NEW CLINICAL RESULTS WITH BETA - ADRENERGIC-RECEPTOR BLOCKERS

(Hypertension, Heart failure and Post-myocardial infarction period)

Ph.D. thesis

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1. Introduction

Beta-adrenergic receptor antagonists are widely used in cardiovascular therapy. Since the early 1960s, when they were introduced for the treatment of angina pectoris and arrhythmias, there has been continuing progress in the field of beta-blockade. Numerous studies have confirmed the beneficial effects of beta-blockers in various forms of ischemic heart disease, heart failure, hypertension and a wide variety of other conditions, such as pheochromocytoma, portal hypertension, hyperkinetic heart syndrome and hyperthyroidism. The pharmacological development has had the aim of improving the $beta_1$-selectivity of the agents, and additional vasodilator activities (alpha-adrenergic receptor blockade or other mechanisms including endothelium derived nitric oxide) were recently introduced. Basically, the beta-adrenergic blocking agents differ in various aspects. Non-selective drugs block both $beta_1$- and $beta_2$-receptors, while the $beta_1$-selective drugs block primarily the cardiac and other $beta_1$-adrenoceptors. Beta-adrenergic blocking agents with other vasodilatory properties have also been introduced, such as the alpha-adrenergic receptor blocker carvedilol or the NO synthesis pathway stimulator nebivolol.

1.1. Effects of beta adrenergic-receptor blockers in hypertension

The mode of action of beta-blockers in hypertension is not fully understood. Initially, it was suggested that the decreased cardiac output is responsible for the blood pressure-lowering effect of the beta-adrenergic blocking agents. However, additional mechanisms, e.g. the inhibition of renin release, may contribute to the pressure-lowering effects, especially in the later phase of treatment. The effects of catecholamines on inotropy and renin release are mainly mediated by the $beta_1$-receptors; consequently it has been suggested that the $beta_1$-receptor selective antagonists may control hypertension more effectively than non-selective agents. Moreover, it has been hypothetized that blockade of the $beta_2$-receptors (by non-selective agents) antagonizes the vasodilatory effects of catecholamines.

Nebivolol and bisoprolol, regarded as highly $beta_1$-selective blockers, are widely used in clinical practice. However, depending on the experimental conditions, values ranging from 4 to 46 have been reported for the selectivity ratio (ratio of $beta_1$- to $beta_2$-blockade) for nebivolol in human ventricular myocardium. Furthermore, clinical

studies have demonstrated that nebivolol possesses an additional NO-mediated vasodilatory effect which was not observed for other beta-blockers (e.g. atenolol and metoprolol). Various mechanisms have been suggested to be responsible for the NO-mediated vasodilatory effect of nebivolol (partial $beta_2$-agonist effect of a metabolite and/or direct effects on the endothelial NO release), but the precise mechanism of action of this effect in humans is still not fully understood.

1.2. Beta adrenergic-receptor blockers in post-myocardial infarction patients with chronic heart failure

The results from earlier large randomized placebo-controlled trials documented that beta-blockers given to patients after acute myocardial infarction (MI) reduced total mortality by 26-36% during long-term follow-up. In these studies there was also a favorable effect reported on non-fatal re-infarction with good tolerability. Beneficial mechanisms of beta-blockers in MI and post-myocardial infarction period may include reduced myocardial oxygen consumption, antagonism of the arrhythmogenic and toxic biochemical effects of catecholamines.

In total there are today more than 50 randomized trials on beta-blockers in patients with a history of acute MI. When these studies were performed chronic heart failure (CHF) was considered a contraindication for beta-blockade. Furthermore, these studies were completed in patients not receiving contemporary therapies such as early thrombolytics, revascularization, angiotensin converting enzyme (ACE) inhibitors, statins, and aspirin. It has therefore been questioned if the effects obtained by beta-blockers in post-MI patients in the 1970s, not receiving contemporary therapy, would be of relevance today.

2. Objectives

2.1. Evaluation of the role of nitric oxide (NO) in the antihypertensive effect of cardioselective beta-blocker nebivolol

The aims of the present study were to evaluate: 1) the antihypertensive efficacy of nebivolol in comparison with bisoprolol in the treatment of mild/moderate essential hypertension, and 2) the clinical relevance of the NO-mediated vasodilatory effect of

nebivolol on clinical endpoints. Bisoprolol was chosen as the comparator because of its extensive usage (alone and in combination), its high $beta_1$ selectivity and the lack of additional vasodilatory action. We report here the results of the first clinical trial in which two highly cardioselective beta-blockers were compared.

