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## PROBUCOL AND MULTIVITAMINS IN THE PREVENTION OF RESTENOSIS AFTER CORONARY ANGIOPLASTY

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### ABSTRACT

**Background** Oxidizing metabolites generated at the site of coronary angioplasty can induce chain reactions that may lead to restenosis. Antioxidants may counter oxidative stress and modify neointimal formation and vascular remodeling. Experimental data and small clinical studies have suggested that antioxidants may prevent restenosis after angioplasty. In a double-blind, randomized trial, we studied whether drugs with antioxidant properties decrease the incidence and severity of restenosis after angioplasty.

**Methods** One month before angioplasty, 317 patients were randomly assigned to receive one of four treatments: placebo, probucol (500 mg), multivitamins (30,000 IU of beta carotene, 500 mg of vitamin C, and 700 IU of vitamin E), or both probucol and multivitamins — all given twice daily. Patients were treated for four weeks before and six months after angioplasty. Patients received an extra 1000 mg of probucol, 2000 IU of vitamin E, both probucol and vitamin E, or placebo 12 hours before angioplasty, according to their treatment assignments. Base-line and follow-up angiograms were interpreted by blind investigators using a quantitative approach.

**Results** The mean ( $\pm$ SD) reduction in luminal diameter six months after angioplasty was  $0.12 \pm 0.41$  mm in the probucol group,  $0.22 \pm 0.46$  mm in the combined-treatment group,  $0.33 \pm 0.51$  mm in the multivitamin group, and  $0.38 \pm 0.50$  mm in the placebo group ( $P=0.006$  for those receiving vs. those not receiving probucol, and  $P=0.70$  for those receiving vs. those not receiving vitamins). Restenosis rates per segment were 20.7 percent in the probucol group, 28.9 percent in the combined-treatment group, 40.3 percent in the multivitamin group, and 38.9 percent in the placebo group ( $P=0.003$  for probucol vs. no probucol). The rates of repeated angioplasty were 11.2 percent, 16.2 percent, 24.4 percent, and 26.6 percent, respectively ( $P=0.009$  for probucol vs. no probucol).

**Conclusions** The antioxidant probucol is effective in reducing the rate of restenosis after balloon coronary angioplasty. (N Engl J Med 1997;337:365-72.)

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THE high incidence of restenosis after balloon coronary angioplasty continues to limit the long-term success of the procedure.<sup>1</sup> Clinical trials of several pharmacologic agents have been conducted in an attempt to prevent restenosis, but none have been found to be useful. Data from studies in animals have demonstrated a beneficial effect of antioxidants on both cell proliferation and arterial remodeling after balloon angioplasty.<sup>2-5</sup> Furthermore, a few small studies have suggested a promising role for drugs with antioxidant properties in the prevention of restenosis in humans.<sup>6-10</sup> We conducted the Multivitamins and Probulcol (MVP) trial to test the hypothesis that the antioxidant probucol, multivitamins (a combination of the antioxidant vitamins E and C and beta carotene), or the combination would reduce the rate and severity of restenosis as assessed by quantitative coronary angiography within the first six months after angioplasty. Probulcol, previously used as a lipid-lowering agent, has powerful antioxidant properties and was therefore selected for this study.

### METHODS

#### Study Design and Study Population

The MVP study was a double-blind, placebo-controlled, randomized trial with four study groups. The protocol was approved by the institutional review board at the Montreal Heart Institute. Patients referred for elective coronary angioplasty were evaluated at least 30 days before the scheduled procedure. Eligible patients were asked to participate and to provide written informed consent. Preliminary evaluation included a medical history taking and

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physical examination, electrocardiography, blood count, and blood chemistry tests including measurements of serum lipids and glucose and liver, kidney, and thyroid function. Patients were eligible if they were scheduled to undergo standard balloon angioplasty on at least one native coronary artery and had at least one target lesion with stenosis of 50 percent or more of the luminal diameter as measured by calipers on the angiogram. We excluded subjects unable to participate in the pretreatment evaluation or unable to return for follow-up; those who had had a myocardial infarction within the previous seven days; patients scheduled to undergo stenting or atherectomy; those who had undergone angioplasty for another lesion in the preceding six months or who were being treated for a restenotic lesion; and patients undergoing angioplasty of a bypass graft or of a bypassed native vessel with a patent graft.

