Low-Dose Metoprolol CR/XL and Fluvastatin Slow Progression of Carotid Intima-Media Thickness
Main Results From the β-Blocker Cholesterol-Lowering Asymptomatic Plaque Study (BCAPS)

B. Hedblad, MD, PhD; J. Wikstrand, MD, PhD; L. Janzon, MD, PhD; H. Wedel, PhD; G. Berglund, MD, PhD

Background—Statins reduce cardiovascular events and progression of carotid intima-media thickness (IMT). β-Blockers are also known to reduce cardiovascular events, but less is known about their effects on carotid IMT.

Methods and Results—We conducted a randomized, double-blind, placebo-controlled, single-center trial to compare the effects of low-dose metoprolol CR/XL (25 mg once daily) and fluvastatin (40 mg once daily) on the progression of carotid IMT during 36 months of treatment in 793 subjects who had carotid plaque but no symptoms of carotid artery disease. Changes in mean IMT in the common carotid artery and maximal IMT in the bulb were the main outcome variables. Death and cardiovascular events were monitored. Progression of IMTmax in the carotid bulb at both 18 and 36 months was reduced by metoprolol CR/XL (20.058 mm/y; 95% CI, 20.094 to 20.023; P = 0.004; and 20.023 mm/y; 95% CI, 20.044 to 20.003; P = 0.014, respectively). Incidence of cardiovascular events tended to be lower in metoprolol CR/XL–treated patients (5 versus 13 patients, P = 0.055). Rate of IMTmax progression in the common carotid at 36 months was reduced by fluvastatin (20.009 mm/y; 95% CI, 20.015 to 20.003; P = 0.002). Women in the fluvastatin group had increased frequency of transiently high liver enzymes.

Conclusions—This is the first randomized trial to show that a β-blocker can reduce the rate of progression of carotid IMT in clinically healthy, symptom-free subjects with carotid plaque. This suggests that β-blockers may have a favorable effect on atherosclerosis development. (Circulation. 2001;103:1721-1726.)

Key Words: drugs n ultrasonics n carotid arteries n trials

Incidence of cardiovascular events in both secondary1 and primary prevention trials2 has been reduced by statins. It has also been shown that statins can reduce the rate of progression of intima-media thickness (IMT) in the carotid arteries.3–6 These results have corroborated the hypothesis of the importance of cholesterol in the development of atherosclerosis.7

β-Blockers have also been shown to reduce cardiovascular events and mortality in secondary8,9 and primary10 prevention studies. In animal studies, β-blockers reduced the degree of diet-induced11 and stress-induced12,13 atherosclerosis, but no direct evidence of an antiatherosclerotic effect of β-blockers, similar to the effects of statins on carotid artery IMT, has been shown in humans.

The objective of the placebo-controlled β-Blocker Cholesterol-Lowering Asymptomatic Plaque Study (BCAPS) was to compare the effect of low-dose metoprolol CR/XL and fluvastatin on the progression of carotid IMT and incidence of myocardial infarction and stroke during 36 months of treatment in subjects who had carotid plaque but no symptoms of carotid artery disease.

Methods

Study Design

BCAPS was a randomized, double blind, placebo-controlled, single-center clinical trial.

Eligibility

The study population consisted of men and women 49 to 70 years of age with plaque in the right carotid artery but with no symptoms of carotid artery disease. Recruitment and screening of participants for the trial were from the Malmö Diet and Cancer cohort.14 A random 50% of those who entered the study between November 1991 and February 1994 (n = 6103) were invited to take part in a study on the epidemiology of carotid artery disease15; 2585 subjects (44%) had carotid plaque (see definition that follows) and were invited to participate in the BCAPS trial; 1548 subjects (60%) came to the enrollment examination (visit 1), which included a 2D B-mode...
ultrasound of the right carotid artery. Seven hundred ninety-seven subjects (435 women) accepted, but 4 subjects were excluded because of protocol violation. None of these subjects had started any study treatment. All participants (n=793) provided written informed consent. The Ethics Committee of Lund University approved the study.