2.2. Evaluation of the effect of metoprolol CR/XL in post-myocardial infarction patients with chronic heart failure (Experiences from MERIT-HF)

The present analysis was performed to determine 1) whether the subgroup of patients with a history of MI in the MERIT-HF trial benefited from beta-blocker therapy, 2) to analyze the subgroup of post-MI patients with a history of revascularization including percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) at randomization, and 3) also a subgroup of post-MI patients with more severe CHF defined as NYHA class III/IV and EF<0.25. In addition 4) we discuss the effects of metoprolol CR/XL in post-MI patients from MERIT-HF with symptomatic CHF, in relation to the effects observed in earlier post-MI studies with metoprolol in patients without, or with only mild CHF studied 25 years ago.

3. Patients and methods

3.1. Comparison of nebivolol with bisoprolol in hypertension

3.1.1. Study population

The patients eligible for the study had a clinical diagnosis of mild to moderate essential hypertension, were aged between 30 and 65 years and had a sitting DBP between 95 and 110 mm Hg and a SBP ≤180 mm Hg at the end of the 4-week placebo run-in period. The patients were either newly diagnosed or previously treated hypertensives who required a change of therapy in consequence of side-effects or poor compliance. Altogether, the study population consisted of 273 patients (129 males and 144 females, mean age: 49±8 years) randomized 1:1 to either 5 mg nebivolol or 5 mg bisoprolol. Conditions leading to exclusion from the study were

known secondary hypertension, malignant hypertension, congestive heart failure, myocardial infarction within the previous 12 months, contraindications for beta-blockers (i.e. atrio-ventricular conduction disturbances, a heart rate <50 beats/min, sick sinus syndrome and bronchial asthma), renal disease (serum creatinine >120 μmol/l), liver, hematological or psychiatric diseases and severe insulin-dependent diabetes mellitus. Approval for the trial was obtained both from the ethics committee at each center and from the national health authorities and all patients gave their informed consent.

3.1.2. Study design

This multicenter, single-blind, randomized, parallel-group 16-week study involved a 4-week placebo run-in, followed by a 12-week treatment period, and was carried out in Hungary and Slovakia (11 centers). The treatment consisted of 5 mg nebivolol or 5 mg bisoprolol once daily (between 8.00 and 11.00 h), except for the days of the scheduled visits, so that the blood pressure measurements of the trough effect could be obtained. The dose range was chosen on the assumption that a 5 mg oral dose of nebivolol was equivalent to a 5 mg oral dose of bisoprolol. The nebivolol used in the study was a racemic mixture of equal proportions of its d- and l-isomers (d,l-nebivolol). In studies reported before the initiation of this trial, it was assumed that the d-enantiomer is the main active form and that the l-enantiomer does not potentiate the blood pressure lowering effect. The administered dose of nebivolol (5 mg) has previously been shown to possess both an endothelium protective effect and venodilatory action. Concomitant therapy of the patients was permitted, apart from antihypertensive medication (diuretics, ACE inhibitors and calcium antagonists), drugs that affect the thyroid function, digitalis and anticoagulants. All concomitant medication (continued from the start or administered for a new condition) during the study period was documented in the case report form.

Computerized randomization listing was performed for 300 patients, with an equal chance for the two treatments. The random numbers (medication code) were assigned to the patients in the respective center in ascending order, following the sequence of patient enrolment.

The primary endpoint of the study was the percentage of responders achieving DBP normalization (≤90 mm Hg) or a DBP reduction of at least 10 mm Hg. Secondary endpoints were the reduction of the SBP, reduction of the heart rate, the incidence of adverse events, laboratory tests and subjective disturbances and symptoms (questionnaire). The questionnaire contained 21 questions concerning the presence of disturbances/symptoms (all the usual problems for a typical hypertensive patient were covered: dyspnea, weakness, chest pain, nausea, dizziness, headache, tiredness, insomnia, anxiety, cold feet, paresthesia, skin problems, diarrhea, edema, impotence, etc.) and 5 different answers were possible, which were scored on a scale between 0 and 4, based on the severity of the problem (no, mild, moderate, severe or very severe symptoms).

3.1.3. Measurments

SBP and DBP (Korotkoff phase V) were measured with a calibrated mercury sphygmomanometer 3 times at 1-minute intervals at each visit, on the same arm of patients in a sitting position, at the level of the heart, after they had been resting for 5 minutes. The lowest value was taken as indicative. The heart rate was read from the radial pulse (3 times at 1-minute intervals). The height (cm) and body weight (kg) were recorded at visits 1 and 5. Altogether 6 clinical visits were planned: 2 during the placebo run-in period and 4 during the treatment phase. A complete medical history, the results of physical examination, the electrocardiogram, and the evaluation of the subjective disturbances and symptoms were recorded. Routine laboratory tests were carried out at visits 1 and 5. Adverse events were monitored throughout the study and recorded at each visit.

