Journal of Clinical and Basic Cardiology

An Independent International Scientific Journal

Journal of Clinical and Basic Cardiology 1998; 1 (1), 10-14

Chronic cardiac insufficiency: therapy with beta-adrenergic blockers

Erdmann E

Indexed in
Chemical Abstracts
EMBASE/Excerpta Medica

Krause & Pachernegg GmbH · VERLAG für MEDIZIN und WIRTSCHAFT · A-3003 Gablitz/Austria

Chronic cardiac insufficiency: therapy with beta-adrenergic blockers

E. Erdmann

Key-words: Heart failure, beta-blocking agents, heart rate, bisoprolol, beta-adrenoceptors

The results of the ISIS-I tests demonstrated that beta-adrenergic blockers have a decidedly positive prognostic effect on secondary prevention of myocardial infarction (Table 1). This applies particularly to patients after major infarctions, and even to patients with cardiac insufficiency symptoms [1] (Fig. 1). In spite of this, the initial reports by Waagstein et al. [2] that therapy with beta-adrenergic blockers leads to an improvement in symptoms and prolongation of life in cardiac insufficiency patients with cardiomyopathy were received rather sceptically. This is not all that surprising, since the treatment of cardiac pump failure with cardiodepressive drugs seems at first glance to contradict traditional therapy which uses substances with a positive inotropic effect or that reduce the pre- and afterload [3, 4]. Current attempts at reorientation are based partly on a better understanding of the pathophysiology of chronic cardiac insufficiency and partly on controlled prospective studies with a large number of cardiac insufficiency patients.

The following text will illustrate the current position on the use of beta-adrenergic blockers in chronic left ventricular failure.

1. Pathophysiological aspects

The human heart is not subject to major sympathoadrenergic stimulation when at rest. Therefore, the administration of beta-adrenergic blockers at the normal levels (eg, bisoprolol 5 mg *p.o.*) has neither a heart rate-reducing nor a negative inotropic effect. However, heart failure leads to a continual sympathetic stimulation (increase in plasma noradrenaline) first during exercise, then at rest. In cases of reduced left ventricular pump function (eg, ejection fraction < 35 %) this in turn leads to a down regulation of beta-adrenoceptors, an increase in guanine nucleotide binding proteins with an inhibitory effect on adenyl cyclase (Gi) and reduced effectiveness of the intracellular cAMP [5]. The administration of adrenergic blockers to patients with cardiac insufficiency and stimulated neurohumoral system leads to a frequency reduction and a decrease in contractility and velocity contraction [6–9].

In humans, the number of beta-adrenoceptors present in the left ventricular myocardium correlates linearly with the maximum attainable contractility after stimulation with noradrenaline (Fig. 2). A reduction in beta-adrenoceptors results in an equivalent percentile reduction in the maximum stimulatable contractility after administration of noradrenaline

Table 1: Beta-blockers after myocardial infarction

1. Standard therapy (after major ventricular wall infarctions)
   a. Fewer reinfarctions
   b. Lower mortality rate
2. Also beneficial for cardiac insufficiency patients

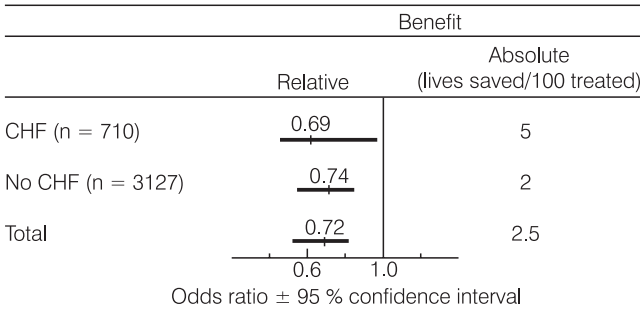

Figure 1: Effects of propanolol on mortality after myocardial infarction (BHAT-Trial). Astonishingly the effect of propanolol in patients with myocardial infarction was especially good in patients with chronic heart failure (CHF). The absolute numbers of lives saved was highest in this cohort.

