PREDICTION OF THE EFFECT OF BISOPROLOL IN CHRONIC HEART FAILURE

PhD thesis

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Contents

Abbreviations

NYHA class: New York Heart Association functional class

LVEF: left ventricular ejection fraction

mPCW: mean pulmonary capillary wedge pressure

MEC: maximal exercise capacity

HR: heart rate

BPs: systolic blood pressure

PP: pulse pressure

PRP: pressure-rate product

ESWT: end-systolic wall tension

ESWT x HR: the product of end-systolic wall tension and heart rate

USCP: The United States Carvedilol Program

CIBIS II: The second Cardiac Insufficiency Bisoprolol Study

MERIT HF: The Metoprolol CR/XL Randomised Intervention Trial in Heart Failure

COPERNICUS: The Carvedilol Prospective Randomised Cumulative Survival Trial

BEST: Beta Blocker Evaluation Survival Trial

Summary

Background:

Several observations suggest that in chronic heart failure when treating patients with beta blockers there is correlation between the intermediate-term (5-6 months) change in left ventricular function and the long-term change in survival of the patients. These observations give crucial importance of the early identification of the subjects, whose reaction in respect of the left ventricular function is not favourable to the treatment. By the closer observation of the predicted non-responders or by avoiding or modifying beta blocker treatment in such patients we can enhance the survival benefit of that therapy.

Aim:

Firstly we aimed at elaborating a predictive model to the reliable prediction of the intermediate-term effect of bisoprolol on left ventricular ejection fraction, mean pulmonary capillary wedge pressure, NYHA functional class, and maximal exercise capacity of patients with chronic heart failure.

Secondly we aimed at validating this model prospectively in a similar, comparable group of patients.

Patients and method:

The derivation sample, i.e. the group of patients where the predictive model was elaborated, consisted of 25 patients (23 men, 2 women) with dilated cardiomyopathy. Their mean age was 53.8 ± 15.9 years. Patients had mild or moderate heart failure (NYHA II – III class). The validation sample, where the predictive model was prospectively validated, consisted of 23 patients (21men, 2 women). Their mean age was 50.4 ± 17.6 years. In both the derivation and validation sample on the top of the conventional therapy (ACE-inhibitors, directly acting vasodilators, diuretics, digitalis and spironolactone) after an uptitration period bisoprolol was given in dose of 7.09 ± 2.14 and 7.24 ± 1.30 mg/day, respectively. As candidate parameters for the prediction in the derivation sample baseline values and short-term (1-month) changes of simple, routinely used, non-invasive parameters were selected. Variables proved to be predictive at significant or borderline significant level in univariate analysis were evaluated in multivariate analysis as well. Sensitivity and specificity, positive and negative predictive accuracy of predictive model were calculated in both derivation and validation groups of the patients.

Results:

Prediction of the intermediate-term change in left ventricular ejection fraction was possible by two independent parameters: by the left ventricular ejection fraction at baseline and by the short-term change in pressure-rate product. Sensitivity of prediction in derivation and validation sample was 100 % and 91.7 %, respectively. Specificity in the derivation and validation sample was 66.7 % and 70.0 %, respectively. Positive predictive accuracy in derivation and validation sample was 80.0 and 78.6 %, respectively. Negative predictive accuracy in the two samples was 100.0 and 87,5 %, respectively.

The short-term change in mean pulmonary capillary wedge pressure was a single ***predictor of the intermediate-term change in mean pulmonary capillary wedge pressure***. Sensitivity in derivation and validation sample was 85.7 and 84.6 %, respectively. Specificity was 66.7 % in both groups of patients. Positive predictive accuracy was 80.0 % in the derivation sample and 78.6 % in the validation sample. Negative predictive accuracy proved to be 75 % in both derivation and validation groups of patients.

The intermediate-term change in NYHA functional class could be predicted by the baseline value of heart rate and NYHA functional class. Sensitivity was in derivation and validation sample 83.3 and 82.4 %, respectively. Specificity was found 100 % in the derivation group and 80 % in the validation group. Positive predictive accuracy was in derivation and validation samples 100.0 and 93.3 %, respectively. Negative predictive accuracy was 62.5 % in the derivation group, and 57.1 % in the validation group of patients.

The 6-month change in maximal exercise capacity was predictable from the baseline value of maximal exercise capacity and NYHA functional class. Sensitivity was 80.0 and 75.0 % in the derivation and validation group of patients, respectively. Specificity proved to be 25.0 and 33.3 % in the two patients' groups. Positive predictive accuracy in derivation and validation sample was 66.7 and 75.0 %, respectively. And negative predictive accuracy was 40.0 % in the derivation sample and 33.3 % in the validation sample.

Conclusion:

In moderately severe chronic heart failure simple non-invasive parameters seem to be applicable to predict reliably the intermediate-term changes produced by bisoprolol in left ventricular ejection fraction and in NYHA functional class. The predictive model can give the possibility of the early identification of non-responders.

Introduction

In recent decades there has been a fundamental change in the view of the pathophysiology of heart failure. It became clear that the pathologically increased activation of the renin-angiotensin-aldosterone and sympathetic nervous system are of overriding importance in the progression of the disease. Nowadays, therefore, treatment modalities in heart failure are directed towards decreasing pathologically elevated neurohormonal activity instead of simple correction of haemodynamic abnormalities. As a consequence of this change of view, the treatment with ACE inhibitors and beta blockers in chronic heart failure has been introduced.

Numerous controlled and uncontrolled clinical trials (1-12) have demonstrated the beneficial effects of beta blockers on clinical symptoms, left ventricular systolic and diastolic function as early as the initial phase of investigation of beta blocker treatment in heart failure. However the data for benefit on survival until the last years were only suggestive. Recently four, large, multicentre, randomised studies proved the beneficial effect of beta blockers on survival in chronic heart failure, as well. The United States Carvedilol Program (USCP) (13), the second Cardiac Insufficiency Bisoprolol Study (CIBIS II) (14) and the Metoprolol CR/XL Randomised Intervention Trial in Heart Failure (MERIT HF) (15) unequivocally demonstrated the survival benefit of carvedilol, bisoprolol and metoprolol, respectively, particularly in the case of patients with mild to moderate (NYHA II-III) heart failure. The Carvedilol Prospective Randomised Cumulative Survival Trial (COPERNICUS) has also been completed recently; it has been the first trial to establish unequivocally the beneficial effects of beta blockers on morbidity and mortality of patients with advanced (NYHA IV) heart failure (16).

Consequently, the question of whether or not to use beta blockers in heart failure has been resolved. However, many new questions have been arisen in part by the survival trials themselves and in part by the widespread clinical use of beta blockers.

One of the most important of these problems is which patients do not respond to the beta blocker therapy, whether it is possible to select them in advance and if so, how. Even the first investigators of the beta blocker treatment in heart failure (1,3,5) had observed that some patients with heart failure derive more benefit from beta blocker therapy than others and some of them may deteriorate during such treatment. The subgroup analysis of almost every large survival trial also identified subgroups, which did not respond favourably to long-term beta blocker therapy.

The subgroup analysis of the CIBIS I study suggested that patients who had a lower baseline left ventricular ejection fraction (≤ 20 %) responded more favourably to the treatment (17). In the CIBIS II study (18) female gender proved to be a positive predictor of survival, in contrast with the results of the MERIT trial (15). The Beta Blocker Evaluation Survival Trial (BEST) has shown that patients with NYHA Class IV heart failure or an ejection fraction of ≤ 20 % did not appear to benefit from bucindolol therapy. Men tended to benefit more than women in this study and a lack of benefit or even a possible harmful effect was experienced in the African-American subgroup (19).

Although the data of the subgroup analysis are contradictory, it is a fact that about 20-50 % of patients do not respond sufficiently in every respect; their clinical condition, parameters characterising left ventricular function or functional capacity remain unchanged or deteriorate (3,5,11,17-18,19-21). The contradictions of the data can be explained by the considerable differences in the pharmacological properties of the drugs, by the different doses of beta blockers in different studies and by the differences in the groups of patients investigated.

The really important question is whether the patients who do not respond sufficiently in the above respect would be non-responders concerning survival, as well. We have no data about the correlation between the changes in NYHA functional class and maximal exercise capacity during beta blocker therapy and survival. It seems likely that there is no close correlation between them, particularly when applying non-cardioselective drugs. On the other hand the MOCHA trial, the subgroup analysis of the Cardiac Insufficiency Bisoprolol Study (CIBIS I) and a controlled study by Engelmeier et al. confirm a connection between the effect of beta blocker on left ventricular function (mainly on the left ventricular ejection fraction) and its effect on survival (5,20,23).

It seems to be presumable that the therapeutic potential of beta blockers could be further enhanced if one could reliably predict before introduction of the drug or in the early treatment phase patients who would not respond. Early withdrawal or modification of beta blocker therapy, or at least close follow up of the non responders, could further increase the survival benefit.

Consequently, it is of great importance to find parameters that could predict the effect of intermediate-term (5-6 months) beta blocker treatment on left ventricular function, and by this means predict the long-term survival before the introduction of the therapy or short-term after introduction.

Efforts to identify responders with respect to the left ventricular function or to different improvement indexes based on a combination of clinical variables, left ventricular function and eventually exercise parameters have provided partly conflicting results. In most, but not all,

studies the haemodynamic consequences of increased sympathetic activity, such as elevated baseline heart rate and its high value at maximal exercise as well as pronounced heart rate changes over time after beta-blockade proved to be reliable predictors of a favourable effect of beta blockers (1,5,12-13,20-22,24-25). Some studies showed that if the underlying disease is dilated cardiomyopathy, one can presume a more favourable response than in the case of ischaemic heart disease (6,12). Higher systolic blood pressure at baseline or hypertension in the case history of the patient was also reported to be a predictor of beneficial effect (21,26). The clinical severity of heart failure, baseline level of left ventricular ejection fraction and diastolic function proved to be predictive in some studies as well (3,5,21,26). The extent and dominant type of myocardial fibrosis were also suggested as having an influence on the change in NYHA functional class and in the left ventricular ejection fraction after 12 months (27).

In spite of previous attempts, there are still no prospective validated data verified to be parameters making the prediction of the effect of beta blocker therapy possible.