3.1.4. Statistical analysis

This study was designed to detect a difference of 10% in the response rate (primary endpoint) between the two groups, assuming a drop-out rate of 10%, a statistical power of 80% and a statistical significance of p=0.05. The assumed response rates of nebivolol (85%) and bisoprolol (75%) were based on previous studies [15, 16]. With these assumptions, the calculated sample size was approximately 280, randomized in

a 1:1 manner. Statistical analysis was carried out with the SAS program (version 8.0) according to the previously set plan of the protocol. The changes in response rate and blood pressures were analyzed by intention to treat (ITT) and per protocol (PP). Patients with a relevant protocol deviation were excluded from the PP analysis.
For evaluation of the primary endpoint, the mean value for the responders was determined in both patient groups (nebivolol- or bisoprolol-treated), using the ITT and PP approaches, and the 95% confidence interval (CI) was calculated for the nebivolol group. Nebivolol treatment was considered to be non-inferior to treatment with bisoprolol if the lower bound of the 95% CI of the nebivolol response rate did not reach the average response rate of bisoprolol -10%. The changes from the baseline within a group were assessed by means of the t-test. The subjective disturbances and symptoms were tested with a questionnaire based on a score scale from 0 to 4, depending on the severity of the adverse event (none, mild, moderate, severe or very severe). The non-parametric Wilcoxon test was used for the evaluation of subjective disturbances and symptoms between groups. The frequency of adverse events between groups was tested by using Fisher's exact test.

3.2. Evaluation of the effect of metoprolol CR/XL in post-myocardial infarction patients with chronic heart failure

3.2.1. Study population

The present analysis deals with the subgroup of patients in the study with a history of being hospitalized for an acute MI that occurred more than 28 days before randomization (n=1926). Furthermore we analyzed the subgroup of post-MI patients with a history of revascularization (PCI or CABG) at randomization (n=856). A subgroup analysis of post-MI patients with more severe CHF (NYHA class III/IV and EF<0.25, n= 384) is also presented.

The MERIT-HF study randomized 3991 patients from February 14, l997 to April 14, l998, and main results have been published previously. Patients enrolled in study were men and women, 40-80 years of age who had had symptomatic CHF, NYHA II-IV for 3 months or more before randomization, an EF $\leq$0.40, and who at the time of enrolment had a heart rate at or above 68 beats/min, receiving optimum standard therapy with diuretics and an ACE inhibitor. If an ACE inhibitor was not

tolerated, other vasodilators, preferably angiotensin II receptor blockers could be used. Digitalis could also be prescribed. Other inclusion criteria were a stable clinical condition during the 2 week placebo run-in phase between enrolment and randomization. Exclusion criteria included an acute MI or unstable angina within 28 days before randomization, indication or contraindication for treatment with beta-blockers or drugs with beta-blocking properties such as amiodarone; beta-blocker treatment within 6 weeks before enrolment; CHF secondary to systemic disease or alcohol abuse; implanted cardiac defibrillator, or procedure such as PCI or CABG planned or performed in the past 4 months; unstable decompensated CHF with pulmonary edema; use of amiodarone within 6 months before enrolment.

3.2.2. Study design

After a single blind placebo run-in phase of two weeks, patients were randomized to metoprolol CR/XL or placebo with starting doses of 12.5 mg or 25 mg once daily. The lower starting dose was recommended for patients in NYHA class III/IV. It was recommended to double the dose every second week to a target dose of 200 mg once daily, or the highest tolerated dose.

3.2.3. Study endpoints

The two primary outcome events were total mortality, and the combined end point of all-cause mortality/all-cause hospitalization (time to first event). In addition to the two primary endpoints, other pre-defined combined endpoints (time to first event) were all-cause mortality/hospitalization due to worsening CHF, and cardiac death/non-fatal acute MI. Further pre-defined endpoints were the total number of hospitalizations due to cardiovascular causes, and due to worsening CHF; and withdrawal of study drug for any cause, and for worsening CHF. In order to make comparisons with the primary endpoint of CAPRICORN we also analyzed the combined endpoint of all-cause mortality/CV hospitalizations (time to first event). This study is used as a reference because it is a recent prospective randomized trial of beta-blocker usage in post-MI patients with CHF. The combined endpoint of all-cause mortality/CV hospitalizations (time to first event) is thus analyzed post-hoc in MERIT-HF, however

both all-cause mortality and CV hospitalizations were pre-defined endpoints in MERIT-HF.

3.2.4. Statistical analysis

Statistical analyses utilized the Cox's proportional hazards model to calculate relative risk and 95% confidence intervals.