### Randomization and Drug Regimen

Beginning 30 days before the scheduled angioplasty, patients were randomly assigned to receive one of four treatments: probucol alone, multivitamins alone, the combination of probucol and multivitamins, or placebo. Two tablets of the multivitamin complex, each of which contained 15,000 IU of beta carotene, 250 mg of vitamin C, and 350 IU of vitamin E (*dl*-alpha-tocopherol), or the matched placebo were administered twice daily. Probuco (two 250-mg tablets; Lorelco, Merrell, Kansas City, Mo.) or matched placebo was also administered twice daily. All patients received an extra dose of 2000 IU of vitamin E, 1000 mg of probucol, both vitamin E and probucol, or placebo 12 hours before angioplasty, according to their random treatment assignments. All patients in whom angioplasty was successful and who did not have procedure-related cardiac complications continued to receive the assigned study treatment until follow-up angiography was performed.

### Angioplasty Procedure and Angiographic Methods

All patients received aspirin (325 mg daily) for the entire study period. Balloon angioplasty was performed according to standard techniques. Control angiography both before and after angioplasty and at follow-up was preceded by the administration of intracoronary nitroglycerin (0.3 mg). The sequence of contrast injections with the exact degree of angulation was recorded for angiography performed before the procedure, immediately after the final balloon inflation, 15 minutes later, and at follow-up. Electrocardiograms were obtained before angioplasty, immediately thereafter, and daily until discharge. Creatine kinase and creatine kinase MB fraction were measured on the evening after the procedure and the following morning.

Patients were excluded from the study if the stenosed coronary-artery segment could not be dilated; if initially successful angioplasty was followed by persistent abrupt closure; if a Q-wave infarction occurred in the territory of the dilated artery; if angioplasty was unsuccessful, necessitating emergency revascularization; or if the results of angioplasty were suboptimal and a stent was implanted.

### Follow-up Evaluation

Patients who underwent successful angioplasty were discharged with one month's supply of the study medication, aspirin, and any other drugs judged necessary. They were specifically asked not to take additional vitamins. Patients returned at one, three, and six months for a new supply of drugs; at this time, pill counts and a clinical evaluation were performed. Patients were assessed for ischemic symptoms and for any symptoms, whether or not they were related to the study medication or the angioplasty procedure. Compliance was further evaluated by measurements of drug levels in serum at each visit. These levels were not made available to investigators during the trial, in order to maintain blinding. Blood-chemistry values assessed at base line were measured again at discharge and at each follow-up visit. The one-month and six-

month visits included treadmill exercise tests. Patients were readmitted for follow-up coronary angiography five to seven months after angioplasty. Those in whom arteriography was performed for clinical reasons before the fifth month returned for another angiographic examination at five to seven months if there was no definite arteriographic evidence of restenosis in one or more dilated segments.

### Assessment of Diet and Dietary Intervention

Each patient had four complete food-intake evaluations; the modified Burke questionnaire<sup>11</sup> was used at base line and a food journal at other visits, with questions to assess the intake of fruit, vegetables, and dietary supplements. Food composition was determined according to the Canadian Nutrient File.<sup>12</sup> Patients were given specific dietary counseling at each visit. The American Heart Association Step 1 diet<sup>13</sup> was taught to all patients. Specific attention was given to vitamins and minerals usually consumed. Daily dietary intake of vitamins E and C and beta carotene was limited, and patients were instructed to avoid vitamin and mineral supplements. The diet met 1990 Canadian standards for all nutrients.<sup>14</sup>

### Measurement of Drug Levels

The levels of probucol and alpha-tocopherol in serum were determined by isocratic reverse-phase high-performance liquid chromatography.<sup>15</sup> All samples were frozen at  $-70^{\circ}\text{C}$  and analyzed in duplicate.

### Quantitative Coronary Angiography

The four coronary arteriograms (obtained before the procedure, immediately after the procedure, 15 minutes after the procedure, and at the final follow-up visit) were analyzed together by experienced technicians supervised by a cardiovascular radiologist who was blinded to the patients' treatment assignments, using the Coronary Measurement System (Medis, Nueneen, the Netherlands).<sup>16</sup> Measurements were made in a single projection, showing the most severe stenosis. The projection that showed the arterial segment with good opacification, as nearly perpendicular to the x-ray beam as possible, was selected for analysis. Whenever possible, the same projection was used in all four arteriograms to allow more accurate comparison. The variation among repeated measurements of the percentage of stenosis in our laboratory is 8.6 percent when frames recorded one to six months apart are analyzed.<sup>17</sup> A change of 15 percent, or roughly 2 SD of the mean variation, was taken to indicate a clinically important change.

### Definitions and End Points

Restenosis was evaluated in terms of both numbers of patients and numbers of dilated coronary-artery segments. All measurements were made by quantitative angiographic methods. Only patients in whom at least one lesion was successfully dilated were included in the analysis of restenosis. Successful dilation was defined as residual stenosis of less than 50 percent of the luminal diameter (as measured 15 minutes after the procedure), with improvement of at least 15 percent in luminal diameter as compared with the measurement before the procedure. The angiogram obtained 15 minutes after angioplasty was used in the analysis of outcomes in order to exclude the effects of early elastic recoil, at least in part, from the assessment of restenosis.

