, tidal volume, ventilation to CO_2 production, and VCO_2/VO_2. It was suggested that carvedilol does so by restricting heart rate response during exercise on which the heart depends more

than its dependence on stroke volume elevation when there is systolic dysfunction.

But what about the use of carvedilol in elderly patients with HF? A paper published recently (21) showed that in a small group of HF patients of age 80±4 ys carvedilol was tolerated by 68 % of them without requiring readmission to hospital or worsening of HF. The small number of patients in this study (19 patients) is a real limitation.

Another question to be answered is whether β-blockers are effective in patients who develop HF soon after myocardial infarction! One recently published paper (22) revised the studies performed on β-blockers and came to a conclusion that the overall use of these agents was associated with a 22.6 % reduction in total mortality and that the relative benefit of β-blockers on mortality after myocardial infarction was similar in the presence or absence of HF with the possibility that the absolute benefit might be more in the former. The ongoing trial CAPRICORN (23) is a randomized double blind placebo controlled study aimed to detect the impact of carvedilol on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. It enrolles 925 patients who had myocardial infarction within the last 21 days and have left ventricular dysfunction with or without HF. EF of these patients is ≤40 % and they are receiving standard therapy for HF.

The target dose of carvedilol is 25 mg b.i.d. Patients are planned to be followed-up every 3 months in the first year and every 4 months thereafter. This study by considering patients early after myocardial infarction is supposed to supply us with rich information about the ability of β-blockers of modifying the remodeling processes well known to take a major part in the pathophysiology of HF and therefore its consequences.

There was always a debate about the savity of using β-blockers in HF patients with NYHA IV. Most of the studies performed before have avoided enrolling patients with severe form of HF and in case they have allowed such category of patients to take part, its share was so restricted. COPERNICUS study (24) gave us recently a clear cut answer. In this study 2200 patients were randomised with different etiologies of HF. They were with NYHA IV (but stable) and EF <25 % despit optimal therapy. Results showed that carvedilol was very well tolerated by patients with severe HF with a 35 % reduction in the risk of all-cause mortality in the carvedilol group compared to placebo. It was so interesting to notice that in patients with some degree of fluid retention and those who even needed positive inotropic or vasodilator drug within 2 weeks, carvedilol reduced their mortality by 50 %.

Patients with symptomless left ventricular dysfunction are being studied in CARMEN study with carvedilol (25).

Bisoprolol in HF

Bisoprolol (a β_1 selective blocker) was tested for its beneficial effects in HF patients with functional class (NYHA III—IV) who were receiving diuretics and vasodilators in a randomized double blind study (CIBIS I) (11) for a period of 1.9±0.1 years. Results showed that bisoprolol caused improvement in functional class in these patients mostly in non-ischemic HF cases, but even though decreases in total mortality, sudden death rate and death due to arrhythmias were noticed in the bisoprolol group these changes were not significant. It was noticed that prognostic improvement was linked to increased left ventricular ejection fraction.

5 years later the results of CIBIS-II (25) appeared, a randomized double blind study aimed to show the effects of bisoprolol in a larger number of HF patients (2647 patients) with NYHA class III or IV. The most common dose of bisoprolol used during the maintenance phase was 10 mg for an average period of follow up 1.3 years during which patients received diuretics and vasodilators (mainly ACEIs) but no calcium antagonist was allowed. The use of digoxin was optional and amiodarone was permited (otherwise no other antiarrhythmic was used). The significantly positive results were the reason behind the premature termination of this study. It was interesting that bisoprolol reduced significantly total mortality rate (by 32 %), cardiovascular mortality, sudden death (by 44 %) and rate of rehospitalization. The greatest effect on mortality was through a 42 % lower rate of sudden death in bisoprolol group while the reduction of death rate due to pump failure was not significant (26 %) the finding which suggests that bisoprolol acts mostly as an antiarrhythmic drug rather than modifying myocardial function. These positive results were seen in patients with idiopathic CMP, ischemic heart disease, and in patients with valvular or hypertensive etiology whether they belonged to NYHA class III or IV, however results should not be extrapolated to patients with severe class IV symptoms and recent instability because safety and efficacy has not been established in these patients due to the fact that only stable patients with class IV were included in the study. An interesting finding was that there were more admissions to hospital for stroke in the bisoprolol group than in the placebo group the finding which was explained by Prof. A. Hjalmarson in his visit to Bratislava as being a consequence of the saved lives of HF patients by bisoprolol. So with older age there will be more chances to meet stroke cases who would have lost that chance (being alive) without using bisoprolol. It was also noticed that the treatment effect did not differ between the participating countries the fact which is a big plus to the accuracy of these results.