Exclusion Criteria
Exclusion criteria were history of myocardial infarction, angina pectoris, or stroke within the preceding 3 months; history of surgical intervention in the right carotid artery; regular use of β-blockers or statins; blood pressure >160 (systolic) or 95 (diastolic) mm Hg; total cholesterol >8.0 mmol/L; hyperglycemia suspected to require insulin treatment; and conditions that in the opinion of the investigator rendered the subject unsuitable for the trial.

Randomization
Participants were randomly assigned to 1 of 4 drug combination groups according to a factorial design: placebo/placebo, metoprolol CR/XL (25 mg once daily)/placebo, fluvastatin (40 mg once daily)/placebo, or metoprolol CR/XL (25 mg once daily)/fluvastatin (40 mg once daily).

Outcome Measures
The primary outcome measures were change in mean IMT (IMT mean) in the common carotid artery (10-mm-long section) and change in maximum IMT (IMT max) in the carotid bulb. Adverse events, laboratory findings (see below), mortality, and incidence of myocardial infarction and stroke were closely monitored.

Baseline Examination and Follow-Up Visits
The first participant was randomized in November 1994, and the 36-month treatment period was completed for all participants by February 1999. During the first year, visits occurred after 1, 3, 6, and 12 months and every 6 months thereafter. Weight was measured every 6 months, and a fasting lipid profile (total cholesterol, LDL lipoprotein, HDL lipoprotein, and triglycerides) was determined every 6 months, and a fasting lipid profile (total cholesterol, LDL lipoprotein, HDL lipoprotein, and triglycerides) was determined every year. Liver transaminases (AST, ALT) and creatine kinase were obtained at every visit during the first year and then every year thereafter. AST or ALT values ≥ 3 times and creatine kinase values ≥10 times the upper limit of normal were considered elevated during the study. Carotid ultrasound investigation was performed at baseline and after 18 and 36 months of treatment. Subjects who developed high serum cholesterol or high triglycerides during the trial were recommended to follow a low-fat diet, and if evidence of high cholesterol values persisted, these subjects (n=68) were referred to an independent specialist of lipid disorders who had no knowledge of the subject’s randomization assignment. Twenty-two of these subjects were prescribed open lipid-lowering therapy. Other conditions, such as high blood pressure, congestive heart failure, or abnormal laboratory values during the trial, were dealt with in accordance with existing guidelines. Vital status was obtained for all subjects at study termination.

The End Point Committee, consisting of 2 independent scientists, validated all clinical end points at the end of the trial. The Data and Safety Monitoring Board, consisting of independent scientists with expertise in fields relevant to BCAPS, regularly monitored toxicity and blinded outcome data.

B-Mode Ultrasound
An Acuson 128 CT system with a 7-MHz transducer was used. The examination procedure and image analysis, which have been described previously,15,16 were performed by specially trained sonographers certified on completion of an extensive educational program. In brief, the right carotid bifurcation was scanned within a predefined window comprising 3 cm of the distal common carotid artery, the bifurcation, and 1 cm of the internal and external carotid arteries for the presence of plaques, defined as focal IMT >1.2 mm. Thickness of the intima-media complex was measured in the far wall according to the leading edge principle with a specially designed, computer-assisted image analyzing system based on automated detection of the echo structures but with the option for manual corrections by the operator.16 Each image was analyzed without knowledge of the subject’s randomization group.

Statistical Analyses
From previous experience,3 it was anticipated that the annual progression rate of the carotid artery IMT mean in the placebo group would be 0.015 mm/y with an SD of 0.030 mm. A sample size of 200 subjects per group, ie, a total of 800 individuals, was determined, which was based on a withdrawal rate of 10%; a significance level of 5% (2 sided), a power of 0.90, and a treatment effect of 75% (fluvastatin) and 30% (metoprolol CR/XL).