4. Results

4.1. Comparison of nebivolol with bisoprolol in hypertension

4.1.1. Patient characteristics

The patient characteristics at entry (sex, age, severity of hypertension and other parameters) were similar for the two groups (nebivolol- vs. bisoprolol-treated). The placebo period of the study was entered altogether by 283 patients and was completed by 273 patients. The main reason for withdrawal at this phase of the study was screening failure (9 patients). One patient was excluded from the study because of an initial protocol violation (the patient was entered without a placebo run-in phase).

Of the 273 patients (nebivolol 138, and bisoprolol 135) who entered the treatment phase, 8 became dropouts (nebivolol 3, and bisoprolol 5). The reasons for the dropout from the study were in some cases clinical adverse events (nebivolol 2 patients vs. bisoprolol 3 patients). Altogether 26 patients were excluded from the PP analysis because of relevant protocol violations (in all 26 cases, drugs not permitted by the protocol were used as concomitant therapy).

4.1.2. Clinical effects (blood pressure and heart rate)

The baseline SBP (nebivolol 153±11.7 mm Hg vs. bisoprolol 153±11.5 mm Hg) and DBP (nebivolol 99±3.1 mm Hg vs. bisoprolol 100±3.1 mm Hg) were similar in the two groups. Both SBP and DBP decreased gradually and significantly upon treatment in both the nebivolol group and the bisoprolol group. The two treatments had similar effects on the mean change from the baseline (difference between visits 1 and 5) in

both SBP (nebivolol -20.5±12.9 mm Hg vs. bisoprolol -20.0±12.0 mm Hg; p=0.7434) and DBP (nebivolol -15.7±6.4 mm Hg vs. bisoprolol -16.0±6.8 mm Hg; p=0.8230).

A high proportion of responders was noted in both groups (nebivolol 92.0%, vs. bisoprolol 89.6%) and there was no relevant difference between the nebivolol and bisoprolol treatments, calculated by either the ITT or the PP method. The calculation of the result of the primary endpoint revealed that the two treatment regimens did not differ from each other significantly on the basis of the changes in DBP.

The baseline sitting heart rates were comparable in the two treatment groups (nebivolol 74.4±9.6 per minute vs. bisoprolol 74.4±8.7 per minute). In both cases, treatment with the drug resulted in a small, but significant reduction in mean heart rate in the first 2 weeks of treatment. Thereafter, the mean heart rate remained stable throughout the rest of the medication period. At the end of the treatment period (visit 5), the difference between the two groups was not significant statistically (nebivolol 68.7±8.5 per minute vs. bisoprolol 68.1±7.5 per minute).

4.1.3. Safety parameters

Altogether 20 of the 274 patients spontaneously reported a total of 20 (7.3%) adverse events during the treatment phase, 8 (5.8%) in the nebivolol group and 12 (8.9%) in the bisoprolol group (no significant difference between treatment groups: $p>0.05$). All adverse events were either mild (55%) or moderate (45%) in intensity. As regards the subjective disturbances and symptoms assessed by means of the questionnaire at the end of the placebo run-in period (visit 1), the baseline score was slightly, but not significantly higher for the group randomized to nebivolol (1.1±2.1) vs. bisoprolol (0.9±1.6). Obviously, these symptoms were not related to the administration of the study drugs because they had already been present for weeks or months before the trial was initiated. During the treatment period, a majority of the disturbances/symptoms improved in both treatment groups. After medication with either nebivolol or bisoprolol for 12 weeks, a clinically relevant and statistically significant ($p<0.02$) effect was demonstrated for the global scores covering the following symptoms: dizziness, weakness, headache and dyspnea. Moreover, chest pain in response to physical effort was significantly reduced in the nebivolol group. The improvement in the disturbances/symptoms during the treatment period led to a significant reduction in the basal score index for both groups at visit 5 (nebivolol -

0.7±1.7 vs. bisoprolol -0.5±1.3; no significant difference between treatment groups: p>0.05). All reports in the questionnaire of a new occurrence of symptoms or worsening of the symptoms were recorded as adverse events. Treatment compliance as measured by the tablet count was found to be high (98%) and similar for both treatments.

Liver function tests (transaminases GOT, GPT and gamma GT), serum creatinine and counts of red blood cells, white blood cells and platelets were evaluated at visit A in order to ensure that patients with a disturbed hepatic function, renal diseases and hematological disorders were not randomized to medication. An additional hematological laboratory test was carried out at the end of the study (visit 5), when there were no clinically significant changes for counts of red blood cells, white blood cells and platelets, indicating that there was no risk of the induction of anemia, leucopenia or disturbances of blood clotting in either treatment group.