In our previous study (28), we tried to predict the beneficial effect of bisoprolol on systolic and diastolic left ventricular function in a group of 25 patients with dilated cardiomyopathy. As regards 6-month changes in left ventricular ejection fraction, the baseline value of left ventricular ejection fraction and short-term changes in pulse pressure and pressure-rate product proved to be predictive. The 6-month changes in mean pulmonary capillary wedge pressure could be predicted most exactly by the baseline value of mean pulmonary capillary wedge pressure, the baseline heart rate and the increase in heart rate during maximal exercise.

The aim of this study was to validate prospectively the results of our above-mentioned investigation, because this is an essential precondition of practical applicability of every predictive model (29). The prospective validation of the results has been done in a group of patients (**validation sample**) formed from March 1999. However, in addition to diuretics, ACE inhibitors and directly acting vasodilators, all these patients were treated with low dose of spironolactone as well before the introduction of beta blocker, on the basis of the preliminary results (B. Pitt, AHA Nov 1998) of the RALES study (30). Because only 12 patients were treated with spironolactone in the previously investigated group of patients, the comparability of the two groups became questionable. Therefore in this study we assessed the data of those 12 patients – from our previously investigated group of patients – who were treated with spironolactone before the introduction of bisoprolol. An additional 13 patients were included in the study from patients referred to our clinic between January 1995 and

April 1997, who fulfilled the inclusion and exclusion criteria of the study and had been treated with low dose of spironolactone in addition to optimal doses of ACE inhibitor, digitalis, diuretics and directly acting vasodilators. These 25 patients composed the **derivation group** of the study, in which it was investigated retrospectively whether simple, non-invasive, routinely used clinical variables at baseline and in the early treatment phase could predict the intermediate-term effects (5-6 months) of bisoprolol on left ventricular systolic and diastolic function, clinical condition and exercise capacity.

The clinical utilisation of these predictive factors was prospectively validated on a similar group of patients (validation sample).

Pharmacological and pharmacokinetic properties of bisoprolol

Bisoprolol investigated in this study is one of the most selective β_1 receptor antagonists. Bisoprolol has no intrinsic sympathomimetic activity and has no membrane-stabilising activity in therapeutically applied doses. Bisoprolol does not possess vasodilator property. Bisoprolol occupies a middle position as regards hydrophilia and lipophilia.

Bisoprolol has a long duration of action. Elimination half-life is 10-12 hours, meaning that bisoprolol may be administered once daily. The high absorption rate (> 90 %) and small first-pass effect result in an absolute bioavailability of 88 %. Bisoprolol has a "balanced clearance", half of the dose is metabolised to inactive metabolites in the liver and the other half is excreted as the unchanged substance via the kidneys.

Acute haemodynamic effects of bisoprolol correspond to the β_1 adrenoreceptor blockade: dose-dependent decrease in heart rate, in blood pressure, in pressure-rate product, in contractility and cardiac index. Bisoprolol decreases the exercise-induced increase in heart rate and increases the peripheral resistance at the beginning of the administration.

In the therapeutically recommended doses bisoprolol is nearly devoid of any β_2 adrenoreceptor antagonistic activity and has therefore no effects on β_2 adrenoreceptor-mediated metabolic effects. Bisoprolol induces no change in the cholesterol fractions in long-term therapy and has no influence on the carbohydrate metabolism.

Methods

Subjects

The **derivation sample** consisted of 25 patients (23 men, 2 women) with idiopathic dilated cardiomyopathy referred to our clinic between February 1994 and April 1997. In the **validation sample** we investigated 23 patients (21 men, 2 women) with idiopathic dilated cardiomyopathy, selected from patients referred to our clinic between March 1999 and December 2000.

Inclusion criteria (in both the derivation and validation group of patients):

- Patients had to have a diagnosis of dilated cardiomyopathy. Diagnostic criteria proposed by the WHO/ISFC Task Force (31) were applied. Coronary angiography was performed in 9 cases in the derivation sample and in 8 cases in the validation sample to exclude coronary artery disease suggested by the presence of risk factors, chest pain or both.
- Symptoms had to include dyspnoe on exertion and fatigue corresponding to class II or III of the New York Heart Association (NYHA).
- Patients only with a history of heart failure longer than one year were included.
- Eligible patients were aged 20-75 years.
- Left ventricular ejection fraction assessed by two-dimensional transthoracic echocardiography was lower than 40 % in every case.
- Patients only with a resting heart rate higher than 70 beats/min, and systolic blood pressure higher than 90 mmHg were enrolled into the study.
- Patients had to be in stable clinical condition for at least 4 weeks prior to enrolment into the study.
- Previous tailored therapy with diuretics, digitalis, ACE inhibitors, nitrate, dihydralazine, low dose of spironolactone had to be used for at least 3 months before introduction of bisoprolol. The doses of the indicated drugs had to be unchanged during the last 3 weeks before the initiation of treatment with bisoprolol.
- Informed consent was obtained from all patients.

Exclusion criteria (in both the derivation and validation group of patients):

- Major contraindications for beta blocker therapy such as chronic obstructive airways disease, unstable insulin-dependent diabetes mellitus, advanced AV block (higher than 1st degree) and sick sinus syndrome were criteria for exclusion.

- Prior beta blocker treatment and alcohol intake greater than 100 g/day in the previous year were exclusion criteria, as well.

Introduction of bisoprolol: The first dose of bisoprolol was 1.25 mg/day, which was uptitrated by doubling the dose twice a week or in case of more severe heart failure (NYHA class III), once a week, up to 10 mg/day. Patients received less than 10 mg if their systolic blood pressure decreased below 80 mmHg or if their resting heart rate was lower than 60 beats/min or when persistent progression in heart failure symptoms appeared. At the end of the titration the mean dose of bisoprolol was 7.09 ± 2.14 mg/day in the derivation sample, and 7.24 ± 1.30 mg/day in the validation sample. Every patient remained on these doses after the titration phase.

One of the patients in the derivation sample did not tolerate the first dose due to symptomatic hypotension and significant progression of heart failure.

In the derivation sample one patient died (sudden death) during the titration phase. In the validation sample also one patient died after the titration phase, during the drug maintenance, due to progression in heart failure.

The data of these three patients were not taken into consideration. Only data of patients whose prediction investigation could be performed from beginning to end were evaluated.

Measurements

Patients underwent clinical and non-invasive cardiac evaluation before the introduction of bisoprolol. During the drug maintenance they were re-evaluated at one month and at 6 months after starting the treatment. Apart from physical examination the evaluated parameters were derived from routinely used non-invasive investigations (electrocardiography, M-mode and 2D transthoracic echocardiography, left ventricular apexcardiography and exercise testing).

The one-month effect of bisoprolol was considered as short-term effect. The short-term change in parameters was defined as the change in variables during the first month of treatment. The 6-month effect of bisoprolol was considered as intermediate-term effect. The intermediate-term change in parameters was defined as the change in value of parameters observed from baseline to 6 months.

Parameters to be predicted (outcome events)

The intermediate-term changes of the following parameters were investigated and an attempt was made to predict them: clinical severity of heart failure (NYHA class), maximal exercise capacity (MEC), left ventricular ejection fraction (LVEF) and pulmonary capillary wedge pressure (mPCW). The changes were classified into two categories: improvement or lack of improvement (parameters unchanged or deteriorated). The changes were expressed as a percentage of baseline values.

The change in ***left ventricular ejection fraction*** on 6 months of bisoprolol treatment in the case of an individual patient was considered as an improvement if the increase in left ventricular ejection fraction was more than 20 % of the baseline value. (It a little bit exceeds the interobserver variability (17.5 %) found in our laboratory, when left ventricular ejection fraction was measured by 2D echocardiography.) Deterioration was established when the decrease in the left ventricular ejection fraction was more than 20 % of the baseline value. The parameter was unchanged if neither increase nor decrease was more than 20 % of the baseline value.

The change in ***mean pulmonary capillary wedge pressure*** on 6 months of therapy in an individual patient was considered as an improvement if the decrease in pulmonary capillary wedge pressure was more than 20 % of the baseline value. (This value was a slightly higher than the interobserver variability (18.6 %) found in our laboratory, when pulmonary capillary wedge pressure was estimated by measuring diastolic rapid filling period from apexcardiography.) Deterioration was established when the increase in the pulmonary capillary wedge pressure was more than 20 % of the baseline value. The parameter was unchanged if neither its increase nor decrease was more than 20 % of the baseline value.

An improvement in ***NYHA functional class*** on 6 months in an individual patient was defined as a decrease in the value of NYHA class of more than or equal to 0.5. Deterioration was established when the increase in NYHA functional class was more than or equal to 0.5. The parameter was considered as unchanged if neither increase nor decrease was established.

The change in ***maximal exercise capacity*** on 6 months of bisoprolol therapy in an individual patient was considered as an improvement if the increase in maximal exercise capacity was more than 25 % of the baseline value. (It exceeds a bit the interobserver variability (24 %) of the three consecutive measurements of the maximal exercise capacity in the case of 10 patients with unchanged clinical condition and on the same therapy.) Deterioration was established when the decrease in maximal exercise capacity was more than 25 % of the baseline value. The parameter was unchanged if neither increase nor decrease was more than 25 % of the baseline value.

Candidate predictive parameters:

To predict the 6 months effect of bisoprolol, baseline values and short-term changes of resting and exercise variables were selected as **candidate predictors**.

The resting variables were as follows: heart rate (HR), systolic blood pressure (BPs), pressure-rate product (PRP) = HR x BPs, pulse pressure (PP) = systolic blood pressure – diastolic blood pressure, NYHA functional class, left ventricular ejection fraction, mean pulmonary capillary wedge pressure, end-systolic wall tension (ESWT) and the product of end-systolic wall tension and heart rate (ESWT x HR).

The exercise variables were the following: maximal exercise capacity (MEC), heart rate at 30 W load (HR30W) heart rate at maximal level of exercise (HRmax), the increase in heart rate from rest to 30 W load (ΔHR30W), the increase in heart rate from rest to maximal level of exercise (ΔHRmax), systolic blood pressure at 30 W load (BP30W), systolic blood pressure at maximal level of exercise (BPmax), the increase in systolic blood pressure from rest to 30 W load (ΔBP30W), the increase in systolic blood pressure from rest to maximal level of exercise (ΔBPmax).