The primary effect variables, changes in IMT mean of the common carotid artery (IMT meanCCA) and carotid bulb (IMT meanBulb), were analyzed for each patient in a linear model (in which all IMT values were log transformed). Change in IMT was defined as the 18- and 36-month value, respectively, while simultaneously considering IMT at baseline. That is, 2 models were formulated with IMT values at 18 and 36 months as the dependent variables, including baseline IMT, the time between measurements, and treatment as covariates. The mean square error from the ANCOVA and Student’s t distribution were used in these calculations. In case of missing 36-month data, the last recorded ultrasound measurements after the baseline examination were used.

Figure 1. Mean change in heart rate (HR), systolic blood pressure (SBP), and carotid artery lumen diameter (LD) in treatment groups from baseline to 18 and 36 months.
The trial did not have adequate statistical power to detect the effects of the combination of fluvastatin and metoprolol CR/XL. In post hoc analyses, the effect of metoprolol CR/XL was evaluated in subjects with serum cholesterol ≥ 6.5 mmol/L at baseline, as were the treatment effect on the combined mean of IMTmaxCCA and IMTmaxBulb and the effect on the combined end point of all-cause mortality and a cardiovascular event (time to first event). A 2-tailed value of $P<0.05$ was considered significant.

The log-rank test was used for comparing clinical event rates. All statistical analyses described were performed according to the intention-to-treat principle.

### Results

**Baseline Characteristics**

The randomization yielded well-balanced treatment groups (Table 1). Mean baseline LDL cholesterol was 4.1 mmol/L. Current medications at baseline or during trial for other cardiovascular compounds (eg, diuretics, calcium channel blockers, ACE inhibitors, aspirin, and postmenopausal hormone replacement therapy for women) were similar in the treatment groups (data not shown). The mean follow-up time was 35.9 months (range, 8 to 40 months).

### Metabolic and Physiological Effects of Treatment

Fluvastatin reduced total cholesterol by 13% (95% CI, −12 to −15) and LDL cholesterol by 23% (95% CI, −21 to −25), whereas cholesterol levels remained unchanged in the placebo group. Serum triglycerides increased 20% (95% CI, 15 to 27) in the metoprolol CR/XL/placebo group, which was not different from the 12% (95% CI, 6 to 18) change in the placebo/placebo group. No effect of metoprolol CR/XL or placebo was observed on other metabolic variables. Compared with the placebo/placebo group, mean heart rate decreased in the metoprolol CR/XL/placebo group by 2.5 bpm (95% CI, −4.2 to −0.7; $P=0.006$), whereas blood pressure (−1.3 mm Hg; 95% CI, −4.2 to 1.6; $P=0.372$) and lumen diameter (−0.027 mm; 95% CI, −0.110 to 0.055; $P=0.515$) were not significantly changed (Figure 1).

### Treatment Effect on Carotid IMT

Baseline ultrasound data are given in Tables 1 and 2. The observed annual IMTmaxCCA progression rate in the placebo/placebo group was 0.013±0.053 mm/y. The annual IMTmax progression rate in the bifurcation in the placebo/placebo group was 0.089±0.154 mm/y. Fluvastatin but not metoprolol CR/XL reduced the rate of progression of IMTmaxCCA compared with placebo after 36 months of treatment (mean difference between groups, −0.009 mm/y; 95% CI, −0.015 to −0.003; $P=0.002$; Table 3).