4.2. Evaluation of the effect of metoprolol CR/XL in post-myocardial infarction patients with chronic heart failure

4.2.1. Study population

In the post-MI group 976 patients were randomized to placebo and 950 to metoprolol CR/XL. Baseline characteristics in the two randomization subgroups were very similar, which may be due to the optimal allocation procedure that was used at randomization.

Of those post-MI patients with a history of revascularization (PCI or CABG) 426 patients were randomized to placebo and 430 to metoprolol CR/XL. In the subgroup of post-MI patients with more severe CHF (NYHA III/IV and EF<0.25) 195 patients were randomized to placebo and 189 to metoprolol CR/XL; mean ejection fraction was low 0.19.

4.2.2. Clinical Events

The MERIT-HF study was stopped early, on October 31, 1998, when the second pre-planned interim analysis showed a highly significant reduction in total mortality in the metoprolol CR/XL group compared to placebo. The two primary outcome events

were total mortality, There were 122 deaths (12.8% per patient year of follow-up) in the placebo group and 74 (7.6%) in the metoprolol CR/XL group. Metoprolol CR/XL decreased total mortality by 40% (p=0.0004), sudden death by 50% (p=0.0004), and death due to worsening CHF by 49% (p=0.021).

Metoprolol CR/XL also decreased the combined endpoint of all-cause mortality/all-cause hospitalization (time to first event) by 14% (p=0.0003); all-cause mortality/CV hospitalization by 22% (p=0.0022); all-cause mortality/hospitalization for worsening CHF by 31% (p<0.0001); and cardiac death/non-fatal myocardial infarction by 45% (p<0.0001).

Metoprolol CR/XL reduced the number of hospitalizations for cardiovascular causes by 17% (0.433 vs 0.361 per patient year of follow-up; p=0.037), and for worsening CHF by 32% (0.237 vs 0.160; p<0.006). A hospitalization verified acute non-fatal MI occurred in 27 patients in the placebo group and 19 patients in the metoprolol CR/XL group (relative risk 0.70, 95% CI 0.39 to 1.26, p>0.20).

The yearly placebo mortality risk was lower in those with a history of revascularization (9.2%) compared to the overall post-MI group of patients (12.8%), and higher in those with severe CHF (24.3%), but data indicated a similar risk reduction with metoprolol CR/XL as in the overall study group of post-MI patients in both these subgroups. In the subgroup with a history of revascularization (PTCA or CABG) there was a significant risk reduction in the combined endpoint of cardiac death/non-fatal myocardial infarction (time to first event) with 39% (95% CI 2% to 63%, p=0.040). As in the overall post-MI subgroup metoprolol CR/XL also reduced total mortality, sudden death, hospitalizations for worsening CHF and the combined endpoint of cardiac death/non-fatal MI in post-MI patients with more severe CHF.

4.2.3. Tolerability

Metoprolol CR/XL was well tolerated. Permanent withdrawal of study medicine due to any cause before closing the study occurred in 154 patients in the placebo group and in 148 patients in the metoprolol CR/XL group (relative risk 0.98, 95% CI 0.78 to 1.22; ns); and due to worsening CHF in 46 and 38 patients, respectively. The mean dose of metoprolol CR/XL was 149 mg once daily. In the subgroup of PMI patients

with severe CHF, discontinuation of study medication occurred more often in the placebo group than in the metoprolol CR/XL group for all discontinuations (45 vs 33 patients), as well as for discontinuation due to worsening CHF (22 vs 9 patients), respectively.

5. Discussion

5.1. Comparison of nebivolol with bisoprolol in hypertension

Beta-blockers were accepted as treatment for hypertension only slowly, and even 7 years after the first report of the antihypertensive effect of propranolol some clinical reports concluded that, because of the reduction in cardiac output, the beta-adrenergic agents should not be used routinely in the treatment of hypertension. Beta-blockers are now regarded by the Joint National Committee as a first-line choice of treatment in hypertension, together with diuretics. Nebivolol is a highly $beta_1$-selective blocker possessing NO-mediated vasodilatory action, which has not been observed for other beta-blockers (e.g. atenolol and metoprolol) used in clinical practice. The principal objective of the present trial was to compare the antihypertensive effect and the safety of nebivolol versus bisoprolol in patients with mild to moderate hypertension. There were no significant differences in mean sitting DBP or sitting SBP between the two treatment groups at any time. At the end of the trial, the sitting DBP and SBP were equally lowered in both treatment groups. This intraindividual reduction within 12 weeks of treatment was statistically significant ($p<0.01$) in both groups. Nebivolol (5 mg) and bisoprolol (5 mg) achieved comparable responder rates as concerns DBP (primary efficacy endpoint). The decreases observed in SBP and DBP upon nebivolol treatment in this study were comparable to previous findings when nebivolol was applied either as single therapy or in combination. Moreover, in three previous studies that included only a relatively small number of patients with mild to moderate hypertension, nebivolol was found to be equally effective to atenolol or metoprolol in lowering blood pressure.

