Prevention of Restenosis After Angioplasty in Small Coronary Arteries With Probucol

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Background—Restenosis remains the major limitation of coronary angioplasty. Coronary stents have reduced the incidence of restenosis in selected patients with relatively large vessels. No strategies to date have demonstrated a beneficial effect in vessels \(<3.0\) mm in diameter. We have shown in the MultiVitamins and Probucol (MVP) Trial that probucol, a potent antioxidant, reduces restenosis after balloon angioplasty. The purpose of this study was to determine whether the benefit of probucol therapy is maintained in the subgroup of patients with smaller coronary vessels.

Methods and Results—We studied a subgroup of 189 patients included in the MVP trial who underwent successful balloon angioplasty of at least one coronary segment with a reference diameter \(<3.0\) mm. One month before angioplasty, patients were randomly assigned to one of four treatments: placebo, probucol (500 mg), multivitamins (beta-carotene 30 000 IU, vitamin C 500 mg, and vitamin E 700 IU), or probucol plus multivitamins twice daily. The treatment was maintained until follow-up angiography was performed at 6 months. The mean reference diameter of this study population was \(2.49\pm0.34\) mm. Lumen loss was \(0.12\pm0.34\) mm for probucol, \(0.25\pm0.43\) mm for the combined treatment, \(0.35\pm0.56\) mm for vitamins, and \(0.38\pm0.51\) mm for placebo (\(P=0.005\) for probucol). Restenosis rates per segment were 20.0% for probucol, 28.6% for the combined treatment, 45.1% for vitamins, and 37.3% for placebo (\(P=.006\) for probucol).

Conclusions—Probucol reduces lumen loss and restenosis rate after balloon angioplasty in small coronary arteries. (Circulation. 1998;97:429-436.)

Key Words: angioplasty • antioxidants • restenosis

Restenosis remains the major limitation of the long-term success of coronary angioplasty.\(^1\) The introduction of stents has significantly reduced the incidence of restenosis,\(^2,3\) but these results were obtained in selected patients with relatively large vessels (diameter \(\geq3.0\) mm). Coronary stenting has initially been limited to such arteries because of the increased risk of subacute thrombosis observed in smaller vessels.\(^4\) Nevertheless, a large number of percutaneous interventions are performed in patients with small coronary arteries. A few preliminary studies of coronary stents implanted in vessels \(<3.0\) mm have provided conflicting results,\(^5-13\) and no strategies to date have definitively demonstrated a significant reduction of restenosis in small coronary vessels.

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We have shown in the MultiVitamins and Probucol (MVP) study that probucol, a potent antioxidant, significantly reduces coronary restenosis after balloon angioplasty.\(^15\) Interestingly, these results were obtained without imposing any restriction relative to vessel size at entry into the trial. Whether the benefit of probucol therapy was maintained in the subgroup of patients with small vessels is not known. Therefore the purpose of this study was to assess the effectiveness of drugs with antioxidant properties (probucol and/or multivitamins) in reducing late lumen loss and preventing restenosis after balloon angioplasty in small coronary arteries (vessels with reference diameter \(<3.0\) mm).

Methods

Study Population and Randomization Procedure

We studied a subgroup of patients included in the MVP trial who underwent balloon angioplasty of at least one coronary segment with a reference diameter \(<3.0\) mm. Details of the MVP trial have been recently published.\(^15\) Briefly, the MVP study was a double-blind, placebo-controlled randomized trial designed to test the hypothesis that probucol and/or multivitamins (a combination of vitamins E and C and beta-carotene) could reduce the rate and severity of restenosis after coronary balloon angioplasty. Patients were eligible if they were scheduled to have standard balloon angioplasty on \(\geq1\) native coronary artery and had \(\geq1\) target lesion with luminal narrowing of \(\geq50\%\) by caliper measurements. Patients were excluded if any of the following occurred: inability to comply with pretreatment or to return for follow-up, recent myocardial infarction (\(\leq7\) days), planned stenting or atherectomy, coronary angioplasty for a restenotic lesion or for another lesion in the preceding 6 months, or angioplasty of a bypass graft or of a bypassed native vessel with a patent graft. Beginning 30 days before scheduled angioplasty, patients were randomly assigned to receive either probucol alone (500 mg twice daily), multivitamins alone (beta-carotene 30 000 IU, vitamin C 500 mg, and vitamin E 700 IU, twice daily), the combination of probucol and multivitamins, or placebo. All patients received an extra dose of vitamin E 2000 IU and/or probucol 1000 mg and/or matched placebos 12 hours before...
angioplasty, according to randomization assignment. All successfully
dilated patients who did not present a periprocedural complication
were maintained on their assigned study regimen until follow-up
angiography was performed at 5 to 7 months.