Measurement and calculation of the parameters studied: Heart rate was assessed from the ECG recordings. Blood pressure was measured in sitting position, using a sphygmomanometer. NYHA functional class was evaluated by two independent investigators. In the case of difference in opinions it was calculated as mean value. Left ventricular ejection fraction was calculated by two-dimensional echocardiographic studies from the apical four-chamber view using an area-length singe-plane method (Simpson method). Pulmonary capillary wedge pressure was estimated by left ventricular apexcardiography from the diastolic rapid filling period, by using a previously described method (32,33). End-systolic wall tension was calculated by Laplace's low according to Quinones (ESWT = BPs x ESD/(PW + IVS), (ESD: end-systolic diameter of left ventricle; PW: posterior wall thickness; IVS: interventricular septal thickness) (34).

Exercise test variables were derived from graded, symptom-limited maximal (estimated with the use of the Borg perceived exercise scale) upright bicycle ergometer tests. The tests started at 30 W load, the load was increased by 30 W after every three minutes. ECG was recorded during the test continuously. Heart rate and blood pressure measurements were carried

out every minute. Before baseline testing, a test was done to familiarise the patients with the procedure.

The measurements and calculations of NYHA functional class, left ventricular ejection fraction, mean pulmonary capillary wedge pressure and MEC after 6 months of bisoprolol treatment were performed by investigators who were blinded in the baseline and short-term values of parameters in the case of every patient.

Statistical analysis

The baseline characteristics of the derivation and validation samples were compared with use of the unpaired Student's t-test. In both the derivation and validation group the differences between variables at baseline and at 1 and 6 months were determined by a standard paired Student's t-test. To investigate the predictability of the 6-month effect of bisoprolol, the intermediate-term changes of left ventricular ejection fraction, pulmonary capillary wedge pressure, NYHA functional class and maximal exercise capacity – as a percentage of baseline values – were compared with the baseline values and short-term changes of the selected possible predictors applying univariate regression analysis. After determination of the predictors by univariate analysis, the most significant predictors ($p < 0.1$) were subjected to analysis by multiple regression to assess the relative contribution of each predictor. The probability of improvement in an individual subject in respect of a given parameter was modelled by the multiple regression model (35) applying the constant and the values of coefficient B.

Applying correlation derived from the derivation sample, all predicted variables were determined in the case of all patients of the validation sample. Then all predicted and observed values of 6-month changes in left ventricular ejection fraction, pulmonary capillary wedge pressure, NYHA functional class and maximal exercise capacity were compared in the validation group of patients. To validate prospectively the correlation derived from the derivation sample, the sensitivity, specificity, positive and negative predictive accuracy of this predictive model were determined in the validation group.

Statistical analysis was performed with the SPSS 9.0 program package. Significance was taken as $p<0.05$. All p values were two-sided. All data are reported as mean ± SD. Interobserver variability was considered as the double the standard deviation of mean values of differences of measurements.

Results

The clinical effect of bisoprolol in the derivation and validation samples

The clinical characteristics of the derivation and validation samples at baseline are shown in *Table 1.* The two groups were comparable in respect of all investigated variables; there was no significant difference between these parameters.

In both the derivation and validation groups of patients the changes characterising the effect of beta-blockade in heart failure could be observed (*Table 2a, 2b*).

Heart rate decreased markedly and significantly in both groups of patients at short-term and remained at that level at intermediate-term (in the derivation sample: 90.9 ± 17.0 → 67.2 ± 9.4 → 62.6 ± 10.6 min^{-1}; in the validation sample: 93.4 ± 15.7 → 66.9 ± 10.8 → 65.5 ± 11.2 min^{-1}). Systolic blood pressure decreased in both groups at 1 month although it was not significant, and increased above the baseline at intermediate-term and this increase proved to be significant compared to baseline (in the derivation sample: 110.3 ± 17.7 → 104.1 ± 11.2 → 118.8 ± 13.6 mmHg; in the validation sample: 105.4 ± 15.5 → 100.8 ± 9.3 → 114.5 ±16.2 mmHg). The pulse pressure showed the same pattern of changes in the derivation group of patients: it decreased at short-term and increased above the baseline at intermediate-term (35.6 ± 8.5 → 33.5 ± 9.3 → 42.4 ± 11.1 mmHg). However, in the validation sample a slight increase in pulse pressure was observed after one month, which became significant at 6 months (30.3 ± 8.9 → 31.4 ±10.1 → 40.9 ± 10.4 mmHg). The changes in pressure-rate product were similar in the two groups of patients, it decreased markedly and significantly at short-term, and moderately increased at intermediate-term (in the derivation sample: 9952.9 ± 2137.7 → 6980.6 ± 1152.4 → 7199.4 ± 1400.5 mmHg x min^{-1}; in the validation sample: 9885.0 ± 1930.1 → 6725.4 ± 1240.7 → 7232.6 ± 1434.5 mmHg x min^{-1}). There was a significant improvement in NYHA class (in the derivation sample: 2.47 ± 0.45 → 2.06 ± 0.58 → 1.68 ± 0.47; in the validation sample: 2.53 ± 0.34 → 2.14 ± 0.48 → 1.74 ± 0.36) and in maximal exercise capacity (in the derivation sample: 49.7 ± 25.7 → 60.2 ± 27.3 → 75.9 ± 35.8 kJ; in the validation sample: 51.3 ± 28.2 → 65.9 ± 25.9 → 74.6 ± 35.2 kJ) already at short-term and further improvement was observed at intermediate-term. While the decrease in mean pulmonary capillary wedge pressure (in the derivation sample: 19.3 ± 7.5 → 16.3 ± 9.7 → 13.8 ± 7.2 mmHg; in the validation sample: 20.5 ± 8.3 → 18.1 ± 8.8 → 14.4 ± 6.4 mmHg) and the increase in left ventricular ejection fraction (in the derivation sample: 32.6 ± 6.4 →

34.2 ± 9.9 → 42.6 ± 10.1 %, in the validation sample: 30.8 ± 6.5 → 33.8 ± 9.9 → 41.6 ± 9.5 %) did not reach the level of significance at short-term, at intermediate-term beneficial changes in parameters became marked and significant.

The increase in heart rate at maximal level of exercise increased slightly in both groups at 6 months, but this increase was not considerable in either derivation or validation group (in the derivation sample: 55.5 ± 22.9 → 54.4 ± 21.3 → 58.3 ± 23.1 min^{-1}, in the validation sample: 49.3 ± 22.8 → 47.9 ± 21.4 → 54.2 ± 23.2 min^{-1}). End-systolic wall tension decreased in both groups at short-term. The change in the derivation sample was not significant, while in the validation sample it proved borderline significant. Compared to its decrease at one month the further decrease was not substantial during the later period of the observation in either group of the patients (in the derivation sample: 323.0 ± 135.0 → 271.7 ± 57.7 → 284.1 ± 162.4 mmHg, in the validation sample: 299.3 ± 64.7 → 269.8 ± 59.3 → 256.4 ± 82.9 mmHg). However, the product of end-systolic wall tension and heart rate decreased significantly and markedly already at short-term and a further decrease was observed at intermediate-term in both groups of patients (in the derivation sample: 28930.4 ± 11696.0 → 18132.4 ± 3998.2 → 17609.4 ± 9675.0 mmHg x min^{-1}, in validation sample: 27166.6 ± 6349.5 → 17843.2 ± 3982.3 → 16017.8 ± 5944.4 mmHg x min^{-1}).

Predictors of intermediate-term changes in left ventricular ejection fraction, pulmonary capillary wedge pressure, NYHA functional class and in maximal exercise capacity in the DERIVATION SAMPLE

In the derivation group of patients after six months of bisoprolol treatment the changes in the parameters to be predicted are shown in *Table 3.* (The change in NYHA class was expressed in absolute value, while the changes in other parameters were expressed as a percentage of the baseline value.)

At intermediate-term the patients were improving clinically, their NYHA functional class decreased significantly ($p<0.001$) from 2.47 to 1.68, the mean value of the decrease was 0.79 NYHA class. The clinical grade of heart failure did not improve in 5 cases, in 3 cases was unchanged and in 2 cases deteriorated.

The left ventricular ejection fraction improved significantly ($p<0.005$) from 32.6 to 42.6 %, the mean value of the increase was 37.0 % of the baseline value. However there were 8 patients whose ejection fraction did not change (the changes in the left ventricular ejection

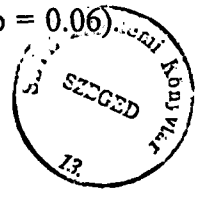
fraction were not more than 20 % of the baseline value). In the case of 3 patients deterioration was observed in the ejection fraction (i.e. the decrease in ejection fraction was more than 20 % of the baseline value).

Similarly, significant changes were seen in the mean pulmonary capillary wedge pressure; it decreased from 19.3 to 13.8 mmHg ($p<0.005$), as well as in the maximal exercise capacity, which increased from 49.7 to 75.9 kJ ($p<0.001$). The mean value of the decrease in pulmonary capillary wedge pressure was 28.8 % and the mean value of the increase in maximal exercise capacity was 73.6 % of their baseline values. However, there were non-responders in regard to the latter parameters as well. The pulmonary capillary wedge pressure increased more than 20 % compared to baseline in one patient and was considered unchanged in 8 patients (i.e. the changes in pulmonary capillary wedge pressure were not more than 20 % of baseline value). The maximal exercise capacity was unchanged in 8 patients (i.e. the changes were not more than 20 % of the baseline value).

Table 4 lists the results of the univariate regression analysis in the derivation sample. For each parameter to be predicted we have indicated only the predictive variables which showed significant or borderline significant ($p < 0.1$) relation to them.

Table 4 shows that the intermediate-term change in the ***left ventricular ejection fraction*** in terms of the percent of baseline value was shown to be in significant relation to the baseline value of left ventricular ejection fraction ($r = -0.57$, $p < 0.05$) and in borderline significant relation to the short-term changes of pulse pressure ($r = -0.41$, $p = 0.1$) and that of the pressure-rate product ($r = -0.41$, $p = 0.1$). This correlation suggests that in treating patients with bisoprolol on intermediate-term the lower the baseline value of left ventricular ejection fraction and the greater the short-term decrease in the pulse pressure and pressure-rate product, the more marked the improvement that can be expected in left ventricular ejection fraction.