A pharmacoeconomic analysis of the results of the CIBIS I was conducted in Germany (26) where it was shown that per 1000 patients-years, saving of 186 719 Deutschmarks resulted showing that treatment with bisoprolol was not only clinically beneficial to HF patients but it was also economically advantageous.

Metoprolol in HF

The beneficial effects of metoprolol were demonstrated in MDC study (27) where 383 patients with idiopathic dilated CMP who received this drug (100—150 mg/day) were followed up for a period of 12—18 months. The results showed reduction in clinical deterioration, improvement in symptoms and cardiac function with the drug being well tolerated. There was a reduction in the sum of death and need for heart transplantation by metoprolol of 34 %. It is worth noting here that mortality alone was not decreased.

The same drug was tested for its long-term benefits in the same category of patients. The duration of follow-up period was 52±32 months and during 7 years of follow-up only 5 % of patients did not tolerate the treatment regimen. Results showed a significant decrease in mortality in the metoprolol group. This decrease was

in all cause mortality with a reduction in the need for heart transplantation as well (28).

In order to evaluate the effects of metoprolol in patients with HF secondary to ischemic heart disease, MIC trial enrolled 52 HF patients (26 cases secondary to ischemic heart disease and the rest secondary to dilated CMP). These patients received metoprolol for 6 months after which they showed a significant increase in EF and exercise tolerance when they were compared to placebo group patients. There was a similar benefit from the use of metoprolol in patients with ischemic heart disease and dilated CMP (29).

The MERIT-HF study (30, 31) showed that the use of metoprolol in HF patients was save and significantly beneficial regardless the etiology of HF. The study has enrolled 3991 HF patients with NYHA class II—IV and EF of 40 % or less. These patients were receiving standard treatment of HF. Results showed that with the use of metoprolol (target dose 200 mg/day) the total mortality was reduced by 34 %, with 38 % decrease in cardiovascular mortality, 41 % decrease in sudden death, and 49 % decrease in mortality from progressive HF. In addition to that there was improvement in NYHA class and a 35 % reduction in the rate of hospitalization for worsening HF among patients of the metoprolol group (32).

The use of metoprolol was associated with other benefit proved by a study (33) which showed that metoprolol caused enhancemnent of cell-mediated immunity and improvement of T-cell function the changes which were correlated to improvement in ejection fraction. The presence of β_2-adrenergic receptors in lymphoid tissue makes lymphocytes susceptable to sympathetic stimulation and through cyclic AMP, mitogen and antigen-induced T-call proliferation, cytotoxic T-lymphocyte function, and the activity of natural killer cells are inhibited. Metoprolol being β-adrenergic antagonist may reverse these changes causing that improvement in cell-mediated immunity.

The benefits of metoprolol extend to include those patients with suspected myocardial infarction and indirect signs of HF where it was shown by a study (34) that the early administration of metoprolol to such patients markedly reduced their mortality.

It seems that the benefit got from the use of beta-blockers is logical since the increased plasma level of norepinephrine in HF (renal and cardiac overflow of catecholamines can increase by 3 and 10 folds respectively) (35) has been associated with deterioration in symptoms, total mortality, life-threatening arrhythmias, and sudden cardiac death (5). This is also a supprot of viewing HF as a continuing process of cardiac remodeling where neurohormonal stimulation is a driving force of the process. Late therapeutical treatment sucess of HF comes from attacking this neurohormonal stimulation.