or isoprenaline [10]. This means that the human heart has no receptor reserve. The logical conclusion is that patients suffering from chronic cardiac insufficiency (NYHA IV) with beta-adrenoceptors of approximately 30 % of the normal level and a high blood concentration of noradrenaline (symptomatic cardiac insufficiency) can only increase their contractility by a maximum of 30 % above the non-stimulated (rest) condition. Assuming that the patient can only achieve the necessary cardiac output through increased noradrenaline concentration and activation of all remaining beta-adrenoceptors which results from it, it is conceivable that the blockage of an additional 10 % of the beta-adrenoceptors through the administration of beta-blockers could lead to a considerable reduction in contractility (of 10 %) and thus possibly to a critical reduction in cardiac output (pulmonary oedema).

Figure 2: The density of beta-adrenoceptors in human myocardium increases with maximal positive inotropic effect. This means, that the linear relationship is indicative of a missing receptor reserve.

From the Dept. of Internal Medicine III, University of Cologne, Germany.
Correspondence to: Prof. Dr. Erland Erdmann, Dept. of Internal Medicine III, University of Cologne, Joseph-Stelzmann-Str. 9, D-50924 Cologne, Germany.

Table 2: Established positive effects of beta-adrenergic blockers

1. Anti-anginal (anti-ischaemic) effects
2. Antihypertensive effects
3. Anti-arrhythmic effects
4. Reduction in infarction mortality rate (by 15–20 %)
5. Symptomatic with hypertrophic obstructive cardiomyopathy
6. Chronic left ventricular failure from dilative cardiomyopathy and after myocardial infarctions
7. Dissecting aortic aneurysm (pressure and heart rate reduction)
8. Symptomatic in mitral valve prolapse syndrome
9. In vasovascular syncope and in QT syndrome
10. Perioperative in coronary heart disease

This leads to the conclusion that high plasma noradrenaline concentrations lead on the one hand to a reduced physiological stimulation of the diseased heart muscle under the administration of noradrenaline due to the additional down regulation of the beta-adrenoceptors, but on the other hand that they could be necessary to maintain adequate cardiac output in patients with severely reduced pump function. The anti-adrenergic effect of the beta-blockers must have a negative inotropic effect in the presence of higher catecholamine concentrations [5], but protects the heart muscle cells from the negative effect of higher noradrenaline concentrations at the same time (further down regulation of the beta-adrenoceptors, tachycardia, cardiac arrhythmia) (Table 2).

1.1. The force-frequency relation of the heart muscle

The sufficient heart muscle increases its contractility as the heart rate increases (Bowditch effect). On the other hand, the insufficient myocardium exhibits a marked decrease in contractility as the heart rate increases (Fig. 3), which leads to the conclusion that higher heart rates (a reduction in the contractility of the individual beats) contributes to an inefficient pump function [11]. In experiments, cardiac insufficiency can actually be caused by continuous tachycardia [12]. The same applies to certain cardiac arrhythmias with permanently increased heart rate [13]. A reduction in the heart rate alone leads to improved pump function. There is apparently no compensatory tachycardia – at least with cardiac insufficiency, rather it must be assumed that the reduction of the increased heart rate is likely to be beneficial for the pump function [14]. There is much evidence which shows that drugs which further increase the heart rate in patients with chronic cardiac insufficiency worsen the patient's prognosis. On the other hand, cardiac glycosides, amiodarone and beta-adrenergic blockers appear to exclusively have a beneficial effect in patients who have previously had an increased heart rate which was reduced through therapy.

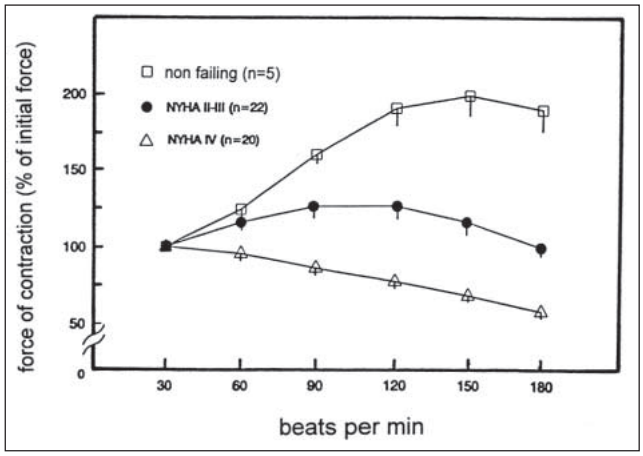

Figure 3: In human myocardium force of contraction increases with the frequency. This is, however, only true for a normal, non-failing myocardium. In heart failure the force of contraction decreases with increasing frequency of contraction. Thus, a high heart rate may lead to deterioration of the patient.