**Angioplasty and Angiographic Methods**

All patients received aspirin 325 mg daily for the entire study period.
Coronary angiography and balloon angioplasty were performed ac-
cording to standard techniques. ECGs were taken before angioplasty,
immediately afterward, and daily until discharge. Creatine kinase level
and MB fraction were measured on the evening after the procedure
and the following morning. Patients were excluded from the study if
there was inability to dilate the stenosis, if an initially successful
angioplasty was followed by persistent abrupt closure, if the procedure
was complicated by a Q-wave infarction in the dilated territory, if
failed angioplasty required emergency bypass surgery, or if suboptimal
angioplasty result was treated with stenting. Intracoronary nitroglyc-
erin (0.3 mg) was given for each target artery for both before and after
dilatation angiography and at follow-up. Angiograms were performed
before angioplasty, immediately after dilatation, 15 minutes after final
balloon inflation and at 5- to 7-month follow-up. Patients in whom
coronary angiography was performed for clinical reasons before the
fifth month returned for repeat angiographic examination at 5 to 7
months if no definite restenosis was present on ≥1 dilated site.

**Quantitative Coronary Angiography and Definition of Restenosis**

The four coronary angiograms (before, immediately after, 15 minutes
after the procedure, and final follow-up) were analyzed together by
experienced technicians supervised by a cardiovascular radiologist
blinded to treatment assignment, using the Coronary Measurement
System.16 Measurements were made in a single projection, showing
the most severe stenosis. The projection showing the arterial segment
with good opacification, as nearly perpendicular to the x-ray beam as
possible, was selected for analysis. Whenever possible, all four mea-
surements were made in the same projection for more accurate
comparison. Variability for repeated measurements of percent stenosis
in our laboratory is 8.6% when analyzing frames recorded 1 to 6
months apart.17 A change of 15% or roughly 2 SD of this variability
in our laboratory is 8.6% when analyzing frames recorded 1 to 6
months if no definite restenosis was present on ≥1 dilated site.

Restenosis was defined as a dichotomous outcome and
was taken to indicate a clinically important change.

Clinical Follow-up

Patients had a clinical evaluation at 1, 3, and 6 months that included
an assessment for ischemic symptoms or any symptoms related or not
To the study medication or the angioplasty procedure. Compliance
with study medications was evaluated by pill counts and drug level
measurements at each visit.18 Drug levels were not made available
during the trial to keep investigators blinded.

Diet assessment and intervention in the MVP study has previously
been described.19 The American Heart Association Step 1 diet was
taught to all patients. Specific dietary counseling was given at each
visit. Daily dietary intake of vitamins E and C and beta-carotene was
limited, and patients were instructed to avoid vitamin and mineral
supplements.

Major secondary clinical end points were death, myocardial infar-
cion, coronary bypass surgery, and repeat angioplasty.

**Statistical Methods**

For the per-protocol population (patients completing trial without
protocol violations, including compliance with study medications
>80%), the primary efficacy end point (late lumen loss) was analyzed
with a two-way ANCOVA on follow-up luminal diameter, control-
ling for postangioplasty luminal diameter and for target vessel distri-
bution extracting treatment effects and interaction. In the intent-to-
treat population, the dichotomous outcome was analyzed similarly by
using multiple logistic regression. All early termination patients were
considered as having restenosis for the intent-to-treat analysis. Patients
who completed the trial with protocol violations were considered as
“restenosis” or “no restenosis,” depending on results of their efficacy
clean end points. The restenosis rate per segment was analyzed by the
generalized estimating equations technique,18 which takes into ac-
count potential dependence between segments in the same patient. All
secondary end points were analyzed similarly to the primary efficacy
end point; depending on the nature of the outcome, ANCOVA, or
multiple logistic regressions were used. Baseline characteristics and
major clinical events of the four study groups were compared using χ²
tests for categorical variables and ANOVA for continuous variables. A
value of P≤.05 was considered to indicate statistical significance.