The primary end point with respect to efficacy was the extent of restenosis, defined as the reduction in the minimal luminal diameter from the angiogram obtained 15 minutes after angioplasty to that obtained at follow-up. In patients who were undergoing angioplasty on more than one lesion, the means of the luminal diameters for all successfully dilated sites 15 minutes after angioplasty and at follow-up were computed. Restenosis was also defined as a dichotomous outcome variable and analyzed in terms of the change in the percentage of stenosis. A patient was defined

as having restenosis if at least one dilated segment had stenosis of 50 percent or more of the luminal diameter at follow-up, with an increase of 15 percent or more in the degree of stenosis from that measured on the angiogram obtained 15 minutes after angioplasty. Only successfully dilated segments were considered in the evaluation of the proportion of segments with restenosis. Major secondary clinical end points were death, myocardial infarction, coronary bypass surgery, and repeated angioplasty.

### Statistical Analysis

A previous study at our institution had shown a mean ( $\pm$ SD) reduction of  $0.38 \pm 0.44$  mm in luminal diameter six months after angioplasty.<sup>18</sup> We calculated that a total of 364 patients were needed for us to be able to detect a 40 percent reduction in luminal loss during the six months after angioplasty, with a power of 0.90 and a two-tailed significance level of 0.05. Assuming a dropout rate of 10 percent and a 90 percent rate of compliance with the protocol, we increased the target sample size by roughly 20 percent to 440 patients.

For the patients who completed the trial without protocol violations (criteria included taking more than 80 percent of the assigned study medications), the primary end point with respect to efficacy — the extent of restenosis — was evaluated with two-way analysis of covariance with control for the luminal diameter 15 minutes after angioplasty and for the distribution of target vessels. In the intention-to-treat analysis, which included all randomized patients with successful angioplasty, the dichotomous outcome (restenosis or no restenosis) was analyzed similarly by multiple logistic regression. All patients who withdrew early were considered to have restenosis for purposes of the intention-to-treat analysis. Patients who completed the trial with protocol violations were considered to have restenosis or no restenosis depending on the measurements obtained at the final angiography.

The proportion of dilated segments with restenosis was analyzed by the generalized-estimating-equations technique,<sup>19</sup> which takes into account potential interdependence among multiple segments in the same patient. All secondary end points were analyzed in a way similar to that used for the primary efficacy end point. Depending on the outcome, analysis of covariance or multiple logistic regression was used. The proportions of patients reporting adverse effects of treatment were compared with use of chi-square tests. An interim statistical analysis, based on the Pocock constant-boundary approach,<sup>20</sup> was scheduled after the first 200 patients completed follow-up (significance levels of 0.0294 were used for both interim and final analyses in order to maintain an overall significance level of 0.05).

## RESULTS

A total of 317 patients had entered the trial when the interim analysis was performed on data for the first 200 patients. The results showed that probucol had a significant effect on the primary efficacy end point ( $P=0.018$ ). The study was therefore stopped when the additional 117 patients completed follow-up.

During the study, 1179 patients were screened, of whom 862 were excluded. Patients were distributed in the four groups as follows: 80 received probucol alone, 78 multivitamins alone, 80 probucol plus multivitamins, and 79 placebo. Selected demographic, clinical, and angiographic characteristics of the groups are shown in Table 1. The only significant differences at base line were in sex and the distribution of target vessels; there were more women in the combined-treatment group, and a greater number of patients were scheduled for dilation of the left anterior descending artery in the multivitamin group.

These variables were not associated with the efficacy end points.

Eleven patients were randomly assigned to study groups but did not undergo angioplasty; seven were treated medically, three required bypass surgery, and one died before the scheduled date of angioplasty. Standard balloon angioplasty was successful in 81 to 84 percent of patients in each study group. There were 51 failures of angioplasty; 36 patients did not meet the angiographic criteria for successful angioplasty, 10 patients underwent stenting, 2 required urgent bypass surgery, and 3 had a Q-wave myocardial infarction within 24 hours after the procedure.

Twelve patients discharged after successful angioplasty did not undergo final arteriography. One of these patients died, three withdrew from the study, three underwent repeated angioplasty, three underwent surgical revascularization without meeting the quantitative criteria for restenosis at early angiography, one with myocardial infarction did not undergo follow-up angiography, and one was excluded because of inadequate angiographic data. Thirteen patients were not adequately compliant with the study regimen (three in the probucol group, three in the combined-treatment group, six in the multivitamin group, and one in the placebo group). The base-line characteristics examined in the 317 patients who underwent randomization were also evaluated in the 255 patients in the intention-to-treat analysis who had successful angioplasty and the 230 of these patients who completed the study without protocol violations. In these populations, the same differences among the groups were found.