The baseline value of end-systolic wall tension and the short-term changes in mean pulmonary capillary wedge pressure proved to be significant univariate predictors ($r = -0.56$, $p < 0.05$; $r = 0.52$, $p < 0.05$, respectively) of the intermediate-term changes of ***mean pulmonary capillary wedge pressure***. A borderline significant correlation could be demonstrated between the intermediate-term changes in mean pulmonary capillary wedge pressure and the baseline values of the product of the end-systolic wall tension and heart rate ($r = -0.50$, $p = 0.06$), and the short-term changes in the end-systolic wall tension ($r = 0.46$, $p = 0.08$) and that of the product of end-systolic wall tension and heart rate ($r = 0.49$, $p = 0.06$).



Accordingly, the greatest improvement in mean pulmonary capillary wedge pressure after 6 months of bisoprolol treatment can be expected in cases where the baseline value of the end-systolic wall tension, and the product of end-systolic wall tension and heart rate is high, and the short-term decrease of mean pulmonary capillary wedge pressure, end-systolic wall tension and the product of end-systolic wall tension and heart rate is pronounced.

Alteration in ***NYHA functional class*** was predictable from its baseline value ($r = -0.66$, $p < 0.005$) and from the baseline value of the resting heart rate ($r = -0.58$, $p < 0.05$). So the chance of improvement in NYHA class at intermediate-term is the greatest when heart failure is more severe and when heart rate is high at baseline.

The intermediate-term changes of the ***maximal exercise capacity*** correlated significantly with the baseline value of NYHA functional class ($r = 0.57$, $p < 0.05$), maximal exercise capacity ($r = -0.56$, $p < 0.05$) and mean pulmonary capillary wedge pressure ($r = 0.55$, $p < 0.05$). Accordingly the higher the baseline value of NYHA functional class and mean pulmonary capillary wedge pressure, and the lower the baseline value of maximal exercise capacity the more marked the improvement in maximal exercise capacity at intermediate-term.

The results of the multiple regression analysis are shown in *Table 5.*

The baseline value of left ventricular ejection fraction ($B = -3.001$, $p = 0.002$), and the short-term decrease in the pressure-rate product ($B = -0.0099$, $p = 0.012$) were found to be independent predictors of intermediate-term changes of ***left ventricular ejection fraction.*** Accordingly, the lower the left ventricular ejection fraction at baseline and the more pronounced the decrease in the pressure-rate product at short-term the more considerable the improvement in the left ventricular ejection fraction at intermediate-term.

Based on these data, in an individual patient the predicted changes of left ventricular ejection fraction after 6 months of treatment with bisoprolol could be calculated by the following equation: $\mathbf{\Delta LVEF\%} = 105.558 - 3.001 \times \mathbf{LVEF}^{a} - 0.0099 \times \mathbf{\Delta PRP}^{b}$ (abbreviations used are indicated in *Table 5*).

The change in the ***mean pulmonary capillary wedge pressure*** related significantly only to the short-term change in mean pulmonary capillary wedge pressure ($B = 2.400$, $p = 0.046$). This means that the more marked the decrease in the mean pulmonary capillary wedge pressure at short-term the more pronounced the improvement in the mean pulmonary capillary wedge pressure at intermediate-term.

The value of intermediate-term change in the mean pulmonary capillary wedge pressure in an individual patient could be predicted by the following equation: **ΔmPCW%** = -21.319 + 2.400 x **mPCW**[b] (abbreviations used are indicated in *Table 5*).

When the multivariate analysis was applied to the prediction of intermediate-term change in ***NYHA functional class***, the baseline value of heart rate (B = -0.014, p = 0.072), and that of NYHA functional class (B = -0.692, p = 0.021) proved to be an independent predictor. Thus the higher the baseline value of heart rate and the more severe the clinical condition of the patient at baseline the more substantial the improvement in NYHA functional class at intermediate-term.

The equation for the calculation of intermediate-term changes in NYHA functional class in an individual subject was the following: **ΔNYHAclass** = 2.164 – 0.014 x **HR**[a] – 0.692 **NYHAclass**[a] (abbreviations used are indicated in *Table 5*).

According to the result of the multiple regression analysis, the baseline value of maximal exercise capacity (B = -1.159, p = 0.138) and that of NYHA functional class (B = 68.427, p = 0.125) proved to be independent predictors of intermediate-term change in ***maximal exercise capacity***. This means that the lower the baseline value of maximal exercise capacity and the more severe the clinical condition characterised by NYHA functional class at baseline, the more marked the improvement in maximal exercise capacity at intermediate-term.

The following equation determined the intermediate-term change in maximal exercise capacity in an individual patient: **ΔMEC%** = -37.802 + 68.427 x **NYHAclass**[a] – 1.159 x **MEC**[a] (abbreviations used are indicated in *Table 5*).

The data described formerly show, that in the derivation sample we could find simple, non-invasive, routinely used variables which can predict the 6 months changes in parameters of crucial importance during bisoprolol treatment before the introduction of the drug or shortly after.

To control the predictive model we used, the predicted values of the parameters (outcome events) were determined for each patient of the derivation group applying the above-mentioned equations. In a next step predicted and observed values of these parameters were compared and sensitivity, specificity, positive and negative predictive accuracy of the predictive model was tested (*Table 6*).

Outstandingly high sensitivity (100 %) and negative predictive accuracy (100 %) was found in the case of ***left ventricular ejection fraction***. That the sensitivity is one hundred percent means that the applied predictive model could predict the improvement in left ventricular ejection fraction for all patients whose left ventricular ejection fraction really improved after 6 months of bisoprolol treatment. That the negative predictive accuracy is one hundred percent means that the left ventricular ejection fraction in all patients whose left ventricular ejection fraction was predicted to be unchanged or deteriorated was really unchanged or deteriorated at the end of 6 months of treatment. In addition to the outstandingly high value of sensitivity and negative predictive accuracy, acceptable specificity (66.7 %) and positive predictive accuracy (80 %) were found as well. When predicting the intermediate-term change in left ventricular ejection fraction a mistake in prediction occurred in only 3 cases (total error rate: 13 %), when instead of not improvement an improvement was predicted. Thus the predictive model applied in this study makes possible reliable prediction concerning left ventricular ejection fraction.

The close correlation ($r = 0.76$, $p < 0.001$) between observed and predicted changes in left ventricular ejection fraction at 6-month therapy with bisoprolol in the derivation group of patients is illustrated in *Figure 1/a.*

In the case of ***mean pulmonary capillary wedge pressure*** we could calculate high sensitivity (85.7 %), acceptable specificity (66.7 %), high positive predictive accuracy (80 %) and a little lower negative predictive accuracy (75 %). That the positive predictive accuracy is 80 % means that the mean pulmonary capillary wedge pressure of 80 % of patients whose mean pulmonary capillary wedge pressure was predicted to be improved by our predictive model really improved at 6-month bisoprolol treatment. That the negative predictive accuracy is 75 % means that in 75 % of patients whose mean pulmonary capillary wedge pressure was predicted to be unchanged or deteriorated the observed value of mean pulmonary capillary wedge pressure was really unchanged or deteriorated after intermediate-term treatment with bisoprolol. Although this can be regarded as quite good prediction (total error rate: 21.7 %), nevertheless we have to be cautious when our therapeutical decision is based on this prediction.

The moderate correlation ($r = 0.52$, $p < 0.05$) between predicted and observed changes in pulmonary capillary wedge pressure at 6-month of bisoprolol treatment in derivation sample is showed in *Figure 2/a.*

As for ***NYHA functional class***, specificity was 100 %, accordingly positive predictive accuracy was also 100 %, sensitivity was 83.3 % and negative predictive accuracy was 62.5

%. This means that false positive cases were not found. Thus all 15 patients whose clinical condition was predicted to improve really improved after 6 months of bisoprolol therapy, while of the patients whose clinical status was predicted not to improve, 5 really deteriorated or were unchanged, but 3 patients improved.

The predictive model applied in this study makes reliable prediction possible concerning NYHA functional class. This accuracy is similar but different in meaning from that found in the case of left ventricular ejection fraction. The total error rate was only 13 %.

After 6-month therapy with bisoprolol the close correlation ($r = 0.74$, $p < 0.001$) between observed and predicted changes of NYHA functional class can be seen in *Figure 3/a.*

In the case of ***maximal exercise capacity*** there was found an acceptable sensitivity (80 %), a very low specificity (25 %), a moderate positive predictive accuracy (66.7 %), and a low negative predictive accuracy (40 %). This means that the prediction of the improvement of maximal exercise capacity was accurate enough, meanwhile the prediction of the no improvement proved to be fairly uncertain. As a consequence in the case of 9 out of 23 patients the intermediate-term changes in maximal exercise capacity were predicted inaccurately, the total error rate was 39 %.

In the derivation group of patients the moderate correlation ($r = 0.66$, $p < 0.001$) between observed and predicted changes in maximal exercise capacity at 6-month treatment with bisoprolol is demonstrated in *Figure 4/a.*

Prospective validation

In patients of the validation sample, before the introduction of bisoprolol and 1 month later the expected 6 months changes in every outcome parameter (left ventricular ejection fraction, mean pulmonary capillary wedge pressure, NYHA functional class, maximal exercise capacity) were predicted by equations derived from multiple regression analysis in the derivation sample. After 6 months the predicted and observed changes in investigated parameters were compared.

The results derived from the validation sample were similar to those obtained from the derivation sample.

Regarding the ***left ventricular ejection fraction*** we did find high sensitivity (91.7 %), moderate specificity (70 %), good positive predictive accuracy (78.6 %), and high negative predictive accuracy (87.5 %). This means that of the patients whose left ventricular ejection fraction was predicted not to improve, the left ventricular ejection fraction of 7 out of 8

patients really deteriorated or were unchanged, while 11 out of 14 patients whose left ventricular ejection fraction was predicted to improve it really improved. This is regarded as good prediction concerning both the improvement and particularly the no improvement; these results are similar to those found in the derivation sample.