**Results**

A total of 317 patients had been included in the MVP trial. From this
collection, 189 patients with at least one successfully
dilated vessel with reference diameter <3.0 mm were selected for
this study. Patients were distributed in the four groups of
treatment as follows: 46 received probucol alone, 45 multivi-
tamins alone, 51 probucol plus multivitamins, and 47 placebo
alone. Baseline demographic, clinical, and angiographic char-
acteristics are shown in Table 2. The only statistically signifi-
cant baseline difference was target vessel distribution, with a
greater number of dilated left anterior descending arteries in
the vitamins only group. This variable did not show associa-
tions with the efficacy end points.

Nine patients discharged after successful angioplasty did not
undergo final angiography. Causes for early termination in-
cluded 1 death, 1 myocardial infarction, and 1 dropout. Three
patients underwent surgical revascularization and 3 patients had
repeat angioplasty despite not having reached quantitative
criteria for restenosis at early angiography. Seven patients were
not adequately compliant to study medications (2 in the
probucol group, 2 in the vitamins, 3 in the combined
treatment, and none in the placebo group).

**Angiographic Analysis**

Quantitative angiographic findings in the per-protocol popu-
lation are shown in Table 2. The mean reference diameter for
this population was 2.49±0.34 mm (range, 1.48 to 2.99 mm),...
with no differences between groups. Lumen loss per patient was $0.12 \pm 0.34$ mm in the probucol only group, $0.25 \pm 0.43$ mm for combined treatment, $0.35 \pm 0.56$ mm for vitamins only, and $0.38 \pm 0.51$ mm for placebo ($P < 0.005$ for probucol versus no probucol and 0.325 for vitamins vs no vitamins). Fig 1 represents the cumulative frequency curves of minimal lumen diameter in all study groups.

Restenosis rates per segment were 20.0% for probucol, 28.6% for the combined treatment, 45.1% for vitamins alone, and 37.3% for placebo ($P < 0.006$ for probucol versus no probucol and 0.374 for vitamins versus no vitamins). Fig 2.

Restenosis rates per patient were 21.7% for probucol, 33.3% for probucol plus vitamins, 46.7% for vitamins, and 40.4% for placebo ($P = 0.005$ for probucol versus no probucol and 0.374 for vitamins versus no vitamins).

Since there is no consensus on the definition of a small coronary artery, we also performed angiographic analysis of segments with reference diameters < 2.7 mm. A total of 131 patients presented at least one successfully dilated segment < 2.7 mm (n = 34, 33, 34, and 30 in the placebo, vitamins alone, combined treatment, and probucol alone groups, respectively). The mean reference diameter of this subgroup of patients was $2.31 \pm 0.27$ mm (range, 1.48 to 2.69 mm), with no differences between groups. The four groups were also comparable for the minimal lumen diameter before (0.77 ± 0.21 mm) and 15 minutes after percutaneous trans-