### Angiographic Analysis

Table 2 summarizes quantitative angiographic findings in the 230 patients who completed the study without protocol violations. The mean reduction in luminal diameter among the patients (the primary efficacy end point) was  $0.12 \pm 0.41$  mm in the probucol group,  $0.22 \pm 0.46$  mm in the combined-treatment group,  $0.33 \pm 0.51$  mm in the multivitamin group, and  $0.38 \pm 0.50$  mm in the placebo group ( $P=0.006$  for patients given probucol as compared with those not given probucol, and  $P=0.70$  for those given vitamins as compared with those not given vitamins). There was no evidence of significant interaction between probucol and multivitamins in the factorial design ( $P=0.13$ ). However, considering that the power of the study to detect such an interaction was 0.33, we performed a post hoc analysis comparing each two of the four groups separately, with adjustment for a possible interaction. The results remained significant for all angiographic end points in the comparison of the probucol and placebo groups. When the 13 non-compliant patients were added to the analysis, the mean reduction in luminal diameter was  $0.13 \pm 0.41$  mm for the probucol group,  $0.23 \pm 0.45$  mm for the

**TABLE 1.** BASE-LINE DEMOGRAPHIC, CLINICAL, AND ANGIOGRAPHIC CHARACTERISTICS OF THE FOUR STUDY GROUPS.\*

CHARACTERISTIC	PLACEBO (N=79)	MULTIVITAMINS (N=78)	PROBUCOL AND MULTIVITAMINS (N=80)	PROBUCOL (N=80)
Mean ( $\pm$ SD) age — yr	60.3 $\pm$ 8.4	57.7 $\pm$ 11.1	57.5 $\pm$ 9.0	58.5 $\pm$ 9.3
	percentage of patients			
Female sex†	22.8	15.4	35.0	18.8
Current or former smoker	82.3	89.7	78.8	83.8
Current smoker	15.2	24.4	25.0	21.3
History of diabetes	8.9	12.8	15.0	5.0
History of hypertension	40.5	39.7	41.3	31.3
Exertional angina (CCS class)				
I	5.1	7.7	11.3	15.2
II	62.0	66.7	55.0	54.4
III	22.8	16.7	22.5	17.7
IV	0	1.3	1.3	2.5
Prior MI	43.0	41.0	42.5	45.0
Prior CABG	6.3	3.9	11.3	5.0
Prior PTCA	11.4	3.9	10.0	10.0
No. of diseased vessels‡				
1	28.6	49.2	41.7	34.9
2	49.2	38.1	35.0	42.9
3	22.2	12.7	23.3	22.2
	percentage of segments			
Target vessel§				
Left anterior descending coronary artery	34.7	56.3	35.9	23.5
Left circumflex coronary artery	30.6	25.4	38.5	39.5
Right coronary artery	34.7	18.3	25.6	37.0
Moderate or severe calcification	4.2	2.8	3.9	1.2
Eccentricity	31.9	32.8	35.1	30.9
Lesion angulation >45 degrees	5.4	2.9	2.6	2.5
Moderate tortuosity	2.8	0	0	4.9
Bifurcation	16.7	9.9	23.1	12.4

\*CCS denotes Canadian Cardiovascular Society, MI myocardial infarction, CABG coronary-artery bypass grafting, and PTCA percutaneous transluminal coronary angioplasty.

†P=0.020 by the chi-square test for the comparison among the groups.

‡The percentages are based on the 255 patients in the intention-to-treat analysis who had successful angioplasty.

§P=0.003 by the chi-square test for the comparison among the groups.

combined-treatment group,  $0.34 \pm 0.51$  mm for the multivitamin group, and  $0.39 \pm 0.51$  mm for the placebo group ( $P=0.003$  for probucol vs. no probucol, and  $P=0.65$  for vitamins vs. no vitamins).

Restenosis occurred in 20.7 percent of the dilated segments in the probucol group, 28.9 percent in the combined-treatment group, 40.3 percent in the multivitamin group, and 38.9 percent in the placebo group ( $P=0.003$  for probucol vs. no probucol, and  $P=0.89$  for vitamins vs. no vitamins). Rates of restenosis among the patients were 25.0 percent in the probucol group, 35.9 percent in the combined-treatment group, 42.2 percent in the multivitamin group, and 42.9 percent in the placebo group ( $P=0.004$  for probucol vs. no probucol, and  $P=0.49$  for vitamins vs. no vitamins). Figure 1 shows the cumulative-

frequency curves for the minimal luminal diameter in all study groups.

