Effect of Controlled Release/Extended Release Metoprolol on Carotid Intima-Media Thickness in Patients With Hypercholesterolemia A 3-Year Randomized Study

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Background and Purpose—β-Adrenergic blockade has in several studies been shown to improve survival after myocardial infarction. In animal experiments β-blockers have also shown an antiatherosclerotic effect. The aim of this study was to test the hypothesis that the β-blocker metoprolol succinate controlled release/extended release (CR/XL), when given to patients with hypercholesterolemia on concomitant lipid-lowering therapy, provides an additional antiatherosclerotic effect to that provided by the statins, measured as carotid intima-media thickness (IMT).

Methods—We conducted a randomized, double-blind, placebo-controlled, single center trial to compare the effect of metoprolol CR/XL (100 mg once daily) and placebo on the progression of carotid IMT during 36 months of treatment in patients with hypercholesterolemia and signs of early atherosclerosis in the carotid artery. Most patients were prescribed lipid-lowering treatment with statins.

Results—A highly significant difference in the progression rate of the composite variable of carotid bulb IMT + common carotid IMT was observed between the metoprolol CR/XL and placebo groups after 1 year of treatment (−0.08 versus −0.01 mm; \( P=0.004 \)), an effect that was sustained after 3 years of follow-up (−0.06 versus +0.03 mm; \( P=0.011 \)). The patients had high levels of total cholesterol at randomization: 9.4 mmol/L in the metoprolol CR/XL group and 8.6 mmol/L in the placebo group. During the study the 2 randomization groups were treated with lipid-lowering drugs, mainly statins, to a similar extent, and total cholesterol was reduced to 6.4 mmol/L at end of follow-up in both groups.

Conclusions—The results from the present study in patients with hypercholesterolemia under concomitant lipid-lowering therapy are the first clinical data to show an antiatherosclerotic effect of β-blockade as additional therapy to statins. The data indicate that statin treatment and treatment with β-blockers affect different mechanisms in the atherosclerotic process and have additive beneficial effects. (Stroke. 2002;33:572-577.)

Key Words: antilipemic agents ▪ atherosclerosis ▪ β blockade ▪ ultrasonography

In several studies β-adrenergic blockade has been shown to improve survival after myocardial infarction.\(^1,2\) Additionally, in the treatment of hypertension, β-blockade seems to have a beneficial effect on the incidence of coronary and cerebrovascular complications.\(^3\) Thus far these effects have been assumed to be mediated by mechanisms such as better myocardial function, antihypertensive effects, antiarrhythmic effects, or reduced oxygen consumption of the myocardium. However, throughout the last decade evidence has accumulated suggesting that β-adrenergic blockers may have an antiatherosclerotic effect as well. These data are primarily based on experimental studies in different animal models.\(^4-6\) It has also been shown that infusion of noradrenaline has an atherogenic effect\(^7\) and that sympathectomy may inhibit this effect.\(^8\) Furthermore, it has been shown that psychosocial stress causes endothelial injury \(^9,10\) and development of atherosclerosis in cynomolgus monkeys.\(^4,11\) These effects were inhibited by treatment with β-blockade.\(^11\) In our earlier studies we also observed that treatment with controlled release/extended release (CR/XL) metoprolol succinate reduced the binding of LDL to arterial proteoglycans.\(^12\) Taken together, these studies suggest that β-blockade may have an antiatherosclerotic effect mediated by a protection of the endothelium as well as a reduced lipoprotein deposition.

The development of the B-mode ultrasound technique has made it possible to noninvasively study early atherosclerotic changes in the carotid arteries by measuring the intima-media complex. In several preventive trials, cholesterol-lowering therapy has been shown to reduce the development of atherosclerosis, measured as carotid intima-media thickness (IMT).\(^13-16\)

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hypercholesterolemia on concomitant lipid-lowering therapy, provides an additional antiatherosclerotic effect to that provided by the statins, measured as carotid IMT.

Subjects and Methods

Study Group: Patients
The ELVA (Effect of Long-Term Treatment of Metoprolol CR/XL on Surrogate Variables for Atherosclerotic Disease) study was a 3-year prospective, randomized, placebo-controlled, double-blind study to evaluate the effect of metoprolol CR/XL on the development of atherosclerosis in the carotid artery.