Disturbing side-effects of non selective beta-blocker therapy, such as excess fatigue, a reduction in physical performance and cold extremities, attributed to a reduction in cardiac output and vasoconstriction, were not encountered during the

present trial. On the other hand, some of the complaints and symptoms reported most commonly by the patients at baseline continuously improved or disappeared in both treatment groups as a result of treatment. A clinically relevant and statistically significant reduction of symptoms during nebivolol or bisoprolol treatment was demonstrated for dizziness, weakness, headache and dyspnea. In accordance with previous reports, these observations suggest that the high $beta_1$-selectivity of the administered beta-blockers and/or the direct vasodilatory action of nebivolol improved the safety profiles of these compounds in this study.

Nebivolol (5 mg once daily) was well tolerated by the patients with hypertension, and adverse events during the 12 weeks of treatment were infrequent, transient and mild to moderate in severity. The overall incidence of spontaneously reported adverse events during the 12-week treatment was slightly, but not significantly lower with nebivolol (5.8%) than with bisoprolol (8.9%). These incidences of adverse events are low in comparison with earlier findings.

Some limitations of the study are as follows: 1) a single-blind approach was used in the treatment phase of the trial and some experimental bias cannot be ruled out. However, a central computerized randomization was used and neither the patients nor the study personnel were aware of the identity of the study drug. Moreover, all trial-related activities (blood pressure measurements, laboratory tests and filling of the questionnare) were carried out without a knowledge of the nature of the administered compound. 2) The sample size and the duration of the study were adjusted so as to detect a 10% difference in the DBP response rate. Consequently, the number of patients enrolled in the study was not high enough to detect significant changes in adverse event rate as a result of the different drug therapies. It can be speculated however, that the differences observed in the adverse event rate during the treatment phase (5.8% in the nebivolol group vs. 8.9% in the bisoprolol group) were due to the different pharmacological characteristics of the study drugs, but the sample size and/or the duration of the study were not adjusted to detect significant changes for this secondary endpoint.

5.2. Evaluation of the effect of metoprolol CR/XL in post-myocardial infarction patients with chronic heart failure

In post-MI patients with symptomatic CHF beta-blockade continues to exert a profound reduction in mortality and morbidity in the presence of contemporary management that includes early and late revascularization, angiotensin converting enzyme inhibitors, aspirin and statins. Metoprolol CR/XL reduced total mortality by 40% (95% CI 0.20 to 0.55; p=0.0004), and sudden death by 50% (95% CI 0.26 to 0.66; p=0.0004). The combined endpoint of all-cause mortality/ hospitalization for worsening CHF was reduced by 31% (95% CI 0.16 to 0.44; p<0.0001), and cardiac death/non-fatal acute MI by 45% (95% CI 0.26 to 0.58; p<0.0001). A post-hoc analysis showed that the outcome in patients with earlier revascularization (44%), and outcome in those with more severe CHF (20%) was similar to the entire post-MI population.

Comparison to CAPRICORN study

The results are corroborated by the results of the CAPRICORN trial, which included a similar number of patients (n=1959). In that study total mortality was reduced by 23% (95% CI 2 to 40; p=0.031). Although positive mortality results were obtained in both trials, it should be pointed out that in the latter trial all patients were included within 3 to 28 days of the index infarction, and most patients in the MERIT-HF study were included more than a year after their infarction. However, 30% of the patients of the CAPRICORN trial had a history of MI prior to the index infarction. Another difference in inclusion criteria was that the patients in the MERIT-HF trial were mandated to have symptomatic CHF in NYHA class II to IV and low EF, while in the CAPRICORN trial the requirement was low EF or wall motion-score index only (regardless of symptoms). The first primary endpoint in the latter trial of all-cause mortality/cardiovascular hospitalization (time to first event) was reduced by 8% (95% CI -7 to 20, p>0.20), which may be compared with 22% (95% CI 9 to 34, p <0.002) in the present analysis of data from MERIT-HF.