Metoprolol CR/XL but not fluvastatin was effective in slowing the progression rate of carotid IMTmaxBulb compared with placebo after 36 months of treatment (mean difference between groups, −0.023 mm/y; 95% CI, −0.044 to −0.003; $P=0.014$; Table 3). This effect was evident already after 18...
TABLE 2. Mean Values for and Mean Change in Common and Bifurcation Carotid IMT at Baseline and at the 18- and 36-Month Follow-Up According to Treatment Groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo</th>
<th>Metoprolol CR/XL</th>
<th>Placebo</th>
<th>Fluvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common carotid IMT&lt;sub&gt;mean&lt;/sub&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects, n</td>
<td>369</td>
<td>364</td>
<td>375</td>
<td>358</td>
</tr>
<tr>
<td>Baseline (±SD)</td>
<td>0.893±0.170</td>
<td>0.912±0.202</td>
<td>0.910±0.186</td>
<td>0.895±0.188</td>
</tr>
<tr>
<td>18 mo (±SD)</td>
<td>0.896±0.176</td>
<td>0.908±0.205</td>
<td>0.913±0.186</td>
<td>0.890±0.196</td>
</tr>
<tr>
<td>36 mo (±SD)</td>
<td>0.917±0.203</td>
<td>0.934±0.220</td>
<td>0.945±0.216</td>
<td>0.905±0.205</td>
</tr>
<tr>
<td>Δ18 mo to baseline (±SD)</td>
<td>0.003±0.100</td>
<td>−0.005±0.121</td>
<td>0.003±0.110</td>
<td>−0.005±0.111</td>
</tr>
<tr>
<td>Δ36 mo to baseline (±SD)</td>
<td>0.024±0.132</td>
<td>0.022±0.132</td>
<td>0.036±0.146</td>
<td>0.011±0.114</td>
</tr>
<tr>
<td>ΔBetween groups at 36 mo (95% CI)</td>
<td>Reference</td>
<td>−0.002 (−0.020 to 0.017)</td>
<td>Reference</td>
<td>−0.025 (−0.044 to −0.007)</td>
</tr>
<tr>
<td>Bifurcation carotid IMT&lt;sub&gt;max&lt;/sub&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects, n</td>
<td>369</td>
<td>364</td>
<td>375</td>
<td>358</td>
</tr>
<tr>
<td>Baseline (±SD)</td>
<td>1.875±0.541</td>
<td>1.936±0.634</td>
<td>1.886±0.570</td>
<td>1.926±0.609</td>
</tr>
<tr>
<td>18 mo (±SD)</td>
<td>1.982±0.572</td>
<td>1.937±0.572</td>
<td>1.954±0.589</td>
<td>1.965±0.554</td>
</tr>
<tr>
<td>36 mo (±SD)</td>
<td>2.133±0.630</td>
<td>2.003±0.624</td>
<td>2.097±0.670</td>
<td>2.095±0.652</td>
</tr>
<tr>
<td>Δ18 mo to baseline (±SD)</td>
<td>0.112±0.376</td>
<td>0.023±0.325</td>
<td>0.072±0.373</td>
<td>0.063±0.334</td>
</tr>
<tr>
<td>Δ36 mo to baseline (±SD)</td>
<td>0.227±0.421</td>
<td>0.154±0.411</td>
<td>0.211±0.455</td>
<td>0.170±0.374</td>
</tr>
<tr>
<td>ΔBetween groups at 36 mo (95% CI)</td>
<td>Reference</td>
<td>−0.073 (−0.133 to −0.013)</td>
<td>Reference</td>
<td>−0.041 (−0.102 to 0.019)</td>
</tr>
</tbody>
</table>

months of treatment (mean difference between groups, −0.058 mm/y; 95% CI, −0.094 to −0.023; P=0.004). Metoprolol CR/XL also reduced the progression rate of IMT<sub>max</sub>Bulb after 36 months of treatment in the subgroup with serum cholesterol ≥6.5 mmol/L (n=270) at baseline (mean difference between groups, −0.053 mm/y; 95% CI, −0.087 to −0.019; P=0.001).