Subjects with primary hypercholesterolemia (n=129) were recruited from screening of subjects from the general population performed at the Wallenberg Laboratory for Cardiovascular Research and also from patients at the lipid clinic of the Sahlgrenska University Hospital. A total number of 1321 subjects came to the screening examination. Inclusion criteria were as follows: willingness to participate, age 20 to 70 years, serum cholesterol >6.5 mmol/L, LDL cholesterol >5.0 mmol/L, and serum triglycerides <4.5 mmol/L. Furthermore, the patients had to fulfill the following ultrasound criteria: (1) maximum IMT in the common carotid artery (IMTmax) >1.0 mm and/or (2) measurable plaque in the carotid artery, arbitrarily defined as a 50% increase in IMT compared with neighboring sites (visually judged). For patients already on lipid-lowering therapy, there was a washout period of 3 to 8 weeks before start of double-blind medication.

Exclusion criteria were as follows: (1) secondary or severe hypertension or significant valvular disease; (2) history of myocardial infarction, cerebrovascular accident, or coronary artery bypass surgery within the past 6 months; (3) pregnant women, nursing mothers, and women of childbearing potential who were not receiving adequate contraception; and (4) concomitant significant life-threatening diseases. Patients were randomized at placebo run-in as follows: 62 to metoprolol CR/XL treatment (100 mg once daily) and 67 to placebo (4 strata: male/smoker, female/smoker, male/non-smoker, female/non-smoker). During the 2 weeks of placebo run-in, 15 subjects from the metoprolol CR/XL group and 11 subjects from the placebo group were withdrawn, for the following reasons: negative ultrasound examinations (n=3 and n=1, respectively); low total cholesterol, low LDL cholesterol, or high triglyceride levels (n=6 and n=4); myocardial infarction (n=1 and n=0); nausea (n=1 and n=2); unwillingness to participate (n=4 and n=2); and other causes (n=0 and n=2). Two subjects in each group reduced the dose during follow-up from 100 to 50 mg. Altogether 12 subjects from the metoprolol CR/XL group and 12 subjects from the placebo group stopped double-blind treatment during follow-up, for the following reasons: myocardial infarction (n=2 and n=1, respectively); atrial fibrillation (n=2 and n=0); angina pectoris (n=1 and n=1); malignancy (n=1 and n=1); minor adverse effects (n=1 and n=5); given metoprolol CR/XL by other physician (n=0 and n=1); moved to other area (n=2 and n=0); compliance (n=1 and n=1); and unwillingness (n=2 and n=2).

After start of double-blind treatment, subjects were followed for 3 years, including 4 ultrasound and physician examinations (once yearly) and additionally 6 visits to the lipid clinic for evaluation of lipid levels. Altogether 42 subjects in the metoprolol CR/XL group and 50 subjects in the placebo group had at least 1 ultrasound follow-up examination. The ethics committee of Göteborg University approved the protocol, and informed consent was obtained from all patients.

Ultrasoundography

Examination Procedure
Examination was performed with an ultrasound scanner (Acuson 128) equipped with a linear 7-MHz transducer and a transducer aperture of 38 mm. The examination included approximately 2 cm of the right common carotid artery, the carotid artery bulb, and 1 cm of the internal and external arteries, as previously described.17

Measurement of IMT and Lumen Diameter
The ultrasound images were analyzed in an automated computerized analyzing system.18 IMT was defined as the distance from the leading edge of the lumen-intima interface to the leading edge of the media-adventitia interface of the far wall. The measurement of IMT in the carotid artery was made in 2 separate segments: along a 10-mm-long segment in the common carotid artery and along a 10-mm-long segment distal to the beginning of the carotid artery bulb, ie, where the echoes from the near and far walls are no longer parallel.17,18 The computer calculated the mean thickness of the intima-media complex of the far wall (as well as the IMTmax value). Lumen diameter was defined by the distance between the leading edges of the intima-lumen interface of the near wall and the lumen-intima interface of the far wall in the common carotid artery. The interobserver variation for IMT has previously been shown to be satisfactory.19

All IMT measurements were analyzed after the study was completed to avoid drift in reading. Two technicians measured IMT: one measured all readings from the common carotid artery and the other all readings from the carotid artery bulb.