In the validation sample the close correlation ($r = 0.73$, $p < 0.001$) between observed and predicted changes in left ventricular ejection fraction after 6 month treatment with bisoprolol is illustrated in *Figure 1/b.*

In the case of ***mean pulmonary capillary wedge pressure***, sensitivity was 84.6 %, specificity was 66.7 %, positive predictive accuracy was 78.6 %, and negative predictive accuracy was 75 %. This means that in 75 % of the patients whose mean pulmonary capillary wedge pressure was predicted not to improve it really deteriorated or were unchanged, while 11 out of 14 patients whose mean pulmonary capillary wedge pressure was predicted to improve the mean pulmonary capillary wedge pressure really improved. Accordingly, the 6-month changes in pulmonary capillary wedge pressure in the validation sample could be predicted adequately by the prediction rule derived from the derivation sample. But accuracy of prediction was lower than in the case of left ventricular ejection fraction.

The moderate ($r = 0.62$, $p < 0.01$) correlation between observed and predicted changes in pulmonary capillary wedge pressure during 6-month bisoprolol therapy in the validation group of patients can be seen in *Figure 2/b.*

The reliable predictability of the 6 months changes in ***NYHA functional class*** is reflected by the high value of the sensitivity (82.4 %) and specificity (80 %). The positive (93.3 %) and negative predictive accuracy (57.1 %) shows that this predictive model is applicable much more reliably to identify the patients whose clinical condition will improve.

Figure 3/b shows the close correlation ($r = 0.73$, $p < 0.001$) between observed and predicted changes in NYHA functional class at 6-month treatment with bisoprolol in the validation sample.

As for ***maximal exercise capacity*** there were good sensitivity (75 %) and positive predictive accuracy (75 %), however both the specificity and negative predictive accuracy were only 33.3 %. This means that the predictability of the no improvement in maximal exercise capacity is quite uncertain, similarly to what was found in the derivation sample.

Moderate correlation ($r = 0.65$, $p < 0.01$) between observed and predicted changes in maximal exercise capacity during 6-month therapy with bisoprolol in the validation group of patients was illustrated in *Figure 4/b.*

Discussion

Using beta-adrenergic blockers in the treatment of chronic heart failure is one of the largest breakthroughs in cardiology in recent decades. While until recently, beta blockers were considered contraindicated for use in patients with heart failure, now these drugs are one of the most important tools in the treatment of heart failure. Beta receptor blocker therapy represents the substantial change in our approach to therapy. Nowadays the aim of the treatment of heart failure is not to obtain short-term success with the rapid correction of haemodynamic condition but to influence beneficially the prognosis of heart failure by favourable alteration the biological properties of the failing heart, even at the expense of short-term deterioration of the haemodynamic condition.

The acute pharmacological effects of β-blocking agents are completely different from their long-term effect. While the beta blockers can cause progression in the symptoms of heart failure and deterioration in left ventricular function at short-term, they can produce considerable symptomatic, haemodynamic and survival benefit at long-term. The rapid blockade of adrenerg mechanisms supporting heart function can be held responsible for unfavourable acute effects of these drugs. The favourable influence on the cardiomyocytes by discontinuing or decreasing the harmful effect of the chronically elevated sympathetic tone can be the background of the long-term benefit. The gradual improvement in contractility (36) and in left ventricular ejection fraction demonstrated by several investigators (3,5,11,13,20) can be explained by this beneficial biological effect on cardiomyocytes prevention of cell loss and restoration of cell function. Nowadays more and more evidence indicates that β-blockade improves not only the systolic but the diastolic left ventricular function (36) as well.

It is not surprising that the improvement in left ventricular function is in close connection with the survival benefit of beta blockers (3,5,12,20,23). Several data suggest that a beneficial survival effect of beta adrenoreceptor blocker can be experienced only in patients whose left ventricular function, particularly left ventricular ejection fraction improves and where the reverse remodelling appears (5,20). Reverse remodelling occurs primarily through a decrease in left ventricular end-systolic diameter and it is characteristic almost exclusively of beta blockers.

Carvedilol in the MOCHA trial (23) produced a dose-related increase in left ventricular ejection fraction and it was associated with near mirror-image reduction of mortality. A similar association was reported previously in a smaller study: the change in the left ventricular ejection fraction appeared to be a valuable parameter in defining the prognosis of patients with dilated

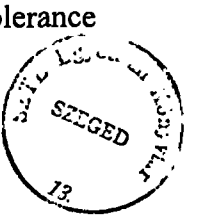
cardiomyopathy treated with metoprolol (5). Moreover, the substudy of 160 patients from the Cardiac Insufficiency Bisoprolol Study population showed that long-term mortality increased for subjects whose left ventricular fractional shortening decreased over 5 months if patients were treated with bisoprolol (20).

Consequently, the early identification of patients whose left ventricular ejection fraction will not improve during beta blocker therapy seems to be of great importance.

Although data regarding the predictive value for long-term outcome of heart failure are so far available only for the intermediate-term alteration in left ventricular ejection fraction (20,23), it appears to be well established that the intermediate-term change of other essential parameters such as the mean pulmonary capillary wedge pressure, and at least in treatment with cardioselective beta blockers, NYHA functional class and maximal exercise capacity can have an importance in the prediction of final outcome as well. The deterioration of these latter parameters in spite of 6 months of therapy raises doubt concerning the beneficial effect of the given drug on long-term prognosis of heart failure. That is why elaborating methods not only for prediction of intermediate-term changes of left ventricular ejection fraction may have clinical significance.

In our follow-up, in both the derivation and validation group of patients the changes of the parameters characterising clinical and haemodynamic condition and left ventricular function during bisoprolol therapy were consistent with the previous favourable observations from uncontrolled and controlled studies in chronic heart failure (1-4,11-12,20,21,27,37-39). As regards the intermediate-term changes of the four essential parameters which were to be predicted, the use of bisoprolol led to improvement in clinical symptoms, increased left ventricular ejection fraction and maximal exercise capacity and decreased mean pulmonary capillary wedge pressure. It is noteworthy that some tendency of improvement was already seen in the case of almost every investigated parameter at short-term. The beneficial haemodynamic effect associated with marked decrease in heart rate (91 $\rightarrow$ 67 min^{-1} in the derivation sample and 93 $\rightarrow$ 67 min^{-1} in the validation group of patients) from its high baseline value and possibly the aggressive pre-study vasodilator treatment can provide explanations. However, there was a further improvement in all of the previous parameters at the 6 months analysis.

With one exception, patients in both validation and derivation group tolerated the initiation and the maintenance of the treatment with bisoprolol. The low percent of intolerance



observed in our study can reflect the generally moderate grade of heart failure and the careful pre-study optimisation of vasodilator and diuretic treatment.

In the derivation sample one patient died suddenly at the beginning of the titration phase. In the validation group one patient died due to progression of heart failure after the titration period, in the first month of the maintenance phase of the treatment.

Predictors of intermediate-term change in left ventricular ejection fraction

Improvement in left ventricular ejection fraction has consistently been reported after treatment with beta blockers in patients with heart failure (4,7,11,13,20,40). Moreover, that improvement proved to be dose-related: greater benefit was produced by higher dosages of beta blockers (20,39,40). Baseline left ventricular ejection fraction evaluated by radionuclide ventriculography (41) and its intermediate-term changes after different drug therapy were found to be significant predictors of the final outcome of chronic heart failure (4,12,20,23,42,43).

The short-term change in pressure-rate product and baseline value of left ventricular ejection fraction proved to be significant multivariate predictors of intermediate-term change of left ventricular ejection fraction in our study. The greater the short-term decrease in the pressure-rate product and the lower the value of the left ventricular ejection fraction at baseline, the more positive the response to bisoprolol.

The short-term decrease in pressure-rate product reflects the short-term decrease of heart rate and systolic blood pressure. While the heart rate at baseline indicates the extent of sympathetic activity, the short-term decrease in heart rate and systolic blood pressure shows the decrease in sympathetic drive that can be achieved by short-term administration of beta blocker. The overwhelming predictive value of the short-term decreases in pressure-rate product may indicate that the patients with higher reduction of sympathetic drive at short-term react more favourably to beta blocker therapy. Considerable decrease in pressure-rate product accompanies pronounced decrease in myocardial oxygen demand and reduction of the chronic energy depletion of cardiomyocytes in heart failure. The more complete restoration of the energy balance can presumably influence the long-term prognosis beneficially.

The progressively higher degree of sympathetic activation when the left ventricular dysfunction is more pronounced (44) can explain why the positive impact of beta-blocker treatment is higher in patients with more deteriorated left ventricular ejection fraction.

Many investigators have observed that patients with very low (14,19,21) and nearly normal (21) left ventricular ejection fraction do not respond optimally to beta blocker treatment. The explanation of these observations may be that in the patients with considerably impaired left ventricular function the amount of viable myocytes is too low for the manifestation of the beneficial effect (27). On the other hand the nearly normal ejection fraction may be accompanied by only slightly elevated sympathetic activation.

The close correlation observed in our study between the left ventricular ejection fraction at baseline and the 6 months changes in this parameter can be explained on the one side by the absence of patients with very low and on the other by nearly normal left ventricular ejection fraction. The values of left ventricular ejection fraction at baseline were ranged between 20 and 40 %.

A less severe grade of heart failure, more aggressive vasodilator treatment and the absence of patients with elevated systolic blood pressure (the values of the systolic blood pressure at baseline in the derivation group of patients were ranged between 80 and 135 mmHg) can explain why, unlike some other observations (21,26), the systolic blood pressure did not show any predictive value in our study.

Exclusion of patients with heart rate lower than 70 beats/min may explain why, in disagreement with earlier metoprolol studies (24,25), we did not find the baseline heart rate to be predictive regarding left ventricular ejection fraction. Similar results were obtained from CIBIS I and CIBIS II studies by Lechat et al. (20,45). But it is known that only patients whose heart rate was higher than 65/min were included in the CIBIS studies.

In our own previous study (28), where patients' baseline parameters reflected more severe clinical condition and the therapy applied differed from the therapy given in this study, in addition to the baseline value of left ventricular ejection fraction and short-term change in the pressure-rate product, the short-term change in the pulse amplitude proved to be a significant predictive factor, as well. This latter parameter proved not to be predictive in this study by multiple regression analysis but it was a borderline significant predictor by univariate regression analysis.

Predictors of intermediate-term change in mean pulmonary capillary wedge pressure

Mean pulmonary capillary wedge pressure is mainly determined by the left ventricular diastolic function, however, in chronic heart failure frequently occurring mitral regurgitation is also an important determinant.

Similarly to observations with other beta blockers (7,13,18), mean pulmonary capillary wedge pressure decreased after intermediate-term treatment with bisoprolol in our study.