1.2. Effects of administration of beta-blockers on beta-adrenoceptors

It has been shown *in vitro* and in cardiac insufficiency patients that the administration of beta-blockers leads to up-regulation of beta-adrenoceptors in the insufficient heart [15]. However, while this is only true of metoprolol and bisoprolol, it is not true of carvedilol, and leads to the assumption that the positive therapeutic effects of the beta-adrenergic blockers on chronic left ventricular failure are not or not only attributable to the increase in beta-adrenoceptors in the myocardium [16]. This also offers a pathophysiological explanation for the beneficial prognostic effect of the beta-adrenergic blockers, namely the reduction in heart rate, the regular increase in the ejection fraction and the anti-adrenergic effect. In any case, it has been proven that the beta-blocker therapy leads to lower plasma noradrenaline concentrations and higher lactate extraction, both of which are positive [8, 12].

2. Beta-blockers after myocardial infarction

Beta-adrenergic blockers definitely have a positive effect on the patients' prognosis in the absence of intrinsic sympathomimetic activity (ISA), though the pathophysiological mechanism of this life-prolonging effect is still not understood [17]. It is known that all positive inotropic drugs (eg, digitalis) lead to an increase in the size of the infarct area [18], but all drugs which have been proven to stimulate the neurohumoral system (catecholamines) are unfavourable for the prognosis after a myocardial infarction. This leads to the conclusion that a reduction in heart rate and plasma noradrenaline concentration are beneficial in the post-infarction stage [19, 20]. For this reason, beta-adrenergic blockers would also have to be beneficial for long-term therapy after a myocardial infarction (heart rate reduction, reduction in plasma noradrenaline concentration, increase in lactate consumption) [21], but it is still not clear how long beta-adrenergic blockers should be administered after such an infarction.

3. The established cardiac insufficiency therapy

It is currently accepted that diuretics, digitalis and ACE inhibitors should be administered for manifest chronic left ventricular failure [3]. Diuretics reduce the pre- and afterload of the heart and therefore the wall tension in the left ventricle. Stimulation of RAAS caused by diuretics is counteracted by ACE inhibitors. Only ACE inhibitors have been proven to lead to prognostic improvement in symptomatic left ventricular failure (NYHA II to NYHA IV). Cardiac glycosides reduce the necessity of inpatient treatment and reduce cardiac insufficiency symptoms by about 20%. It can also be assumed that ACE inhibitors are indicated for reduced pump function (EF of the left ventricle < 35 %) because they reduce the frequency of left ventricular failure. It is not known whether ACE inhibitors should always be used in combination with diuretics or not, but it is certain that diuretics are principally indicated together with ACE inhibitors for hydropic cardiac insufficiency.

The results of the ELITE study indicate that ACE inhibitors can be replaced with losartan, which may reduce the incidence of acute cardiac death and is even more effective than ACE inhibitors.

If we are to continue to strive for an improvement of the rather poor prognosis of chronic left ventricular failure in spite

Table 3: Effects of beta-adrenergic blockers on chronic cardiac insufficiency

Study	Illness	n	beta-blocker (dose) p.o. (day)	Symptomatic improvement	Reduction in mortality rate
MDC	DCM	194	metoprolol (108 ± 51 mg)	+	18 %
CIBIS I	CHD/DCM	320	bisoprolol	++	20 % for all
CIBIS II	CHD/DCM	1.300	(1.25–5 mg) bisoprolol	++	53 % for DCM absolut 30 %
US trials	CHD/DCM	623	carvedilol (12.5–50 mg)	++	67 %

DCM = dilative cardiomyopathy, CHD = coronary heart disease

of diuretics, digitalis and ACE inhibitors, then selected drugs must be applied in addition to the established therapy. This has already been done with beta-adrenergic blockers in large controlled studies. The results correlate closely to a reevaluation of our conventional therapeutic procedure [22, 23].