Comparison to prior early studies

In the three early post-MI beta-blocker studies performed in the 1970s, mortality was reduced by 26 to 36%. It is of interest to note that in these early studies the annual placebo mortality during the first year was 6, 11, and 13%, respectively, which may be compared with 11.8% in CAPRICORN. The rather similar first year placebo mortality rate in these earlier beta-blocker studies and the latter study needs an explanation. One might have had expected a significantly higher mortality rate in the latter study because of enrolment of sicker patients. The most likely explanation for the similarity of the first years' annual placebo mortality rate between the earlier studies and the latter study is the improvement in the management of post-MI patients during the past 20 years including the use of thrombolytics, revascularization, aspirin, ACE-inhibitors and statins.

Another observation is the divergence in annual placebo mortality rate between the first year and the second year noted in the three earlier studies. This is of interest since the majority of patients in MERIT-HF were included more than a year after their index MI. During the period of 12-24 months after the index infarction in the earlier timolol, propranolol and metoprolol studies, the annual placebo mortality rate was 3, 5 and 4%, which is much lower than the 12.5% annual placebo mortality rate in the current study (second or more years after MI). Thus, despite modern therapy provided to post-MI patients in MERIT-HF, the annual placebo mortality rate past the first year of the index infarction was 2-3 times higher than that observed past the first year in the earlier post-MI studies in patients without CHF. This shows that the MERIT-HF trial included a high-risk population of post-MI patients not studied in the earlier trials. However, there are reports indicating beneficial effects on prognosis in subgroups of patients with increased heart size and symptoms of mild CHF from the three earlier beta-blocker trials.

Subgroups with previous revascularization or severe CHF

The present subgroup analysis in a large population of the MERIT-HF trial shows that metoprolol CR/XL has marked beneficial effects on mortality and morbidity in post-

MI patients with CHF. These benefits extend to patients with earlier revascularization, as well as to those with more severe CHF.

In the MERIT-HF study, 44% of patients had a previous revascularization compared to 11% in CAPRICORN. However, in the latter study, 46% of patients received early thrombolysis or primary percutaneous intervention for their index infarction. It is gratifying to note that beta-blockers exert their beneficial effects in a broad spectrum of patients post-MI with different management strategies related to revascularization.

Sudden death and non-fatal re-infarction

A striking observation from the early post-MI studies with timolol, propranolol and metoprolol was that the effect of the beta-blockers on sudden death was more marked than on other modes of death. Sudden death was reduced by 30-45% compared to 26-36 % reduction in total mortality in these studies. Very similar findings were noted in the present study, where sudden death was reduced by 50% and total mortality by 40%. In the Cardiac Insufficiency Bisoprolol Study II (CIBIS II) sudden death was reduced with 44%, and total mortality with 34%. In the CAPRICORN trial, sudden death was reduced by 26% (95% CI 6 to 49, p=0.098).

Beta-blockers appear to produce a more pronounced and consistent reduction in sudden death compared to ACE inhibitors. The proven clinical benefit observed with beta-blockers in CHF has been in patients already receiving optimal treatment with ACE inhibitors. Thus the beneficial effect of beta-blockers is additional to that of the ACE-inhibitors.

Another issue that needs to be addressed is the effect of beta-blockers on non-fatal re-infarction. The CAPRICORN trial showed a significant 41% reduction in the rate of non-fatal myocardial re-infarction (95% CI 10 to 61; p=0.014), a similar reduction was observed in the present analysis of post-MI patients in MERIT-HF (although not statistically significant because of low power: 27 vs.19 patients; relative risk 0.70, 95% CI 0.39 to 1.26, p>0.20). These effects are also in agreement with the three earlier major beta-blocker studies in post-MI patients, which all showed a reduction in non-fatal re-infarction, in the Timolol trial by 28%, in the BHAT trial by 16%, and in the Metoprolol trial by 35%. This further supports the idea that the

effects observed with beta-blockers 25 years ago are of relevance also today in presence of all other post-MI therapies for prevention of not only deaths but also of non-fatal re-infarctions.

Comparison to ICD therapy

Our data should be viewed in light of the recently published Multicenter Automatic Defibrillator Implantation Trial II (MADIT II). This study demonstrated in 1232 patients with LVEF $\leq$ 0.30 and prior MI a 31% decrease in total mortality, presumably from sudden death, in those randomized to receive an implantable defibrillator. Eighty-eight percent of these patients had their MI more than 6 months prior to randomization. The survival benefit was noted at 9 months. The improved survival, however, was associated with an increase in CHF hospitalization. In a very similar population, our data show that metoprolol CR/XL resulted in 40% and 50% decrease in total mortality, and sudden death, respectively.

In addition, the survival curves began to separate at three months, and more importantly metoprolol CR/XL resulted in a significant (32%) reduction of CHF hospitalization.