#### Major Clinical End Points

The numbers of deaths, myocardial infarctions, and bypass operations were very small (Table 3). Rates of repeated angioplasty were 11.2 percent in the probucol group, 16.2 percent in the combined-treatment group, 24.4 percent in the multivitamin group, and 26.6 percent in the placebo group ( $P=0.009$  for probucol vs. no probucol, and  $P=0.75$  for vitamins vs. no vitamins).

#### Side Effects and Drug and Lipid Levels

Diarrhea was reported by 15.6 percent of the probucol group, 32.8 percent of the combined-treat-

**TABLE 2.** QUANTITATIVE ANGIOGRAPHIC ANALYSIS OF THE 230 PATIENTS WHO COMPLETED THE STUDY WITHOUT PROTOCOL VIOLATIONS.\*

VARIABLE	PLACEBO (N=62)	MULTIVITAMINS (N=54)	PROBUCOL AND MULTIVITAMINS (N=56)	PROBUCOL (N=58)	P VALUE†	
					PROBUCOL VS. NO PROBUCOL	VITAMINS VS. NO VITAMINS
millimeters						
Minimal luminal diameter						
Before PTCA	0.85±0.26	0.83±0.32	0.88±0.28	0.91±0.29	0.15	0.47
Immediately after PTCA	1.84±0.38	1.78±0.37	1.83±0.37	1.99±0.39	0.05	0.04
15 Min after PTCA	1.80±0.38	1.73±0.34	1.76±0.35	1.91±0.36	0.14	0.02
At follow-up	1.43±0.58	1.40±0.55	1.54±0.61	1.79±0.45	0.006	0.70
Reference diameter						
Before PTCA	2.74±0.49	2.77±0.47	2.67±0.47	2.81±0.49	0.88	0.42
Immediately after PTCA	2.76±0.49	2.74±0.46	2.65±0.48	2.83±0.49	0.88	0.14
15 Min after PTCA	2.73±0.47	2.73±0.46	2.64±0.45	2.80±0.46	0.91	0.22
At follow-up	2.75±0.52	2.75±0.49	2.67±0.57	2.84±0.51	1.0	0.23
Gain immediately after PTCA	0.99±0.38	0.96±0.32	0.95±0.34	1.08±0.34	0.42	0.16
Gain 15 min after PTCA	0.95±0.38	0.90±0.31	0.88±0.30	1.00±0.34	0.79	0.09
Total loss (immediately after PTCA to follow-up)	0.41±0.51	0.39±0.50	0.29±0.49	0.20±0.39	0.015	0.57
Early loss (immediately after PTCA to 15 min after PTCA)	0.03±0.17	0.06±0.17	0.07±0.17	0.08±0.17	0.42	0.31
Late loss (15 min after PTCA to follow-up)	0.38±0.50	0.33±0.51	0.22±0.46	0.12±0.41	0.006	0.70

\*Plus-minus values are means ±SD. PTCA denotes percutaneous transluminal coronary angioplasty. To keep the level of significance for the group of three tests at  $\alpha=0.05$ , the levels of significance for testing interaction ( $\alpha_1$ ) and main effects ( $\alpha_2$  and  $\alpha_3$ ) should be reduced (e.g., if  $\alpha_1=0.01$  and  $\alpha_2=\alpha_3=0.02$ , the Bonferroni inequality yields  $\alpha \leq \alpha_1 + \alpha_2 + \alpha_3 = 0.05$ ).

†P values for late loss are based on two-way analysis of covariance (interaction between probucol and vitamins) of the luminal diameter at follow-up, with control for the luminal diameter 15 minutes after angioplasty and the distribution of target vessels. All other P values are based on similar analyses of covariance except for reference and base-line minimal luminal diameters, which are based on analysis of variance.

ment group, 7.8 percent of the multivitamin group, and 1.6 percent of the placebo group ( $P=0.001$ ). Yellow skin pigmentation was observed in 56 percent of all patients taking multivitamins.