The combined mean of IMT<sub>mean</sub>CCA and carotid IMT<sub>max</sub> Bulb was significantly reduced after 18 months of treatment by metoprolol CR/XL compared with placebo (mean difference between groups, −0.031 mm/y; 95% CI, −0.050 to −0.011; P=0.002) but not by fluvastatin compared with placebo (mean difference between groups, −0.007 mm/y; 95% CI, −0.026 to 0.001; P=0.476). After 36 months, both metoprolol CR/XL and fluvastatin reduced this composite variable (mean difference for metoprolol CR/XL, −0.012 mm/y; 95% CI, −0.023 to −0.001; P=0.030; for fluvastatin, −0.011 mm/y; 95% CI, −0.022 to −0.001; P=0.034).

In neither the common carotid artery nor the bifurcation was any significant interaction observed; ie, neither an additive nor a synergistic effect could be detected between the metoprolol CR/XL and fluvastatin groups.

Incidence of Clinical Events During Follow-Up

Of the participants, 18 had a cardiovascular event (1 subject suffered a fatal and 7 had a nonfatal myocardial infarction; 2 died suddenly because of ischemic heart disease; 8 suffered a nonfatal stroke). The cardiovascular event rate tended to be lower in patients treated with metoprolol CR/XL compared with patients not treated with metoprolol CR/XL (5 versus 13 patients, P=0.055; Figure 2, top). The corresponding numbers in patients treated and not treated with fluvastatin were 7 and 11 patients, respectively (P=0.350). The combined end point of all-cause mortality and a cardiovascular event (time to first event) was significantly lower in patients with than without treatment with metoprolol CR/XL (8 versus 19 patients, P=0.031; metoprolol CR/XL group: 4 deaths, 3 myocardial infarctions, and 1 stroke; placebo group: 7, 5, and 7, respectively; Figure 2, bottom).

Tolerability

Permanent withdrawal from randomized treatment was 15% in the metoprolol CR/XL/placebo group, 21% in the fluvastatin/placebo group, and 23% in the placebo/placebo group. The withdrawal rate in the group receiving the combination of the 2 drugs was 25%. Compared with women without corresponding treatment, women receiving treatment with fluvastatin had an increased frequency of transiently high
Liver enzymes (10.2% versus 1.8%, \(P\), 0.001). Incidence of cancer or minor adverse events did not differ between the treatment groups.

**Discussion**

This is the first evidence from a large-scale randomized controlled study to show that a \(\beta\)-blocker can reduce the rate of progression of carotid IMT in subjects with carotid plaque but with no symptoms of carotid artery disease. The results may indicate favorable effects on early stages of atherosclerosis development. The results also indicated a beneficial effect on the incidence of cardiovascular events and the combined end point of all-cause mortality and a cardiovascular event (time to first event), although the statistical power was low. The effect was achieved in asymptomatic middle-aged men and women and with a very low dose of metoprolol CR/XL (25 mg once daily) that did not decrease blood pressure. The results may point to an important role of the autonomic nervous system in atherosclerosis development in otherwise healthy people with carotid plaque.

**Study Group**

The treatment groups were recruited from a screening of the general population as part of a large-scale screening procedure in a diet/health project.\textsuperscript{14,15} At 51 to 55 years of age, almost 35% of the participants had plaque; at 61 to 65 years of age, 56% were found to have plaque.\textsuperscript{15} The background population to which the findings in this trial can be generalized is thus very large.

**Ultrasound Findings**

The increase of IMTmean CCA in the placebo/placebo group of BCAPS (0.013 mm/y) is of the same order as findings in some other major studies that used the ultrasound technique,\textsuperscript{3,4} in which progression rates in the placebo/placebo group varied from 0.006 to 0.030 mm/y. The progression rate for IMT\textsubscript{max} in the bifurcation (bulb) in the BCAPS placebo/placebo group (0.089 mm/y) is also comparable to the progression rate in the Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC-II) study (0.100 mm/y).\textsuperscript{4}