The mean pulmonary capillary wedge pressure has been repeatedly reported as a significant predictor of outcome of chronic heart failure in the effect of different drug therapy (39,42,46,47). Results of those studies showed that the higher the value of mean pulmonary capillary wedge pressure, the worse the long-term prognosis of chronic heart failure. Generally, the therapy decreasing the pathologically high mean pulmonary capillary wedge pressure improves the prognosis, too (48,49).

Concerning the as yet not demonstrated predictive value of intermediate-term change of mean pulmonary capillary wedge pressure for long-term outcome during treatment with a beta blocker, it is a reasonable presumption that the gradual decrease in mean pulmonary capillary wedge pressure can be the consequence of the same positive biological effect of beta blockers on cardiomyocytes which favourably affects the survival of the patients as well.

To date, only one study (26) has attempted to determine which patients have the highest diastolic function improvement with beta blockade. In this investigation the baseline left ventricular end-diastolic pressure was an independent predictor of change of left ventricular end-diastolic pressure. In other studies, mean pulmonary capillary wedge pressure or variables closely related to it were only components of complex improvement indexes (11,21).

According to our earlier data (28) the six-month effect of bisoprolol on mean pulmonary capillary wedge pressure related positively to the baseline value of mean pulmonary capillary wedge pressure and heart rate and negatively to the increase in heart rate during maximal exercise.

In this study treating patients with bisoprolol the intermediate-term change in mean pulmonary capillary wedge pressure could be predicted from its short-term change. The positive correlation obtained shows, that a higher decrease in mean pulmonary capillary wedge pressure at short-term goes together with more pronounced decrease in mean pulmonary capillary wedge pressure at intermediate-term. Not easy to explain this finding. One can speculate that longer-term positive effect in respect of mean pulmonary capillary wedge pressure can be awaited if the well known immediate effect of beta blockers, such the reduction of heart rate and decrease in the

myocardial ischaemia, affect the mean pulmonary capillary wedge pressure positively already in the early phase of treatment. The substantial reduction in a high heart rate can result in several favourable changes already at short-term: it decreases myocardial ischaemia, improves the left ventricular diastolic relaxation, enhances the contractility and ejection performance of the myocardium.

It is worth noting, that in our study the mean pulmonary capillary wedge pressure decreased already at 1 month treatment with bisoprolol. This early positive effect can be attributed at least partly to such immediate pharmacological effect as the heart rate reducing property of the beta blockers.

The early decrease in mean pulmonary capillary wedge pressure indicating reduction the left ventricular wall tension and going together with improvement in myocardial oxygen balance may have a role in the later appearing beneficial alteration of cardiomyocytes.

Adding this early positive haemodynamic effect to the later appearing beneficial biologic effect on the cardiomyocytes can result in greater decrease in mean pulmonary capillary wedge pressure at intermediate-term treatment of patients.

Predictors of intermediate-term changes in NYHA functional class

There are numerous reports, coinciding with the clinical experiences, which verify that the clinical grade of heart failure (NYHA class) is predictive for the long-term outcome of chronic heart failure (46,47,50). Treatment, with the exception of positive inotropes, decreasing the clinical grade of heart failure increases the chance of survival of the patients as well.

The intermediate-term effect of beta blockers on NYHA class seems to be different according to their cardioselectivity. Contrary to the consistently recorded benefit when treating patients with cardioselective drugs (4,11,12,39), in the intermediate-term effect of non-selective preparations the improvement in NYHA class is less common and more moderate (16,40). The beneficial effect of bisoprolol recorded in our study is in accord with the effect of other cardioselective beta blockers. The time course of the change of NYHA class, the gradually appearing benefit is consistent with the theory that the favourable clinical effect is the manifestation of the positive biological effect of the drug on cardiomyocytes. This positive biological effect becomes evident gradually as the improvement in parameters characterising haemodynamic condition, left ventricular function and global clinical state.

Baseline NYHA class and heart rate were found to be valuable predictors of the intermediate-term changes in NYHA functional class by univariate and multiple regression analysis.

The higher sympathetic activity, when the clinical grade of heart failure is more severe and the heart rate is high, and the observation that the effect of beta-blockers (such as bisoprolol) is more pronounced in the case of high sympathetic activity before beta blocker therapy, can be an acceptable explanation for the predictive value of the above parameters. According to the results of some studies, less benefit can be expected if heart failure is more severe (19,21). In this respect it is important to emphasise that patients included in our study had symptoms corresponding to class II or III of the New York Heart Association.

Predictors of intermediate-term change in maximal exercise capacity

Maximal exercise capacity has predicted the final outcome in chronic heart failure in many studies (47,51,52,53). Drug treatment with favourable effect on long-term outcome, not causing neuroendocrine activation, mostly increases exercise capacity as well. Although the effect of beta blockers on maximal exercise capacity, particularly the effect of non-selective preparations, can dissociate from the beneficial effect on the left ventricular function. Contrary to our positive result, bisoprolol did not increase symptom-limited exercise capacity in one study (48). The lack of effect of beta blockers on symptom-limited exercise capacity despite benefit on left ventricular function can be explained by the beta blockade-induced limitation of the heart rate and the cardiac index at maximal exercise. This effect is the most pronounced when using non-selective drugs causing complete beta blockade. The data on the effect of cardioselective beta-blockers on maximal exercise capacity are contradictory (11,12).

Our uncontrolled data showed that the intermediate-term treatment with bisoprolol considerably improved the maximal exercise capacity. The explanation for this can be the increase of heart rate reserve in spite of the lower heart rate at maximal level of exercise, improvement of left ventricular systolic and diastolic function and the absence of blockade of β_2 receptors in the peripheral arteries.

In our study the intermediate-term change in maximal exercise capacity could be closely predicted from the baseline value of the maximal exercise capacity and NYHA functional class. The higher the value of the NYHA class and the lower the value of the maximal

exercise capacity at baseline, the more beneficial the effect of bisoprolol can be expected on maximal exercise capacity at intermediate-term.

The more favourable beta blocker effect when the sympathetic activation is high can explain that observation. More severe heart failure and more decreased maximal exercise capacity can indicate patients with higher sympathetic activity.

Applicability of the predictive model, prospective validation

In our study the predictive model elaborated to predict the 6 months effect of bisoprolol on left ventricular ejection fraction, mean pulmonary capillary wedge pressure, NYHA functional class and maximal exercise capacity seems to be particularly valuable regarding prediction of the changes in left ventricular ejection fraction and NYHA functional class. This is indicated by the outstandingly high negative predictive accuracy connected with the prediction of the left ventricular ejection fraction and high positive predictive accuracy connected with the prediction of NYHA functional class. Using this predictive model it seems to be possible to predict reliably the patients whose left ventricular ejection fraction will deteriorate or remain unchanged after 6 months of bisoprolol therapy. Similarly we can choose with outstanding accuracy before the introduction of bisoprolol, the patients whose clinical condition will improve during 6 months of bisoprolol treatment.

The possibility to predict reliably the patients whose ejection fraction will not improve during 6 months of bisoprolol administration can be regarded as the greatest success of the predictive model described in this paper. Previous data show that the deterioration of the left ventricular systolic function during intermediate-term (5-6 months) treatment with beta blockers is accompanied by an increase in mortality (20). Thus the reliable prediction of "no improvement" of the left ventricular ejection fraction at intermediate-term treatment with beta blocker can select accurately after short-term treatment the patients for whom the beneficial survival effect of bisoprolol will be uncertain. Accordingly, in these cases an opportunity presents to discontinue or modify the therapy with beta blockers, change to an other beta blocker (54) or to follow up these selected patients more closely.

In the validation group of patients the high value of sensitivity, specificity, positive and negative predictive accuracy in the case of left ventricular ejection fraction and NYHA functional class shows that the predictive model derived from the derivation sample is applicable to all patients characterised by the inclusion and exclusion criteria of this study.

Limitations of the study

There is a limited applicability of the results for the whole spectrum of heart failure population as only patients with dilated cardiomyopathy were studied, the clinical grade of heart failure was mostly mild to moderate, and mainly men were investigated. The number of patients in both derivation and validation sample was limited. The results need to be verified in a larger patient population including patients with more severe heart failure too and not only patients with dilated cardiomyopathy but also to ischaemic heart disease as well as enrolment of women in an adequate proportion is needed. It should also be emphasised that our observations cannot be automatically extrapolated to other beta blockers, especially to carvedilol that differs in many respects from bisoprolol.

Despite these limitations and the preliminary status of the findings, the present study can be of significance as a first step towards further investigations aiming to increase the therapeutic effectiveness of beta blockers in heart failure

Conclusions

1. The well-known, favourable effects of beta blocker therapy when treating patients with chronic heart failure, i.e. the increase in left ventricular ejection fraction, the decrease in mean pulmonary capillary wedge pressure, the improvement of NYHA functional class and maximal exercise capacity were reproducible in 48 patients with dilated cardiomyopathy treated with bisoprolol for six months.

2. By elaborating a predictive model and by validating it prospectively I was able to prove, that by application of simple, non-invasive parameters, used in the everyday clinical practice the intermediate-term (6-month) effects of bisoprolol on symptoms, on left ventricular systolic and diastolic function and maximal exercise capacity are predictable reliably.

3. The model proved to be especially reliable for the early identification of the patients whose left ventricular ejection fraction did not improve after 6 months treatment with bisoprolol. According to previous data (Lechat et al. – Circulation 1997) by this way we can select the cases in whom the long-term favourable survival effect of bisoprolol is much too questionable.

4. The model proved to be similarly reliable to identify those patients in whom the intermediate-term treatment with bisoprolol resulted in significant clinical improvement, i.e. improvement in NYHA class.

5. The predictive model elaborated in this study affords possibility the early identification of responders and non-responders to long-term bisoprolol treatment. Further investigation, closer follow up of non-responders and modification or early withdrawal of beta blocker treatment can increase the therapeutic potential of beta blocker therapy in chronic hear failure.