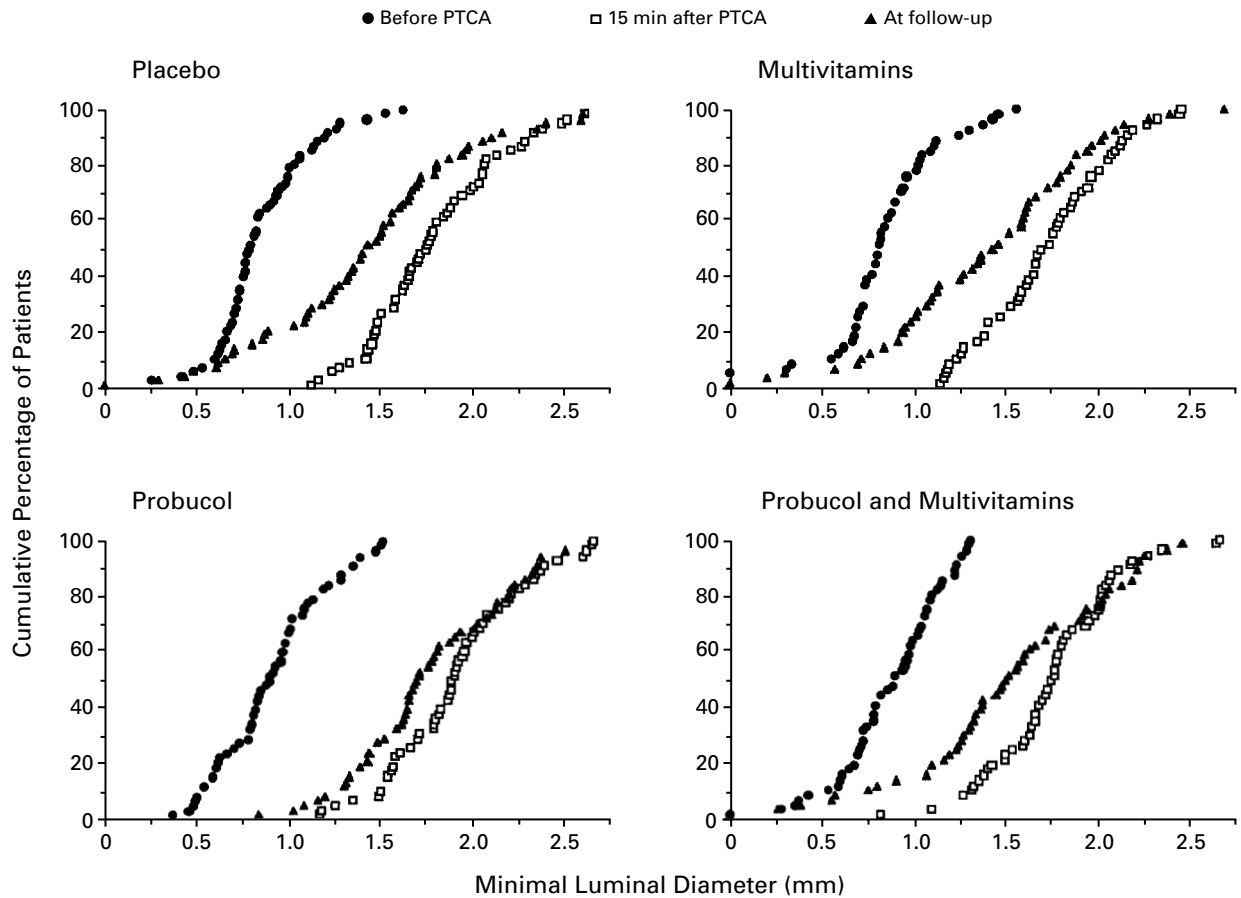
Probucol and alpha-tocopherol levels had already reached plateaus at the time of angioplasty (Table 4). Total and low-density lipoprotein (LDL) cholesterol levels at follow-up were 9 percent and 3 percent lower, respectively, in the probucol group than in the placebo group. As expected, probucol also reduced high-density lipoprotein cholesterol levels by 41 percent.

### DISCUSSION

To date, no pharmacologic approach has been conclusively shown to prevent coronary restenosis after balloon angioplasty. Four small studies suggested that probucol treatment, started before angioplasty, may prevent restenosis, but they were not double-blinded and two did not use quantitative angiographic methods.<sup>6-9</sup> The reported rate of restenosis was, nevertheless, as low as 8 percent when probucol was given from 30 days before angioplasty.<sup>6</sup> Data from our study now provide strong evidence that probucol therapy initiated 30 days before angioplasty and given for 6 months thereafter prevents restenosis, as documented angiographically. As compared with placebo, probucol given alone resulted in decreases of 68 percent in late reductions in luminal diameter,

47 percent in the proportion of dilated coronary-artery segments with restenosis, and 58 percent in the need for repeated angioplasty. The importance of beginning therapy with probucol before angioplasty appears critical, considering the negative results of the Angioplasty plus Probucol/Lovastatin Evaluation, in which probucol and lovastatin treatment was started between 48 hours before and 24 hours after angioplasty.<sup>21</sup> Data suggesting that probucol accumulates slowly in tissue<sup>22</sup> probably explain these results.