Other beta-blockers in HF

Researche is ongoing using different other beta-blockers as is the case of a non-selective beta-blocker bucindolol which was tested for its beneficial actions in the BEST study (36). It started in the year 1995 with a planned follow-up period of 4.5 years. It enrolled 2800 patients with class III and IV HF of ischemic and idiopathic etiologies. In this study there was relatively a large percentage of African-Americans and a small percentage of women. This study was prematurely terminated when it showed no significant benefit from bucindolol and even a trend towards increased mortality in African-Americans. Otherwise, there was a non-significant total reduction in mortality of 10 % with bucindolol, reduction in sudden death, death due to pump failure and hospitalization but all these results were not significant (37). The reason behind such unexpected results remains to be explained. Whether there is no enough response to bucindolol by African-Americans or the absence of α_1-antagonism property in this drug influences its actions is still unknown.

Xamoterol failed to benefit HF patients. Xamoterol is a mild β_1-adrenoreceptor agonist at rest and during light exercise but at high sympathetic tone or during heavy exercise it acts as a β_1-adrenorecptor antagonist (38). The data available to us show that xamoterol in patients with mild to moderate HF has beneficial effects as it improves symptoms and increase exercise tolerance (39) Positive results were obtained in the late 80s by the studies of McAlpine et al. (40) and Pouleur et al. (41) when they tested xamoterol in a limited number of patients with severe HF where improvement in exercise tolerance was noticed in some patients in addition to hemodynamic stabilization, but as it has been shown in the early 90s (38) it caused excess in mortality and was not associated with improvement in exercise tolerance when used in a large number of patients with severe form of HF. This was the reason behind the premature termination of that study. The reasons for that discrepancy between the results of these studies could be the fact that in the earlier studies fever patients received ACEIs, in addition to that more patients had ischemic heart disease where they showed benefit from xamoterol due to the improvement in myocardial ischemia rather than improvement in congestive HF. One point can be added, that the clinical condition of the later study's patients was worse than that in the previous ones. It is worth noting the fact that xamoterol acts also as a beta-agonist during the night and this may explain the increased rates of mortality especially when increasingly deleterious beta-stimulation is to be expected.

Beta-blockers and sudden cardiac death

It is convenient to mention that the ability of beta-blockers to reduce the incidence of sudden death represents according to some authors the cornestone for their beneficial effects as it was shown by BHAT trial that propranolol was able dramatically to reduce sudden death in postinfarction patients (42) Hjalmarson has summarized some of the work done in the field of beta-blockers and the protection against sudden death by the following: About half of all death after myocardial infarction are sudden death most of which are thought to be due to ventricular fibrillation. Beta-blockers have been found to decrease significantly the risk of sudden death as seen in BHAT, MIAMI, and ISIS-1 studies. Data from 24 postinfarction studies with long-term follow-up show an average 20 % mortality reduction over 2 years and 13 % mortality reduction in 28 short-term trials within 2 weeks after the onset of myocardial infarction (43).

And now what about presenting some information worth noting (44):

(a) Results of SOLVD heart failure study indicated that in contrast to enalapril, beta-blockers were renoprotective (in both placebo and ACEIs group). This was explained that possibly

beta-blockade would lower ACEI-induced raised plasma renin activity, decrease dependence on angiotensin II for mainraining glomerular filtration rate and allow for the safe introduction of ACEIs.

(b) UKPDS which enrolled 1148 hypertensive patients with type II diabetes to receive captopril or atenolol to achieve tight or less tight control of blood pressure for a follow-up period for a median of 8.4 years showed that atenolol was superior to captopril in all seven primary clinical end-points (relating to any diabetes-related end-point, deaths related to diabetes, all-cause mortality, myocardial infarction, stroke, peripheral vascular disease, and microvascular disease). Very interesting was the absence of a HF problem with atenolol in addition to a non-significant 142 % excess in sudden death in the captopril group. The incidence of peripheral vascular disease was not more in the atenolol group. Surprises continued by the results which showed that changes in albuminuria and serum creatinine over the 9 year observation period was the same in both drug groups, and that glycated haemoglobin (HbA1c) was significantly higher in the beta-blocker group in the first 4 years, but not in the last 5-years of observation. Hypoglycaemic problems were the same in both drug groups.

From the above data of great positive results when a β-blockers is used, it seems that with confidence we can say: it is wise to put every HF patient with low ejection fraction on therapy with a β-blocker unless a contraindication exists.

There is a great need to emphasize the benefits of β-blockers to physicians and general practitioners and to present practical guidelines for their wider use.

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Received January 3, 2001.
Accepted June 6, 2001.