Metoprolol CR/XL 25 mg once daily was effective in slowing the progression of IMT\textsubscript{max} in the bifurcation, whereas no significant effect was seen on IMT measurements in the common carotid artery. Fluvastatin, on the other hand, slowed progression in the common carotid, but not to a significant extent in the bifurcation. However, after 3 years of follow-up, the combined mean of IMT\textsubscript{mean CCA} and IMT\textsubscript{max Bulb} was significantly reduced by both metoprolol CR/XL and fluvastatin. In the Effect on Long-term treatment of metoprolol CR/XL on surrogate Variables for Atherosclerosis disease (ELVA) study (a 3-year randomized study by O. Wiklund, MD, PhD, et al, on the effect of metoprolol CR/XL on carotid IMT in subjects with hypercholesterolemia that has been submitted for publication), a significant effect of metoprolol CR/XL was observed in the common carotid artery. That study, in contrast to BCAPS, included only patients with hypercholesterolemia and used 100 mg instead of 25 mg metoprolol CR/XL. The finding that fluvastatin reduced the progression rate of IMT\textsubscript{mean CCA} corroborates the results of several earlier trials evaluating the effect of statins on IMT in the common carotid artery.\textsuperscript{3–6} In 1 study,\textsuperscript{6} a statin was also shown to slow progression of the bifurcation measurement. Different intervention effects of statins and \(\beta\)-blockers in different parts of the arterial tree cannot be excluded, and it may be that the pathophysiological mechanisms involved in the development of atherosclerosis might differ between straight arterial parts and bifurcations.

Further studies are needed to investigate the dose-dependent effects of metoprolol CR/XL in different arterial regions. However, we find it highly interesting that a dose as low as 25 mg metoprolol CR/XL once daily, a dose very seldom used to treat hypertension or angina pectoris, has an effect on carotid artery IMT. This illustrates the importance of the autonomic nervous system in the pathophysiology of atherosclerosis development. Stress-induced, sympathetic nervous system–mediated adhesion of platelets in bifurcations and atherosclerosis development have been shown in animal studies to be prevented by \(\beta\)-blocker treatment.\textsuperscript{11–13,17,18} Furthermore, \(\beta\)-blockers have been shown to increase the production of prostacyclin in animals,\textsuperscript{19} which may be another factor of importance for the antiatherosclerotic effect observed after \(\beta\)-blocker treatment. Studies in humans suggest that atherosclerotic
lesions are predominantly localized at sites of low shear stress\textsuperscript{20–22} in regions with nonlaminar, low flow with recirculation and stagnant flow zones. One might speculate that these flow disturbances may be lessened by \( \beta \)-blocker treatment.\textsuperscript{22} We observed no significant change in carotid artery lumen diameter, indicating that vasodilatation was not responsible for the observed effect of metoprolol CR/XL.

**Clinical Implications**

The findings of an antiatherosclerotic effect of metoprolol CR/XL extend the knowledge of the beneficial effects of \( \beta \)-blockers. The evidence of a clinical benefit of \( \beta \)-blockers in primary and secondary prevention of patients with hypertension,\textsuperscript{10} previous myocardial infarction,\textsuperscript{8} and heart failure\textsuperscript{6} is extended in this study to middle-aged subjects with plaque in the carotid bifurcation. The strength of the evidence of a beneficial effect of \( \beta \)-blockers in the studies cited here,\textsuperscript{8–10} however, it should be pointed out that the study group in BCAPS has a relatively low cardiovascular risk (ie, hypertensives and patients with total cholesterol > 8.0 mmol/L were excluded).

**Conclusions**

The results from the BCAP study provide the first evidence in humans that a \( \beta \)-blocker can slow progression of carotid IMT. The results may indicate favorable effects on early stages of atherosclerosis development. The possible different intervention effects of statins and \( \beta \)-blockers on atherosclerosis development need further exploration.

**Acknowledgments**

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**References**


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