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Table 1. Clinical characteristics observed at baseline in the derivation and validation patient groups and their comparison

	Derivation group	**Validation group**	**p**
Age (years)	53.8 ±15.9	50.4 ±17.6	N.S.
Gender (males %)	91	95	
MEC (kJ)	49.7 ± 25.7	51.3 ± 28.2	N.S.
LVEF (%)	32.6 ± 6.4	30.8 ± 6.5	N.S.
mPCW (mmHg)	19.3 ± 7.5	20.5 ± 8.3	N.S.
NYHA class	2.47 ± 0.45	2.53 ± 0.34	N.S.
HR (min^{-1})	90.9 ± 17.0	93.4 ± 15.7	N.S.
BPs (mmHg)	110.3 ± 17.7	105.4 ± 15.5	N.S.
Therapy %			
ACE inhibitor	100	100	
Spironolactone	100	100	
Diuretic	100	100	
Digoxin	74	72	

MEC: maximal exercise capacity, LVEF: left ventricular ejection fraction, mPCW: mean pulmonary capillary wedge pressure, NYHA class: New York Herat association functional class, HR: heart rate, BPs: systolic blood pressure

N.S.: non-significant

Table 2a Effect of 6 months of bisoprolol treatment in the derivation sample

	Baseline value	**After 1 month of treatment**	**After 6 months of treatment**
HR (min^{-1})	90.9 ± 17.0	67.2 ± 9.4[a]	62.6 ± 10.6[a]
BPs (mmHg)	110.3 ± 17.7	104.1 ± 11.2 N.S.	118.8 ± 13.6[d]
PP (mmHg)	35.6 ± 8.5	33.5 ± 9.3 N.S.	42.4 ± 11.1[b]
PRP (mmHg x min^{-1})	9952.9 ± 2137.7	6980.6 ± 1152.4[a]	7199.4 ± 1400.5[a]
LVEF (%)	32.6 ± 6.4	34.2 ± 9.9 N.S.	42.6 ± 10.1[a]
mPCW (mmHg)	19.3 ± 7.5	16.3 ± 9.7 N.S.	13.8 ± 7.2[b]
NYHA class	2.47 ± 0.45	2.06 ± 0.58[a]	1.68 ± 0.47[a]
MEC (kJ)	49.7 ± 25.7	60.2 ± 27.3[d]	75.9 ± 35.8[a]
ΔHRmax (min^{-1})	55.5 ± 22.9	54.4 ± 21.3 N.S.	58.3 ± 23.1 N.S.
ESWT (mmHg)	323.0 ± 135.0	271.7 ± 57.7 N.S.	284.1 ± 162.4[d]
ESWT x HR (mmHg x min^{-1})	28930.4 ± 11696.0	18132.4 ± 3998.2[b]	17609.4 ± 9675.0[a]

[a] $p < 0.001$

[b] $p < 0.005$

[c] $p < 0.01$

[d] $p < 0.05$

N.S.: non-significant

HR: heart rate, BPs: systolic blood pressure, PP: pulse pressure, PRP: pressure-rate product, LVEF: left ventricular ejection fraction, NYHA class: New York Heart Association functional class, MEC: maximal exercise capacity, ΔHRmax: the increase in heart rate from rest to maximal level of exercise, ESWT: end-systolic wall tension, ESWT x HR: the product of end-systolic wall tension and heart rate

Table 2b. Effect of 6 months of bisoprolol treatment in the validation group

	Baseline value	**After 1 month of treatment**	**After 6 months of treatment**
HR (min^{-1})	93.4 ± 15.7	66.9 ± 10.8[a]	65.5 ± 11.2[a]
BPs (mmHg)	105.4 ± 15.5	100.8 ± 9.3 N.S.	114.5 ± 16.2[d]
PP (mmHg)	30.3 ± 8.9	31.4 ± 10.1 N.S.	40.9 ± 10.4[c]
PRP (mmHg x min^{-1})	9885.0 ± 1930.1	6725.4 ± 1240.7[a]	7232.6 ± 1434.5[a]
LVEF (%)	30.8 ± 6.5	33.8 ± 9.9 N.S.	41.6 ± 9.5[a]
mPCW (mmHg)	20.5 ± 8.3	18.1 ± 8.8 N.S.	14.4 ± 6.4[a]
NYHA class	2.53 ± 0.34	2.14 ± 0.48[a]	1.74 ± 0.36[a]
MEC (kJ)	51.3 ± 28.2	65.9 ± 25.9[d]	74.6 ± 35.2[a]
ΔHRmax (min^{-1})	49.3 ± 22.8	47.9 ± 21.4 N.S.	54.2 ± 23.2 N.S.
ESWT (mmHg)	299.3 ± 64.7	269.8 ± 59.3[d]	256.4 ± 82.9[d]
ESWT x HR (mmHg x min^{-1})	27166.6 ± 6349.5	17843.2 ± 3982.3[a]	16017.8 ± 5944.4[a]

[a] $p < 0.001$

[b] $p < 0.005$

[c] $p < 0.01$

[d] $p < 0.05$

N.S.: non-significant

HR: heart rate, BPs: systolic blood pressure, PP: pulse pressure, PRP: pressure-rate product, LVEF: left ventricular ejection fraction, NYHA class: New York Heart Association functional class, MEC: maximal exercise capacity, ΔHRmax: the increase in heart rate from rest to maximal level of exercise, ESWT: end-systolic wall tension, ESWT x HR: the product of end-systolic wall tension and heart rate

Table 3. Effect of 6 months of bisoprolol treatment on the parameters to be predicted in the derivation group

	Baseline value	**After 6 months of bisoprolol treatment**	**Change after 6 months of bisoprolol treatment***	**P<**
NYHA class	2.47 ±0.45	1.68 ± 0.47	-0.79 ± 0.61	0.001
LVEF	32.6 ± 6.4 %	42.6 ± 10.1 %	37.0 ± 42.8 %	0.001
mPCW	19.3 ± 7.5 mmHg	13.8 ± 7.2 mmHg	-28.8 ± 33.6 %	0.005
MEC	49.7 ± 25.7 kJ	75.9 ± 35.8 kJ	73.6 ± 78.4 %	0.001

(* The change after 6 months of bisoprolol treatment in NYHA class was expressed in absolute value, while the changes in left ventricular ejection fraction, mean pulmonary capillary wedge pressure and maximal exercise capacity were expressed as a percentage of the baseline value.)

NYHA class: New York Heart Association functional class, LVEF: left ventricular ejection fraction, mPCW: mean pulmonary capillary wedge pressure, MEC: maximal exercise capacity

Table 4. Results of the univariate regression analysis

Variable to be predicted	Predictor parameter	r	p
ΔLVEF %	LVEF[a]	-0.570	0.017
	PP[b]	-0.413	0.100
	PRP[b]	-0.409	0.100
ΔmPCW %	ESWT[a]	-0.556	0.031
	mPCW[b]	0.522	0.046
	ESWT x HR[a]	-0.498	0.059
	ESWT[b]	0.463	0.082
	ESWT x HR[b]	0.491	0.063
ΔNYHA class	NYHA class[a]	-0.656	0.004
	HR[a]	-0.579	0.015
ΔMEC %	NYHA class[a]	0.571	0.021
	MEC[a]	-0.564	0.023
	mPCW[a]	0.552	0.041

[a] Baseline values

[b] Short-term changes (differences between the values of the parameters at short-term bisoprolol treatment and at baseline)

r: coefficient of correlation

ΔLVEF %: the change in left ventricular ejection fraction at intermediate-term expressed as a percentage of baseline value, ΔmPCW %: the change in mean pulmonary capillary wedge pressure at intermediate-term expressed as a percentage of baseline value, ΔNYHA: the change in New York Heart Association functional class at intermediate-term expressed as an absolute value, ΔMEC %: the change in maximal exercise capacity at intermediate-term expressed as a percentage of baseline value

LVEF: left ventricular ejection fraction, PP: pulse pressure, PRP: pressure-rate product, ESWT: end-systolic wall tension, mPCW: mean pulmonary capillary wedge pressure, ESWT x HR: the product of end-systolic wall tension and heart rate, NYHA class: New York Heart Association functional class, HR: heart rate, MEC: maximal exercise capacity

Table 5. Results of multiple regression analysis

Variable to be predicted	Predictor variables	B	p	P
ΔLVEF %	LVEF[a]	-3.001	0.002	0.002
	PRP[b]	-0.0099	0.012	
ΔmPCW %	mPCW[b]	2.400	0.046	0.046
ΔNYHA class	HR[a]	-0.014	0.072	0.004
	NYHA class[a]	-0.692	0.021	
ΔMEC %	MEC[a]	-1.159	0.138	0.025
	NYHA class[a]	68.427	0.125	

[a] Baseline values

[b] Short-term changes (differences between the values of the parameters at short-term bisoprolol treatment and at baseline)

B: coefficient

ΔLVEF %: the change in left ventricular ejection fraction at intermediate-term expressed as a percentage of baseline value, ΔmPCW %: the change in mean pulmonary capillary wedge pressure at intermediate-term expressed as a percentage of baseline value, ΔNYHA: the change in New York Heart Association functional class at intermediate-term expressed as an absolute value, ΔMEC %: the change in maximal exercise capacity at intermediate-term expressed as a percentage of baseline value

LVEF: left ventricular ejection fraction, PRP: pressure-rate product, mPCW: mean pulmonary capillary wedge pressure, HR: heart rate, NYHA class: New York Heart Association functional class, MEC: maximal exercise capacity

Table 6. Sensitivity, specificity, positive and negative predictive accuracy of the predictive model **in the derivation group**

	LVEF	mPCW	NYHA class	MEC
Number of true positive cases	12	12	15	12
Number of false positive cases	3	3	0	6
Number of true negative cases	8	6	5	2
Number of false negative cases	0	2	3	3
Sensitivity (%)	100.0	85.7	83.3	80.0
Specificity (%)	66.7	66.7	100.0	25.0
Positive predictive accuracy	80.0	80.0	100.0	66.7
Negative predictive accuracy	100.0	75.0	62.5	40.0
Total error rate (%)	13.0	21.7	13.0	39.0

LVEF: left ventricular ejection fraction, mPCW: mean pulmonary capillary wedge pressure, NYHA class: New York Heart Association functional class, MEC: maximal exercise capacity

Table 7. Sensitivity, specificity, positive and negative predictive accuracy of the predictive model **in the validation group**

	LVEF	mPCW	NYHA class	MEC
Number of true positive cases	11	11	14	12
Number of false positive cases	3	3	1	4
Number of true negative cases	7	6	4	2
Number of false negative cases	1	2	3	4
Sensitivity (%)	91.7	84.6	82.4	75.0
Specificity (%)	70.0	66.7	80.0	33.3
Positive predictive accuracy	78.6	78.6	93.3	75.0
Negative predictive accuracy	87.5	75	57.1	33.3
Total error rate (%)	18.2	22.7	18.2	36.4