### TABLE 1. Baseline Demographic, Clinical, and Angiographic Characteristics of the Four Study Groups

<table>
<thead>
<tr>
<th></th>
<th>Placebo Alone</th>
<th>Vitamins Alone</th>
<th>Probucol + Vitamins</th>
<th>Probucol Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (intent-to-treat population)</td>
<td>47</td>
<td>45</td>
<td>51</td>
<td>46</td>
</tr>
<tr>
<td>Age, y (mean±SD)</td>
<td>59.5±8.2</td>
<td>57.8±10.9</td>
<td>57.0±8.9</td>
<td>57.7±9.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Ever smoked</td>
</tr>
<tr>
<td>Current smoker</td>
</tr>
<tr>
<td>History of diabetes</td>
</tr>
<tr>
<td>History of hypertension</td>
</tr>
<tr>
<td>Exertional angina (CCS class)</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>IV</td>
</tr>
<tr>
<td>Prior MI</td>
</tr>
<tr>
<td>Prior CABG</td>
</tr>
<tr>
<td>Prior PTCA</td>
</tr>
<tr>
<td>No. of diseased vessels</td>
</tr>
<tr>
<td></td>
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<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>% of Segments</th>
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</thead>
<tbody>
<tr>
<td>Target vessel*</td>
</tr>
<tr>
<td>Left anterior descending</td>
</tr>
<tr>
<td>Left circumflex</td>
</tr>
<tr>
<td>Right coronary artery</td>
</tr>
<tr>
<td>Moderate or severe calcification</td>
</tr>
<tr>
<td>Eccentricity</td>
</tr>
<tr>
<td>Lesion angulation &gt;45°</td>
</tr>
<tr>
<td>Moderate tortuosity</td>
</tr>
<tr>
<td>Bilirucation</td>
</tr>
</tbody>
</table>

CCS indicates Canadian Cardiovascular Society; MI, myocardial infarction; CABG, coronary artery bypass grafting; and PTCA, percutaneous transluminal coronary angioplasty.

*P = 0.006 based on χ² test.
luminal coronary angioplasty (PTCA) (1.57 ± 0.28 mm), and the acute gain immediately (0.86 ± 0.36 mm) and at 15 minutes (0.84 ± 0.40 mm) after PTCA. Lumen loss per patient was then 0.08 ± 0.30 mm for the probucol only group, 0.27 ± 0.49 mm for the combined treatment, 0.24 ± 0.45 mm for vitamins alone, and 0.34 ± 0.53 mm for placebo alone (P = .09 for probucol versus no probucol and 0.42 for vitamins versus no vitamins). Restenosis rate per segment was 21.6% in the probucol only group, 29.3% for probucol plus vitamins, 44.4% for vitamins alone, and 32.4% for placebo (P = .055 for probucol vs no probucol and 0.322 for vitamins versus no vitamins).

### Figure 1.
Cumulative distribution curves of the minimum lumen diameter before and 15 minutes after angioplasty (PTCA, percutaneous transluminal coronary angioplasty) and at follow-up for the four study groups of the per-protocol population.