Serum Lipids
Serum cholesterol and triglycerides were analyzed at the Wallenberg Laboratory by enzymatic methods.20,21 HDL was determined after precipitation of apolipoprotein B-containing lipoproteins with manganese chloride and dextran sulfate. LDL was calculated as described by Friedewald et al.22

Statistical Analysis
The study protocol stated that the 2 randomization groups should be compared after 1, 2, and 3 years of follow-up. Furthermore, an analysis was performed that took into account all available measurements in the 92 subjects with at least 1 ultrasound follow-up examination. In this analysis the change was determined as the regression coefficient for all available measurements (between 2 and 4) in IMT over time in each patient. The results were weighted inversely proportional to the variances and pooled by use of the technique suggested by Mantel.21

With the exception of the Mantel test, all other statistics were analyzed with the use of SPSS for Windows 8.0. Differences between the metoprolol CR/XL and the placebo groups were analyzed by the independent samples t test. Differences in categorical variables were tested by χ2 test. Values are mean and SD except in figures (mean and SE).

Results
A total of 92 patients had at least 1 ultrasound follow-up investigation. One-year ultrasound follow-up data were available for 40 patients in the metoprolol CR/XL group and 52 in the placebo group. Corresponding figures were 38 versus 48 patients for the 2-year follow-up and 35 versus 44 patients for the 3-year follow-up. Baseline characteristics for subjects with at least 1 ultrasound follow-up examination are shown in Table 1; there were no significant differences between the 2 randomization groups. During follow-up, heart rate decreased in the metoprolol CR/XL group (Figure 1, top). Mean values for systolic blood pressure in the metoprolol CR/XL and placebo groups were 138±21 versus 138±20 mm Hg at baseline (P<0.20; Table 1) and 132±16 versus 135±21 mm Hg at the 3-year follow-up (P>0.20). Mean differences are shown in Figure 1. Corresponding values for diastolic blood pressure were 80±7
versus 81±7 mm Hg (P>0.20; Table 1) and 77±9 versus 78±8 mm Hg (P>0.20), respectively.

At the baseline examination, 2 subjects in the metoprolol CR/XL group (diuretics [n=1] and calcium antagonist [n=1]) and 5 subjects in the placebo group (diuretics [n=1], angiotensin-converting enzyme [ACE] inhibitor [n=1], calcium antagonist [n=1], combination of diuretics and ACE inhibitor [n=1], and combination of ACE inhibitor and calcium antagonist [n=1]) were on antihypertensive drug therapy. Corresponding numbers at the 3-year follow-up examination were 2 subjects in the metoprolol CR/XL group (diuretics [n=1] and calcium antagonist [n=1]) and 7 subjects in the placebo group (diuretics [n=2], ACE inhibitor [n=1], calcium antagonist [n=3], and combination of diuretics and ACE inhibitor [n=1]), respectively.

**Cholesterol-Lowering Therapy in the Metoprolol CR/XL Group and the Placebo Group During Follow-Up**

Subjects were treated with statins before inclusion (31% in the metoprolol CR/XL group and 27% in the placebo group). All lipid-lowering drugs were withdrawn 3 to 8 weeks before start of double-blind medication.

The cumulative mean daily dose of simvastatin (prescribed to 80% of all patients) at the 1-, 2-, and 3-year visits was 8.6, 10.1, and 12.1 mg in the metoprolol CR/XL group. Corresponding values in the placebo group were 7.9, 9.7, and 11.6 mg, respectively (P>0.20). Corresponding values for pravastatin (prescribed to 13% of all patients) were 5.8, 5.5, and 4.6 mg (metoprolol CR/XL) and 3.1, 2.8, and 2.5 mg (placebo; P>0.20). At the 1-, 2-, and 3-year visits, 90%, 92%, and 100% of subjects, respectively, were treated with any lipid-lowering treatment (statins, cholestyramine, colestipol, or gemfibrozil) in the metoprolol CR/XL group. Corresponding values for the placebo group were 98%, 96%, and 96%, respectively (P>0.20 for differences).

The patients had high levels of total cholesterol at randomization, 9.4 mmol/L in the metoprolol CR/XL group and 8.6 mmol/L in the placebo group, which were reduced to 6.4 mmol/L at end of follow-up in both groups. Additionally, LDL cholesterol levels were reduced to a similar extent in both groups (Figure 2). There were no significant differences in HDL cholesterol or serum triglycerides between the metoprolol CR/XL group and the placebo group at any time during the study (Table 2).