4. Controlled studies of the effect of beta-blockers on chronic cardiac insufficiency

Large controlled studies that combined bisoprolol, metoprolol and carvedilol with diuretics, digitalis and ACE inhibitors yielded positive results in chronic left ventricular failure patients [16, 24, 25] (Table 3).

In a double-blind, placebo-controlled study of chronic cardiac insufficiency (NYHA III to IV) with bisoprolol (CIBIS Study), 641 patients were treated with bisoprolol in addition to basic therapy with diuretics and ACE inhibitors (Fig. 4). The ejection fraction for all patients was under 40 %, and the average length of treatment before the study was 1.9 years [24]. 67 patients on placebo and 53 patients on bisoprolol died. 90 patients on placebo and 61 patients on bisoprolol had to be hospitalized because of cardiac decompensation. The difference in mortality rate for all groups was not statistically significant. 23 of 115 patients with idiopathic dilative cardiomyopathy on placebo and only 11 of 117 patients on bisoprolol died. This difference is statistically significant, but resulted from a sub-group analysis and was not the primary goal of the study (Fig. 4). In any case, this clearly indicates that bisoprolol reduces the number of chronic cardiac insufficiency deaths in dilative cardiomyopathy patients. In these tests, it was surprising that no reduction in the mortality rate was found in patients suffering from chronic cardiac insufficiency stemming from a coronary heart disease (postmyocardial infarction). There is no plausible explanation for this, and it could be coincidence. For this reason, the CIBIS-II study was begun, in which the prognosis of both postmyocardial infarction subjects and subjects suffering from dilative cardiomyopathy undergoing bisoprolol therapy is being researched. The results of this study should be available in 1998. More than 2500 patients have already been enrolled in the two year study.

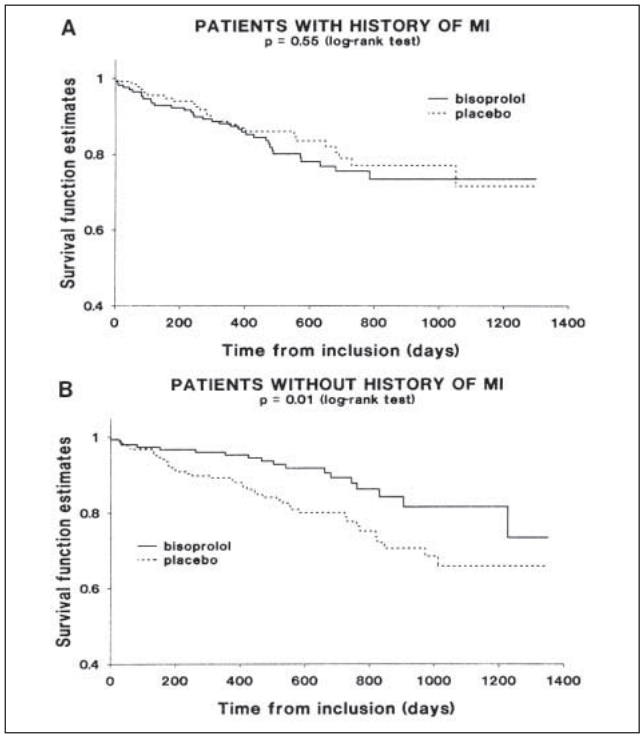

Figure 4: Survival curves (Kaplan-Meier) of CIBIS-patients with and without history of myocardial infarction.

383 patients suffering from moderately severe cardiac insufficiency (NYHA II and III) were observed in the MDC study. All patients had an ejection fraction under 40 % as a result of an idiopathic dilative cardiomyopathy and were treated with either a placebo or metoprolol in addition to diuretics, digitalis or ACE inhibitors. 5 mg metoprolol was administered twice daily over two to seven days as a test dose. The target medication was gradually increased to 100–150 mg metoprolol per day. The primary endpoint of the study was seen as death and the necessity of heart transplant, and 34 % fewer patients in the metoprolol group reached this point. This study has been criticised because the necessity of heart transplant was not viewed as a hard criterion. In spite of this, the study shows the favourable result of beta-blocker therapy under the pre-specified criteria for patients suffering from chronic cardiac insufficiency.