### Table 2. Quantitative Angiographic Analysis of Per-Protocol Population

<table>
<thead>
<tr>
<th></th>
<th>Placebo Alone (n=47)</th>
<th>Vitamins Alone (n=39)</th>
<th>Producol + Vitamins (n=46)</th>
<th>Producol Alone (n=41)</th>
<th>P, Producol vs No Producol</th>
<th>P, Vitamins vs No Vitamins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal lumen diameter, mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-PTCA</td>
<td>0.80 ± 0.23</td>
<td>0.83 ± 0.23</td>
<td>0.84 ± 0.24</td>
<td>0.79 ± 0.23</td>
<td>.997</td>
<td>.314</td>
</tr>
<tr>
<td>Immediately after PTCA</td>
<td>1.72 ± 0.36</td>
<td>1.65 ± 0.29</td>
<td>1.70 ± 0.30</td>
<td>1.82 ± 0.34</td>
<td>.125</td>
<td>.067</td>
</tr>
<tr>
<td>15 min after PTCA</td>
<td>1.69 ± 0.35</td>
<td>1.61 ± 0.31</td>
<td>1.66 ± 0.30</td>
<td>1.75 ± 0.33</td>
<td>.273</td>
<td>.083</td>
</tr>
<tr>
<td>Final follow-up</td>
<td>1.31 ± 0.52</td>
<td>1.26 ± 0.53</td>
<td>1.41 ± 0.52</td>
<td>1.63 ± 0.34</td>
<td>.005†</td>
<td>.325†</td>
</tr>
<tr>
<td>Reference diameter, mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before PTCA</td>
<td>2.51 ± 0.36</td>
<td>2.53 ± 0.30</td>
<td>2.46 ± 0.33</td>
<td>2.53 ± 0.35</td>
<td>.660</td>
<td>.629</td>
</tr>
<tr>
<td>Immediately after PTCA</td>
<td>2.55 ± 0.37</td>
<td>2.51 ± 0.29</td>
<td>2.45 ± 0.34</td>
<td>2.57 ± 0.37</td>
<td>.656</td>
<td>.148</td>
</tr>
<tr>
<td>15 min after PTCA</td>
<td>2.52 ± 0.36</td>
<td>2.51 ± 0.31</td>
<td>2.45 ± 0.35</td>
<td>2.56 ± 0.37</td>
<td>.874</td>
<td>.246</td>
</tr>
<tr>
<td>Final follow-up</td>
<td>2.52 ± 0.36</td>
<td>2.50 ± 0.34</td>
<td>2.43 ± 0.42</td>
<td>2.61 ± 0.35</td>
<td>.895</td>
<td>.091</td>
</tr>
<tr>
<td>Acute gain, mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediately after PTCA</td>
<td>0.89 ± 0.43</td>
<td>0.89 ± 0.30</td>
<td>0.93 ± 0.26</td>
<td>1.00 ± 0.37</td>
<td>.231</td>
<td>.065</td>
</tr>
<tr>
<td>Acute gain, mm</td>
<td>0.90 ± 0.45</td>
<td>0.82 ± 0.34</td>
<td>0.93 ± 0.33</td>
<td>0.96 ± 0.28</td>
<td>.435</td>
<td>.089</td>
</tr>
<tr>
<td>Total lumen loss, mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediately after PTCA</td>
<td>0.41 ± 0.50</td>
<td>0.39 ± 0.54</td>
<td>0.29 ± 0.46</td>
<td>0.18 ± 0.36</td>
<td>.009</td>
<td>.327</td>
</tr>
<tr>
<td>Early loss, mm</td>
<td>0.03 ± 0.18</td>
<td>0.04 ± 0.17</td>
<td>0.05 ± 0.17</td>
<td>0.07 ± 0.17</td>
<td>.625</td>
<td>.751</td>
</tr>
<tr>
<td>Late loss, mm</td>
<td>0.38 ± 0.51</td>
<td>0.35 ± 0.56</td>
<td>0.25 ± 0.43</td>
<td>0.12 ± 0.34</td>
<td>.005†</td>
<td>.325†</td>
</tr>
</tbody>
</table>

+Values are mean ± SD. PTCA denotes percutaneous transluminal coronary angioplasty. To keep the level of significance for the family of three tests at α = .05, the levels of significance for testing interaction (α₁) and main effects (α₂, α₃) should be reduced (eg, if α₁=0.01 and α₂=α₃=0.02, the Bonferroni inequality yields α=α₁+α₂+α₃=0.05).  
†Values are based on two-way ANCOVA (probucol × vitamins) on the follow-up lumen diameter controlling for 15 minutes post-PTCA lumen diameter and target vessel distribution. All other Probability values are based on similar ANCOVA except for reference and baseline minimal lumen diameters (ANOVA).
remains unclear, small vessel size remains a major limitation of role of vessel diameter on restenosis after balloon angioplasty for the four study groups are provided in Table 3. Restenosis rates per patient. A, Restenosis rates per segment. B, Restenosis rates per patient.

Clinical End Points
The major clinical events were distributed as follows: One myocardial infarction and one death occurred (both in the combined treatment group), and there were four coronary artery bypass graft surgeries (three in the vitamins alone group and one in the probucol group). Rates of repeat angioplasty were 19.6%, 26.7%, and 27.7% in the probucol, combined treatment, and placebo groups, respectively ($P=0.07$ for probucol versus no probucol and 0.63 for vitamins versus no vitamins).

Total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides levels, as well as α-tocopherol and probucol levels for the four study groups are provided in Table 3.