Our study design included 30 days of pretreatment to ensure adequate control of the oxidative stress that occurs early after angioplasty. Damaged endothelium, activated platelets, and neutrophils at the angioplasty site can generate reactive intermediates.<sup>23</sup> These oxidizing metabolites can induce chain reactions that result in endothelial dysfunction<sup>24</sup> and oxidation of LDL.<sup>25</sup> Macrophages activated by oxidized LDL and dysfunctional endothelium can, in turn, release several growth factors that promote tissue proliferation. Extracellular changes also occur as metalloproteinases are secreted, accompanied by an increase in matrix synthesis.<sup>26</sup> Cross-linking of collagen could cause chronic vascular constriction.<sup>27</sup> Furthermore, endothelial dysfunction may hinder beneficial vascular remodeling by limiting flow-dependent changes in arterial dimensions.<sup>28</sup>



**Figure 1.** Cumulative Distribution of the Minimal Luminal Diameter before Angioplasty, 15 Minutes after Angioplasty, and at Follow-up among Patients in the Four Study Groups Who Completed the Study without Protocol Violations. The curves clearly favor probucol at follow-up. PTCA denotes percutaneous transluminal coronary angioplasty.

**TABLE 3.** MAJOR CLINICAL EVENTS IN THE FOUR STUDY GROUPS.\*

OUTCOME	PLACEBO (N=79)	MULTIVITAMINS (N=78)	PROBUCOL AND MULTIVITAMINS (N=80)	
			PROBUCOL (N=80)	PROBUCOL AND MULTIVITAMINS (N=80)
number (percent)				
Death	1 (1.3)	0	1 (1.2)	0
Myocardial infarction	0	1 (1.3)	2 (2.5)	2 (2.5)
CABG	2 (2.5)	5 (6.4)	1 (1.2)	2 (2.5)
Repeated PTCA†	21 (26.6)	19 (24.4)	13 (16.2)	9 (11.2)

\*CABG denotes coronary artery bypass grafting, and PTCA percutaneous transluminal coronary angioplasty.

†P=0.009 for the comparison of probucol with no probucol, and P=0.75 for the comparison of vitamins with no vitamins, by multiple logistic regression.

The powerful antioxidant effects of probucol<sup>29</sup> may have prevented endothelial dysfunction<sup>30</sup> and LDL oxidation<sup>31</sup> in our patients; this drug may also have modified neointimal formation and vascular remodeling, which are involved in the process of restenosis. Other mechanisms of action have to be considered, however, in view of the disappointing results of therapy with multivitamins in this study. The hypocholesterolemic effect of probucol is weak and is unlikely by itself to be responsible for the positive results, considering that high-dose lovastatin started 7 to 10 days before angioplasty failed to prevent restenosis in a recent trial.<sup>32</sup> The role of probucol in reverse cholesterol transport and interleukin secretion, however, may have contributed to our good results. In particular, inhibition by probucol of the secretion of interleukin-1 by macrophages<sup>33</sup> may have decreased the secretion of metalloproteinases by smooth-muscle cells<sup>34</sup> and affected remodeling of the extracellular matrix. Whether probucol acted by pre-

TABLE 4. LIPID AND DRUG LEVELS IN THE FOUR STUDY GROUPS.\*

VARIABLE†	PLACEBO	MULTIVITAMINS	PROBUCOL AND MULTIVITAMINS	PROBUCOL	P VALUE	
					PROBUCOL VS. NO PROBUCOL	VITAMINS VS. NO VITAMINS
Total cholesterol (mmol/liter)						
At base line	6.04±1.00	6.17±1.05	6.25±1.15	6.03±1.01	0.81	0.20
At PTCA	5.33±0.76	5.75±1.10	4.81±0.90	4.44±1.02	0.001	0.002
At follow-up	5.39±0.93	5.86±1.12	5.15±0.97	4.88±1.06	0.001	0.009
LDL cholesterol (mmol/liter)						
At base line	3.93±0.99	4.15±0.98	4.16±1.04	3.93±0.92	0.96	0.09
At PTCA	3.38±0.77	3.94±1.10	3.20±0.85	2.92±0.97	0.001	0.001
At follow-up	3.35±0.92	3.97±1.10	3.46±0.90	3.24±1.00	0.02	0.002
HDL cholesterol (mmol/liter)						
At base line	1.17±0.37	1.13±0.32	1.12±0.31	1.10±0.29	0.35	0.86
At PTCA	1.07±0.37	0.96±0.27	0.68±0.21	0.64±0.26	0.001	0.28
At follow-up	1.18±0.40	1.10±0.36	0.77±0.26	0.70±0.26	0.001	0.94
Triglycerides (mmol/liter)						
At base line	2.08±0.99	1.98±1.17	2.15±1.02	2.21±1.36	0.33	0.58
At PTCA	1.94±1.02	1.90±1.13	2.10±1.02	1.94±1.13	0.51	0.66
At follow-up	1.92±1.01	1.77±0.85	2.03±0.99	2.09±1.25	0.13	0.47
Total cholesterol:HDL cholesterol ratio						
At base line	5.50±1.61	5.97±1.97	6.03±1.83	5.78±1.59	0.39	0.08
At PTCA	5.45±1.69	6.55±2.31	7.80±2.42	7.88±5.29	0.001	0.17
At follow-up	5.07±1.77	5.80±2.01	7.07±2.15	7.81±4.15	0.001	0.99
Alpha-tocopherol (μmol/liter)						
At base line	32.1±11.7	32.5±14.2	31.9±10.2	30.2±11.6	0.46	0.55
At PTCA	26.2±8.4	63.6±24.8	59.2±15.2	22.7±7.3	0.10	<0.001
At follow-up	28.8±9.4	60.8±17.4	64.8±21.0	24.0±7.4	0.87	<0.001
Probucol (μmol/liter)						
At base line	0.18±1.17	0.00±0.00	0.00±0.00	0.00±0.00	0.28	0.28
At PTCA	0.08±0.54	0.11±0.75	61.8±29.7	59.0±29.3	<0.001	0.65
At follow-up	0.00±0.00	0.00±0.00	59.6±30.5	65.7±35.6	<0.001	0.41