Carvedilol was tested in 1094 patients suffering from chronic cardiac insufficiency with an ejection fraction of $\leq$ 35 % [16]. In addition to diuretics, digitalis and ACE inhibitors, 398 patients received placebo and 696 received carvedilol. The total mortality rate among the patients on placebo was 7.8 % and 3.2 % among patients on carvedilol. The study was prematurely ended as a result of the prolonged survival among patients on carvedilol. The carvedilol therapy was much more effective in terms of the frequency of hospitalisation and the incidence of cardiac insufficiency. The fact that 6 patients died during the run-in phase has been widely criticised, but this has been observed in almost all large cardiac insufficiency studies and does not detract from the results of the study.

In March 1998, the safety and scientific committees of the CIBIS-II trial recommended to stop this investigation, because those patients, which had received bisoprolol, experienced a 30 % reduction in mortality. The benefit was irrelevant of the cause of heart failure in NYHA III-IV (CHD/DCM). The final results were reported at the European Congress of Cardiology 1998 but have not been published yet.

5. What the beta-blocker studies mean for our therapy

Bisoprolol and metoprolol seem to further improve the prognosis of patients suffering from dilative cardiomyopathy when taken in addition to diuretics, digitalis and ACE inhibitors [26]. Carvedilol appears to improve the prognosis regardless of the cause of the cardiac insufficiency. The results of the CIBIS-II study, in which bisoprolol has been administered to postmyocardial infarction subjects and subjects suffering from dilative cardiomyopathy under controlled circumstances, are convincing. Thus, we now know that bisoprolol improves the prognosis for patients suffering from dilative cardiomyopathy and for all patients with a reduced ejection fraction and cardiac insufficiency symptoms (Table 3, 4).

Table 4: Discontinuation of therapy in beta-adrenergic blocker studies

	Discontinuation Rates	
	Placebo	beta-blocker
MDC [2]	16 %	12 %
CIBIS [24]	26 %	23 %
US trials [16]	7.8 %	5.7 %

6. Practical suggestions for therapy with beta-adrenergic blockers

At present beta-adrenergic blockers should only be given to patients with reduced pump function of the left ventricle and cardiac insufficiency symptoms when the patient is in a more or less stable condition under digitalis, diuretic and beta-blocker therapy, ie, when the diuretic dosage did not have to be acutely increased within the last 14 days. It is vital that the dosage starts at 1/10 of the target dosage and is increased gradually in 14 day increments. It is also advisable that the patients undergo a complete clinical examination before each dosage increase (auscultation of the lungs, checking body weight and checking for malleolar oedema). Experience has shown that too rapid a dosage increase is generally linked with intolerance of beta-adrenergic blockers. Improvement of the cardiac insufficiency symptoms cannot be expected until three to six months after induction, which makes any rapid dosage increase unnecessary and hazardous. The CIBIS study dosage schedule is shown in Figure 5.

The normal contraindications for beta-blocker therapy must of course be followed. Simple cardiac insufficiency does not appear to be a contraindication with proper dosage and when the proper safety measures are followed (Table 5).

The administration of beta-adrenergic blockers to patients suffering from chronic left ventricular failure should never be considered an acute measure, and is therefore superfluous in intensive care or for decompensated cardiac insufficiency – except for the treatment of absolute tachyarrhythmia or other tachycardia. In this case, normal dosing indications for beta-blockers apply.

In our opinion, cardiac insufficiency therapy with beta-adrenergic blockers can be considered to be very safe when carried out properly. Many patients have already benefited from it and the prognosis for this syndrome has improved significantly in recent years.