**Carotid IMT and Lumen Diameter During Follow-Up**

At baseline there were no significant differences in IMT, lumen diameter, or plaque occurrence between the 2 random-
ization groups (Table 1). Furthermore, no significant difference was observed for common carotid IMT between subjects with (n/H11005/92) or without (n/H11005/11) an ultrasound follow-up examination (0.893 ± 0.198 and 0.874 ± 0.164 mm, respectively; P > 0.20). Corresponding values for carotid bulb IMT were 1.32 ± 0.44 and 1.29 ± 0.33 mm, respectively (P > 0.20).

IMT in the carotid bulb decreased significantly in the metoprolol CR/XL group compared with placebo after 1 year of treatment (0.13 versus 0.02 mm; P = 0.017; Figure 3); at this point there was no significant difference in change in common carotid IMT between the study groups (P = 0.10). A highly significant difference in the progression rate of the composite variable of carotid bulb IMT + common carotid IMT was, however, observed between the metoprolol CR/XL and placebo groups after 1 year of treatment (−0.08 versus −0.01 mm; P = 0.004; Figure 3). This effect was sustained after 3 years of follow-up (−0.06 mm versus +0.03 mm; P = 0.011). After 3 years of follow-up, a significant difference in progression rate in common carotid IMT between the metoprolol CR/XL and placebo groups was observed (P = 0.035) but not in the carotid bulb IMT (P = 0.12). There were no significant differences in mean values for lumen diameter in the carotid artery between the 2 randomization groups during follow-up (Figure 1, bottom).

The results of the regression analysis that took into account all available measurements in the 92 patients with at least 1 follow-up ultrasound examination showed a slower progression in common carotid IMT in the metoprolol CR/XL group than in the placebo group (P = 0.036). This analysis did not show a
significant difference between the 2 study groups ($P=0.254$). The regression analysis for the composite variable mean of common carotid IMT and carotid bulb IMT showed a significant difference between the 2 study groups ($P=0.039$).

**Discussion**

The aim of this 3-year placebo-controlled study was to investigate the effect of the $\beta_1$-selective $\beta$-adrenergic blocker metoprolol CR/XL on IMT in the carotid artery in patients with primary hypercholesterolemia on concomitant lipid-lowering therapy. The results showed a highly significant difference in the progression rate of the composite variable of carotid bulb IMT + common carotid IMT between the metoprolol CR/XL and placebo groups after 1 year of treatment, an effect that was sustained after 3 years of follow-up. The decrease in IMT in the metoprolol CR/XL group was not secondary to an increase in lumen diameter; indeed, lumen diameter decreased slightly during follow-up. The data indicate that lipid-lowering treatment and treatment with $\beta$-blockers have additive beneficial effects.

Our results suggest a beneficial effect of $\beta$-blockade on atherosclerosis development in patients with hypercholesterolemia, beyond that provided by lipid-lowering treatment with statins. The included patients represent a wide spectrum of disorders, from mild to severe hypercholesterolemia and from minor IMT thickening to extended plaques. Thus, they represent a large proportion of patients with hypercholesterolemia at risk for coronary heart disease or stroke.

IMT of the common carotid artery is commonly used as a surrogate variable for generalized atherosclerosis, including coronary atherosclerosis. Furthermore, IMT in the common carotid artery and the carotid bulb has been shown to correlate with coronary atherosclerosis, as measured by coronary angiography, and a yearly increase of IMT in the common carotid artery of 0.03 mm/y has been shown to be associated with a relative risk of 3.9 for any coronary event in men with coronary artery disease.

The inclusion criteria of the study were set to define a group with hypercholesterolemia and atherosclerosis. For ethical reasons it was not possible to study the effect of metoprolol CR/XL in patients with hypercholesterolemia without lipid-lowering treatment. The patients had high levels of total cholesterol at randomization: 9.4 mmol/L in the metoprolol CR/XL group and 8.6 mmol/L in the placebo group. During the study the 2 randomization groups were treated with lipid-lowering drugs, mainly statins, to a similar extent, and total cholesterol was reduced to 6.4 mmol/L at end of follow-up in both groups. The on-treatment levels of HDL cholesterol and triglycerides were similar in the 2 randomization groups. Our data thus showed a beneficial effect of metoprolol CR/XL on atherosclerosis development in patients with hypercholesterolemia treated with statins. These data indicate that statins and $\beta$-blockers act on different mechanisms in the atherosclerotic process and have additive beneficial effects.