\*Plus-minus values are means ±SD. PTCA denotes percutaneous transluminal coronary angioplasty, LDL low-density lipoprotein, and HDL high-density lipoprotein. P values are based on two-way analyses of variance (interaction between probucol and vitamins).

†To convert values for cholesterol to milligrams per deciliter, divide by 0.02586. To convert values for triglycerides to milligrams per deciliter, divide by 0.01129. To convert values for alpha-tocopherol to milligrams per deciliter, divide by 23.22.

venting neointimal formation, improving arterial remodeling, or both, cannot be adequately addressed by angiography.

We also examined our patients with intravascular ultrasonography after angioplasty and at follow-up, with the angioplasty operators blinded to the results. The serial tomographic views of the arterial wall and lumen provided by ultrasound will enable us to determine the effects of probucol on remodeling and proliferation.

In contrast to probucol, multivitamins had no significant effect on the rate of angiographic restenosis or on major clinical end points. Vitamin E is a lipophilic antioxidant present in LDL<sup>35</sup> and cellular membranes.<sup>36</sup> A daily dose of 1400 IU was chosen on the basis of data showing higher serum levels at doses over 1000 IU daily.<sup>37</sup> We also administered an additional dose of 2000 IU of vitamin E 12 hours before angioplasty, because stable plasma levels of hydrogen peroxide were observed with such a regimen during bypass surgery.<sup>38</sup> We opted for a multivitamin complex because of the capacity of vitamin C to regenerate the antioxidant activity of vitamin E<sup>39</sup> and because

beta carotene can modulate endothelial function and possibly interacts directly with nuclear receptors.<sup>40</sup>

Considering that probucol and multivitamins are both antioxidants, it is not clear why multivitamins did not prevent restenosis but probucol did. Moderately intense dietary intervention was carried out with all patients and included limitation of vitamin intake, instructions to avoid vitamin and mineral supplements, and teaching of the Step 1 diet. Smoking habits, which may modify antioxidant requirements, were similar in all groups. Probucol may simply be a more powerful antioxidant than multivitamins. Alternatively, other properties may have contributed to this result. Indeed, the effects of probucol, vitamin E, and beta carotene on atherosclerosis<sup>40</sup> and vascular reactivity<sup>41</sup> are not clearly related to their antioxidant properties in studies in animals. The possibility that the vitamins used in our patients, including the dose given 12 hours before angioplasty, paradoxically acted as prooxidants must also be considered.<sup>42</sup> This phenomenon might also explain the tendency for probucol to have better results when given alone than when combined with multivitamins.

Finally, we focused on standard balloon angioplasty because of the different pathophysiology of restenosis in stented arteries. Interestingly, stents have been proved to reduce restenosis only in large arteries with short lesions, whereas there was no limitation on vessel size or the length of lesions in this trial.

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## APPENDIX

The following participated in the MVP study: *Associate Investigators* — D. Bois, R. Bonan, J. Crépeau, M. DeBelder, R. Gallo, D. Gossard, G. Gosselin, M. Joyal, M. Juneau, M. Naruszewich, and J.-F. Tanguay; *Quantitative Coronary Angiography Laboratory* — F. Bélanger, M.-J. Dussault, and C. Desjardins; *Data Coordination* — L. Blain, S. Bujold, M. Caron, J. Chaput, D. Larocque, and A.-M. Poitras; *Data Entry and Analysis* — R. Aubut, C. Dupont, F. Harel, and J. Perrault; *Study Monitoring* — E.L. Alderman, K.M. Detre, D. Faxon (chairman), and A. Rosen.

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