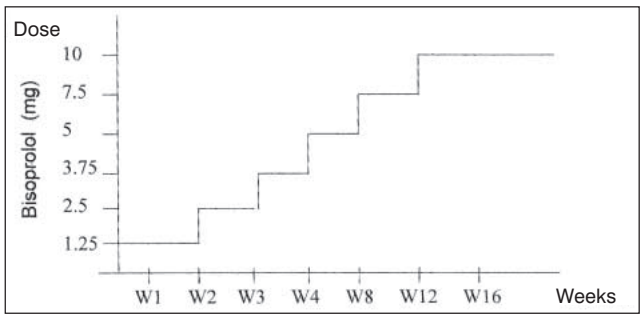

Figure 5: The titration of bisoprolol in patients of CIBIS-II-study.

Table 5: Therapeutic recommendations for treating chronic cardiac insufficiency with beta-adrenergic blockers

1. Only with patients who have been stable for longer than two weeks
2. Only in addition to diuretics, digitalis and ACE inhibitors
3. Not when the diuretic dosage had to be increased recently
4. Out-patient therapy for NYHA I-III
5. In-patient therapy for NYHA IV
6. Test dose and starting dose: 1/10 of the target dosage
7. Dosage increase every two weeks
8. Target dosage: 2 x 5 mg bisoprolol, 2 x 100 mg metoprolol, 2 x 25 mg carvedilol
9. A full clinical examination of the patient before each dosage increase
10. Improvements should not be expected until 3–6 months after induction