From previous experience, a yearly progression rate of common carotid artery IMT$_{\text{max}}$ of at least 0.015 mm/y would have been expected in patients with hypercholesterolemia without lipid-lowering treatment. However, the observed values in the present study were much lower, with no increase in carotid artery IMT during the first year in the placebo group (see Figure 3). The institution of lipid-lowering therapy in the placebo group probably explains this finding. This may also partly explain the decrease in IMT during the first year in the metoprolol CR/XL group; however, at the 1-year ultrasound examination the decrease in IMT was more pronounced in the $\beta$-blocker group compared with placebo, which is perhaps best illustrated in the composite variable of common carotid and carotid bulb IMT (Figure 3, bottom).

Baseline blood pressures were normal, and during follow-up no significant difference was observed in blood pressure between the metoprolol CR/XL and the placebo groups. The explanation for this finding is probably that metoprolol CR/XL has no or only a small blood pressure–lowering effect in people with normal blood pressure. Furthermore, only a minor fraction of the study subjects were on antihypertensive drug treatment.

In long-term prevention trials, metoprolol CR/XL has been found to reduce the incidence of coronary and cerebrovascular complications in hypertensive patients, as well as in patients surviving myocardial infarction. The mechanisms involved in these preventive effects of metoprolol are not clear. The results obtained could not easily be ascribed to the well-established antihypertensive, cardiac anti-ischemic, and antiarrhythmic effects of metoprolol. Additional factors may involve prevention of the final thromboembolic process and retarded progression of atherosclerotic lesions, or both, as summarized below.

The possible role of an antiatherosclerotic effect of metoprolol CR/XL is supported by the results of several animal studies. In addition, $\beta$-blockers other than metoprolol have been shown to reduce the formation of atheroma in different animal models, such as rabbits, chickens, and monkeys. The main results from the Beta-Blocker Cholesterol-Lowering Asymptomatic Plaque Study (BCAPS) were recently published. In this study a low-dose $\beta$-blocker (metoprolol CR/XL 25 mg once daily) was shown to reduce carotid bulb IMT in a 3-year follow-up study in clinically healthy people with a carotid plaque. This study was performed in mainly normcholesterolemic people. The present study, which showed an effect of metoprolol CR/XL (100 mg once daily) in patients with hypercholesterolemia on concomitant lipid-lowering therapy, and the BCAPS trial provide the first evidence that shows an effect of $\beta$-blockade on progression of atherosclerosis in humans. Whether a very low dose, such as that used in BCAPS, only affects the carotid bulb and a common dose, such as that used in the ELVA study, affects both the common carotid and carotid bulb IMT must be investigated in further studies.

Several factors may contribute to an antiatherosclerotic effect of metoprolol CR/XL. The atherogenic effect of sympathetic activation can be assumed to result from a complex interaction of hemodynamic factors and an array of biochemical processes. The observed antiatherogenic effects of metoprolol CR/XL and certain other $\beta$-blockers could be due to a combination of the following: $\beta$-blockade in the central nervous system leading to a reduction in peripheral sympathetic nerve discharge; $\beta$-blockade in the heart leading to hemodynamic changes caused by reduced heart rate, blood pressure, and...
contractility; and \(\beta\)-blockade in biochemical systems leading to reduced atherogenic activity, i.e., increased production of prosta-
cyclins\(^{28}\); inhibition of platelet accumulation\(^{29}\); decreased affin-
ity of LDL to proteoglycans in the vessel wall\(^{13}\); and decreased endothe-

tial injury.\(^{10}\) These different effects of \(\beta\)-blockade are
probably complex and cannot be elucidated in this small study.
Further studies are therefore necessary to try to define the pathophysiological mechanisms involved.

In summary, previous studies have shown a beneficial effect of \(\beta\)-blockade in primary and secondary prevention trials as well as a beneficial effect on atheroma development in different animal models. The results from the present study in patients with hypercholesterolemia under concomitant
lipid-lowering treatment are the first clinical data to show an
antatherosclerotic effect of \(\beta\)-blockade as additional therapy to statins. The data indicate that statin treatment and treatment with \(\beta\)-blockers affect different mechanisms in the athero-
sclerotic process and have additive beneficial effects.

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