Discussion
Few studies have analyzed the possible influence of vessel size on restenosis after coronary balloon angioplasty. Hirshfeld et al. reported a reduced restenosis rate in vessels $\geq 2.9$ mm (34%) compared with smaller vessels (44%). This inverse relation between vessel size and restenosis has also been observed in the balloon angioplasty arm of two stent trials and in one intravascular ultrasound study. Balloon oversizing in small coronary arteries resulting in greater vascular injury may explain this observation. However, other studies have failed to show the same relationship or even suggested a negative effect of increased vessel size. Although the potential role of vessel diameter on restenosis after balloon angioplasty remains unclear, small vessel size remains a major limitation of coronary stenting. The use of stents has initially been restricted to vessels with a reference diameter $\geq 3.0$ mm because of the increased risk of thrombotic occlusion in smaller vessels. A subgroup of the Benestent trial emphasized the high risk of subacute thrombosis when stents were implanted in small arteries (6.9%) compared with vessels $>3.0$ mm (0.9%). However, there have been recent preliminary reports involving a limited number of patients in which stenting coronary arteries slightly $<3.0$ mm in size was attempted. Most of these studies have suggested that this approach could be safe when high pressure inflations were performed to improve stent expansion. Unfortunately, as shown by intravascular ultrasound studies, a high percentage of stents are inadequately deployed even after high pressure inflations. Furthermore, there are no angiographic parameters that can predict the adequate expansion of stents. The long-term risk of leaving an inadequately deployed stent in a small coronary artery is unknown. Also, the effectiveness of coronary stenting for the reduction of restenosis in small vessels has not been clearly demonstrated. Subgroup analyses from the Stress and Start trials have both reported a reduction in the restenosis rate with stenting compared with balloon angioplasty in patients with coronary arteries smaller than 3.0 mm. In addition, a meta-analysis of the angiographic outcomes in the Benestent-1 and Stress-1 and 2 trials has suggested that stenting had a greater impact on lowering restenosis if vessels were between 2.6 and 3.4 mm in diameter. In vessels $<2.6$ mm, restenosis rates for stenting (38%) and balloon angioplasty (42%) were comparable. Furthermore, other studies have found restenosis rates as high as 45% when stents were deployed in coronary arteries $<3.0$ mm. However, it is important to note that there has been no large randomized trial conducted specifically to determine whether stenting reduces restenosis in small coronary arteries. Thus the data on the use of stents in small coronary arteries are incomplete and conflicting and the issue remains unresolved at the present time.

The effectiveness of probucol on the prevention of restenosis has been previously suggested by several small studies and recently confirmed by the MVP trial. This substudy of the MVP trial is the first to demonstrate a reduction of restenosis after balloon angioplasty in coronary arteries $<3.0$ mm, with a mean vessel reference diameter of 2.49 mm. Compared with placebo, probucol given alone resulted in reductions of 68% in late lumen loss and of 46% in the restenosis rate per segment. This translates into a restenosis rate per patient as low as 21.7% in the group treated with probucol alone. When arteries $<2.7$ mm were evaluated (mean reference diameter, 2.31 mm), restenosis rate per segment remained similarly low (21.6%). The beneficial effect of probucol on the prevention of restenosis in small coronary arteries has also been suggested by one other study involving a limited number of patients (n=78). In that study, the effectiveness of probucol was restricted to arteries $\geq 2.7$ mm, with a resultant restenosis rate of 24% in the probucol group compared with 75% in the control group.

Probucol has powerful antioxidant effects that may control the oxidative stress occurring after angioplasty. Oxidizing species generated by damaged endothelium, activated platelets,
TABLE 3. Lipid and Drug Levels for the Four Study Groups