LVEF: left ventricular ejection fraction, mPCW: mean pulmonary capillary wedge pressure, NYHA class: New York Heart Association functional class, MEC: maximal exercise capacity

Figure 1/a

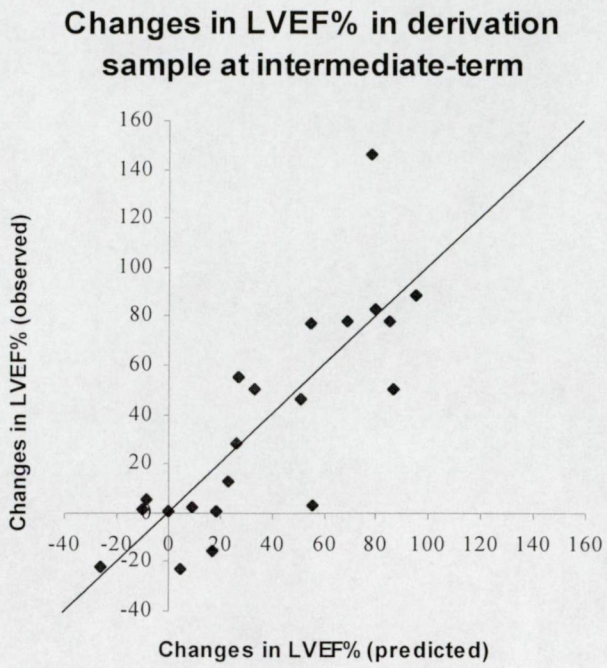

Figure 1/b

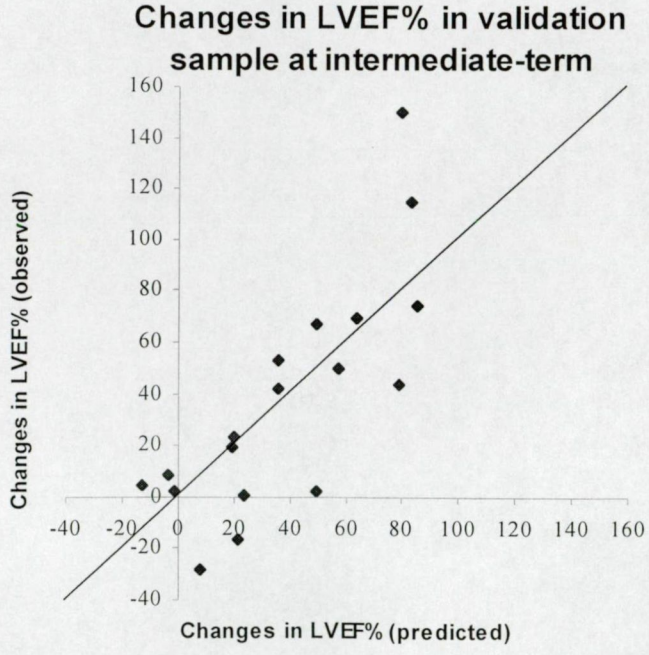

Figure 2/a

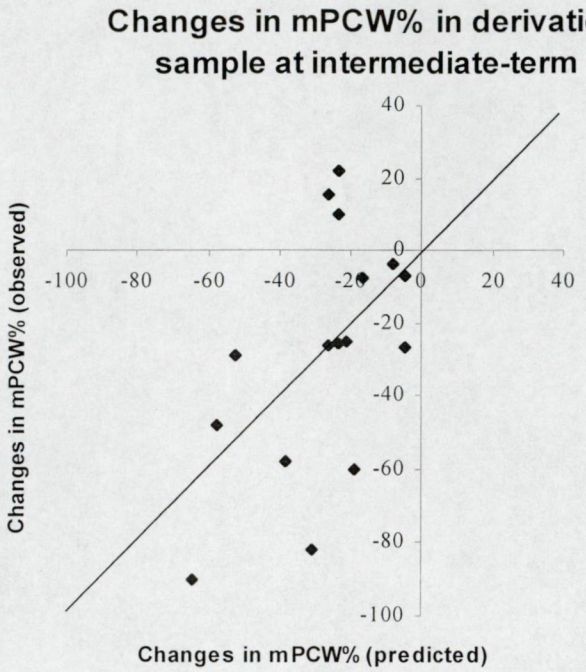

Figure 2/b

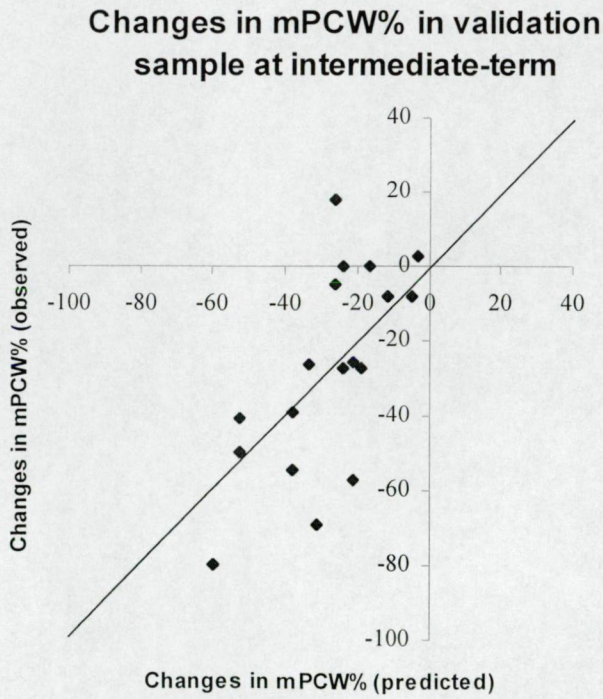

Figure 3/a

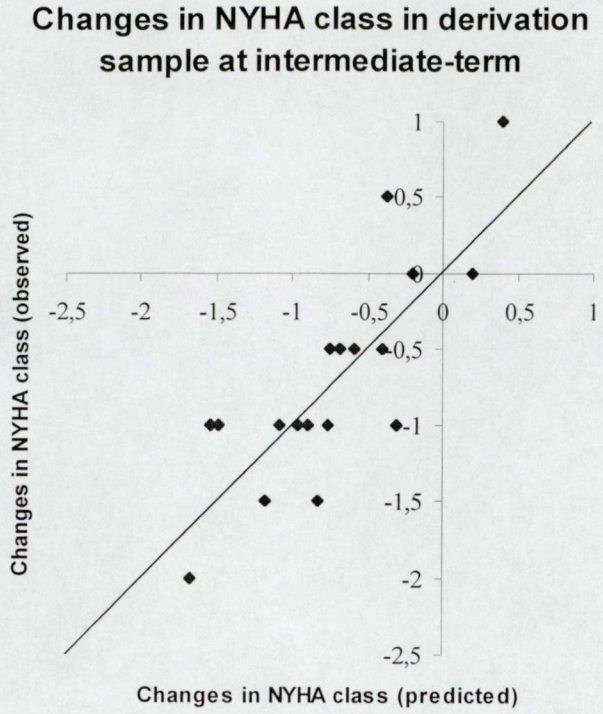

Figure 3/b

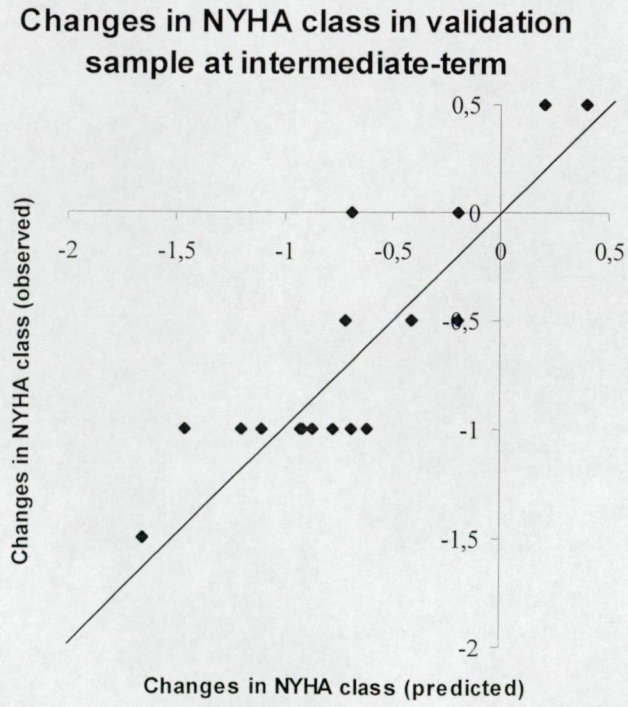

Figure 4/a

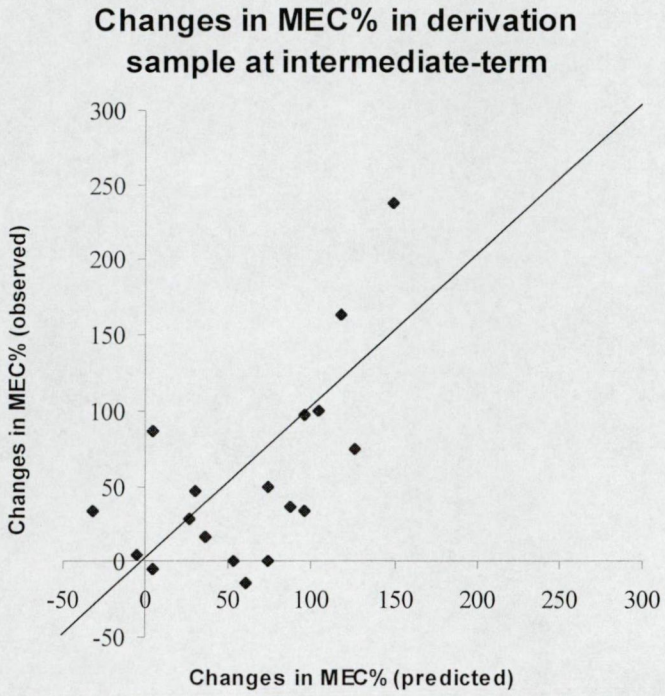

Figure 4/b