References

1. Ryan T et al. ACC/AHA Guidelines for the Management of patients with acute myocardial infarction. JACC 1996; 28: 1328–428.
2. Waagstein F, Bristow M, Swedberg K, Camerini F, Fowler M, Silver M, Gilbert E, Johnson M, Goss F, Hjalmarson A, for the Metoprolol in Dilated Cardiomyopathy (MDC) Trial Study Group. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. Lancet 1993; 342: 1441–6.
3. Cleland J, Bristow M, Erdmann E, Remme W, Swedberg K, Waagstein F. Beta-blocking agents in heart failure. Should they be used and how? Eur Heart J 1996; 17: 1629–39.
4. West J, Miller N, Parker K, Senneca D, Ghandour G, Clark M, Greenwald G, Heller R, Fowler M, DeBusk R. A comprehensive management system for heart failure improves clinical outcome and reduces medical ressource utilization. Am J Cardiol 1997; 79: 58–63.
5. Böhm M, Deutsch H, Hartmann D, La Rosée K, Stäblein A. Improvement of postreceptor events by metoprolol treatment in patients with chronic heart failure. JACC 1997; 30: 992–6.
6. Anderson F, Port D, Reid B, Larrabee P, Hanson G, Bristow M. Myocardial catecholamine and neuropeptide Y depletion in failing venticles of patients with idiopathic dilated cardiomyopathy. Circulation 1992; 85: 46–53.
7. Binkley P, Lewe R, Lima J, Al-Awwa A, Unverferth D, Leier C. Hemodynamic-inotropic response to ß-blocker with intrinsic sympathomimetic activity in patients with congestive cardiomyopathy. Circulation 1986; 74: 1390–8.
8. Di Lenarda A, Gregori D, Sinagra G, Lardieri G, Perkan A, Pinamonti B, Salvatore L, Secoli G, Zecchin M, Camerini F, The heart muscle disease study group. Metoprolol in dilated cardiomyopathy: Is it possible to identify factors predictive of improvement? J Card Fail 1996; 2: 87–102.
9. Woodley S, Gilbert E, Anderson J, O'Connell J, Deitchman D, Yanowitz F, Mealey P, Volkman K, Renlund D, Menlove R, Bristow M. ß-blockade with bucindolol in heart failure caused by ischemic versus idiopathic dilated cardiomyopathy. Circulation 1991; 84: 2426–41.
10. Schwinger R, Böhm M, Erdmann E. Evidence against spare or uncoupled ß-adrenoceptors in the human heart. Am Heart J 1990; 119: 899–911.
11. Erdmann E. Zellbiologische kardiale Veränderungen bei transplantations-pflichtiger Herzinsuffizienz. Z Herz-, Thorax-, Gefäßchir 1997; 11 (Suppl. 1) 1–6.
12. Laser A, Neubauer St, Tian R, Hu K, Gaudron P, Ingwall J, Ertl G. Long-term beta-blocker treatment prevents chronic creatine kinase and lactate dehydrogenase system changes in rat hearts after myocardial infarction. JACC 1996; 27: 487–93.
13. Hoes A, Grobbee D, Lubsen J, Man in't Veld A, Van der Does E, Hofman A. Diuretics, ß-blockers and the risk for sudden death in hypertensive patients. Ann Intern Med 1995; 123: 481–7.
14. Levine H. Optimum heart rate of large gailing heart. Am J Cardiol 1989; 61: 633–6.
15. Engelmeier R, O'Connell J, Walsh R, Rad N, Scanlon P, Gunnar R. Improvement in symptoms and exercise tolerance by metoprolol in patients with dilated cardiomyopathy: A double-blind, randomized, placebo-controlled trial. Circulation 1985; 72: 536–46.
16. Packer M, Bristow M, Cohn J, Colucci W, Fowler M, Gilbert E, Shusterman N, for the US Carvedilol Heart Failure Study Group. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. N Engl J Med 1996; 334: 1349–55.
17. Böhm M, Erdmann E. Betablockertherapie bei Herzinsuffizienz. Fortschr Med 1996; 114: 167–9.
18. Lichstein E, Hager D, Gregory J, Fleiss J, Rolnitzky L, Bigger J, for the Multicenter Diltiazem Post-Infarction Research Group. Relation between beta-adrenergic blocker use, various corelates of left ventricular function and the chance of developing congestive heart failure. JACC 1990; 16: 1327–32.
19. Kannel W, Kannel C, Paffenbarger R, Cupples L. Heart rate and cardiovascular mortality: The Framingham study. Am Heart J 1987; 113: 1489–94.
20. Schwinger R, Böhm M, Schmidt U, Karczewski P, Bavendiek U, Flesch M, Krause E-G, Erdmann E. Unchanged protein levels of SERCA II and phospholambin but reduced Ca^{2+} uptake and Ca^{2+} ATPase activity of cardiac sarcoplasmic reticulum from dilated cardiomyopathy patients compared with patients with nonfailing hearts. Circulation 1995; 92: 3220–8.
21. Vantrimpont P, Rouleau J, Wun C, Ciampi A, Klein M, Sussex B, Arnold J, Moyé L, Pfeffer M, for the SAVE Investigators. Additive beneficial effects of beta-blockers to angiotensin-converting enzyme inhibitors in the survival and ventricular enlargement (SAVE) study. JACC 1997; 29: 229–36.
22. Di Lenarda A, Secoli G, Perkan A, Gregori D, Lardieri G, Pinamonti B, Sinagra G, Zecchin M, Camerini F and the Heart Muscle Disease Study Group. Changing mortality in dilated cardiomyopathy. Br Heart J 1994; 72 (Suppl): 46–51.
23. Pop T. Betablocker in der antiarrhythmischen Therapie: Fakten und Hoffnungen. Herz-Kreisl 1996; 28: 63–8.
24. CIBIC Investigators and Committees. A randomized trial of ß-blockade in heart failure. Circulation 1994; 90: 1765–73.
25. Fisher M, Gottlieb S, Plotnick G, Greenberg N, Patten R, Bennett S, Hamilton B. Beneficial effects of metoprolol in heart failure associated with coronary artery disease: A randomized trial. JACC 1994; 23: 943–50.
26. Wikstrand J, Kendall M. The role of beta receptor blockade in preventing sudden death. Eur Heart J 1992; 13 (Suppl. D): 111–20.

Mitteilungen aus der Redaktion

Besuchen Sie unsere

zeitschriftenübergreifende Datenbank

☑ **Bilddatenbank** ☑ **Artikeldatenbank** ☑ **Fallberichte**

e-Journal-Abo

Beziehen Sie die elektronischen Ausgaben dieser Zeitschrift hier.

Die Lieferung umfasst 4–5 Ausgaben pro Jahr zzgl. allfälliger Sonderhefte.

Unsere e-Journale stehen als PDF-Datei zur Verfügung und sind auf den meisten der marktüblichen e-Book-Readern, Tablets sowie auf iPad funktionsfähig.

☑ **Bestellung e-Journal-Abo**