Despite concerted effort, only 68% of post-MI patients who are ideal candidates to receive beta-blockers (excluding CHF) do so. Beta-blockers are substantially less prescribed in post-MI patients with CHF. Therefore, it is much more cost effective to adopt strategies that lead to a much wider use of beta-blockers in post-MI patients with CHF and impaired LVEF before considering measures to mandate the implantation of automatic defibrillators.

6. Summary

In our study we evaluated the clinical effects of some $beta_1$-selective adrenergic blockers in hypertension, heart failure and post-myocardial infarction period. We compared 1) the antihypertensive efficacy and safety of the highly $beta_1$-selective adrenergic antagonist nebivolol with bisoprolol in the treatment of mild to moderate essential hypertension, and 2) the effects of the metoprolol succinate controlled

release/extended release (CR/XL) on the clinical endpoints versus placebo (post-hoc analysis of the MERIT-HF trial).
Conclusions:

Ad.1.

a) We report here the results of the first clinical trial in which two highly cardioselective beta-blockers were compared. There were no significant differences in mean sitting DBP or sitting SBP between the two treatment groups at any time. At the end of the trial, the sitting DBP and SBP were equally lowered in both treatment groups. This intraindividual reduction within 12 weeks of treatment was statistically significant ($p<0.01$) in both groups. Nebivolol (5 mg) and bisoprolol (5 mg) achieved comparable responder rates as concerns DBP (primary efficacy endpoint).

b) Our data demonstrate that beta-blocker therapy was well tolerated by the patients with hypertension, and adverse events during the 12 weeks of treatment were infrequent, transient and mild to moderate in severity. Disturbing side-effects of non selective beta-blocker therapy, such as excess fatigue, a reduction in physical performance and cold extremities, attributed to a reduction in cardiac output and vasoconstriction, were not encountered during the present trial. On the other hand, some of the complaints and symptoms reported most commonly by the patients at baseline continuously improved or disappeared in both treatment groups as a result of treatment. The overall incidence of spontaneously reported adverse events during the 12-week treatment was slightly, but not significantly lower with nebivolol (5.8%) than with bisoprolol (8.9%). In accordance with previous reports, these observations suggest that the high $beta_1$-selectivity of the administered beta-blockers and/or the direct vasodilatory action of nebivolol improved the safety profiles of these compounds in this study.

c) The findings of the present trial indicate that nebivolol (5 mg once daily) is an effective antihypertensive agent with vasodilatory properties. Its clinical benefit (as concerns the responder rate, DBP and the occurrence of adverse

events) was demonstrated to be equal to that of 5 mg bisoprolol. Nebivolol (5 mg) may therefore be recommended as a useful first-line treatment option for the management of patients with mild to moderate essential hypertension.

Ad. 2.

a) The present study is a pre-specified subgroup analysis of a double blind, randomized trial: the Metoprolol CR/XL Randomized Intervention Trial in Heart Failure (MERIT-HF) and includes 1926 patients with a previous MI and symptomatic heart failure (EF≤0,40). Metoprolol CR/XL reduced total mortality by 40% (95% CI 0.20 to 0.55; p=0.0004), and sudden death by 50% (95% CI 0.26 to 0.66; p=0.0004). The combined endpoint of all-cause mortality/ hospitalization for worsening CHF was reduced by 31% (95% CI 0.16 to 0.44; p<0.0001), and cardiac death/non-fatal acute MI by 45% (95% CI 0.26 to 0.58; p<0.0001). A post-hoc analysis showed that the outcome in patients with earlier revascularization (44%), and outcome in those with more severe CHF (20%) was similar to the entire post-MI population.

b) Our data compared to the recently published Multicenter Automatic Defibrillator Implantation Trial II (MADIT II), which included very similar patients, we demonstrated that metoprolol CR/XL resulted in 40% and 50% decrease in total mortality, and sudden death, respectively. In addition, the survival curves began to separate at three months, and more importantly metoprolol CR/XL resulted in a significant (32%) reduction of CHF hospitalization. Despite concerted effort, only approximately 68% of post-MI patients who are ideal candidates to receive beta-blockers (excluding CHF) do so. Beta-blockers are substantially less prescribed in post-MI patients with CHF. Therefore, it is much more cost effective to adopt strategies that lead to a much wider use of beta-blockers in post-MI patients with CHF and impaired LVEF before considering measures to mandate the implantation of automatic defibrillators.

c) Available data demonstrate that with contemporary management of MI, including early and late revascularization, ACE-inhibitors, aspirin and statins,

beta-blockers still have a very important role in secondary prevention in the presence of CHF. Furthermore, beta-blockers demonstrate a pronounced reduction of sudden cardiac death, which is the mode of death of the majority of patients with coronary heart disease.

7. List of publications

7.1. Full papers related to the subject of the thesis

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