<table>
<thead>
<tr>
<th></th>
<th>Placebo Alone</th>
<th>Vitamins Alone</th>
<th>Probucol + Vitamins</th>
<th>Probucol Alone</th>
<th>P, Probucol vs No Probucol</th>
<th>P, Vitamins vs No Vitamins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol, mmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>6.04±0.92</td>
<td>6.11±0.90</td>
<td>6.12±1.09</td>
<td>5.94±0.96</td>
<td>.765</td>
<td>.384</td>
</tr>
<tr>
<td>At PTCA</td>
<td>5.27±0.79</td>
<td>5.64±0.99</td>
<td>4.86±0.91</td>
<td>4.40±1.04</td>
<td>&lt;.001</td>
<td>.003</td>
</tr>
<tr>
<td>Follow-up</td>
<td>5.50±0.89</td>
<td>5.79±1.00</td>
<td>4.84±1.10</td>
<td>4.84±1.10</td>
<td>&lt;.001</td>
<td>.051</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>3.88±0.91</td>
<td>4.04±0.88</td>
<td>4.06±0.96</td>
<td>3.79±0.84</td>
<td>.819</td>
<td>.105</td>
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<tr>
<td>At PTCA</td>
<td>3.30±0.77</td>
<td>3.75±0.91</td>
<td>3.23±0.87</td>
<td>2.89±1.03</td>
<td>&lt;.001</td>
<td>.003</td>
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<tr>
<td>Follow-up</td>
<td>3.41±0.93</td>
<td>3.89±0.99</td>
<td>3.17±1.02</td>
<td>3.17±1.02</td>
<td>.041</td>
<td>.008</td>
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<tr>
<td>HDL cholesterol, mmol/L</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.21±0.39</td>
<td>1.17±0.37</td>
<td>1.10±0.31</td>
<td>1.12±0.30</td>
<td>.119</td>
<td>.575</td>
</tr>
<tr>
<td>At PTCA</td>
<td>1.10±0.40</td>
<td>0.98±0.32</td>
<td>0.68±0.21</td>
<td>0.65±0.27</td>
<td>&lt;.001</td>
<td>.362</td>
</tr>
<tr>
<td>Follow-up</td>
<td>1.20±0.43</td>
<td>1.13±0.41</td>
<td>0.69±0.27</td>
<td>0.69±0.27</td>
<td>&lt;.001</td>
<td>.854</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2.11±1.03</td>
<td>2.12±1.73</td>
<td>2.12±1.01</td>
<td>2.29±1.42</td>
<td>.638</td>
<td>.676</td>
</tr>
<tr>
<td>At PTCA</td>
<td>1.96±1.10</td>
<td>2.01±1.39</td>
<td>2.12±0.96</td>
<td>1.92±1.13</td>
<td>.819</td>
<td>.491</td>
</tr>
<tr>
<td>Follow-up</td>
<td>2.00±1.10</td>
<td>1.71±0.77</td>
<td>2.17±1.30</td>
<td>2.17±1.30</td>
<td>.187</td>
<td>.136</td>
</tr>
<tr>
<td>Total- to–HDL cholesterol ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>5.37±1.45</td>
<td>5.68±1.84</td>
<td>5.91±1.58</td>
<td>5.64±1.65</td>
<td>.301</td>
<td>.229</td>
</tr>
<tr>
<td>At PTCA</td>
<td>5.28±1.57</td>
<td>6.22±2.00</td>
<td>7.60±2.05</td>
<td>8.62±6.66</td>
<td>&lt;.001</td>
<td>.935</td>
</tr>
<tr>
<td>Follow-up</td>
<td>5.06±1.58</td>
<td>5.57±1.70</td>
<td>7.22±2.30</td>
<td>8.29±5.11</td>
<td>&lt;.001</td>
<td>.551</td>
</tr>
<tr>
<td>Alpha-tocopherol, μmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>32.6±12.4</td>
<td>30.2±13.7</td>
<td>31.1±7.7</td>
<td>30.7±13.0</td>
<td>.827</td>
<td>.634</td>
</tr>
<tr>
<td>At PTCA</td>
<td>26.3±9.4</td>
<td>61.6±24.8</td>
<td>60.8±15.7</td>
<td>22.1±6.3</td>
<td>.379</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Follow-up</td>
<td>29.5±9.4</td>
<td>57.9±15.2</td>
<td>64.7±18.0</td>
<td>24.1±7.1</td>
<td>.780</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Probucol, μmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.00±0.00</td>
<td>0.00±0.00</td>
<td>0.00±0.00</td>
<td>0.00±0.00</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>At PTCA</td>
<td>0.00±0.00</td>
<td>0.00±0.00</td>
<td>59.8±27.1</td>
<td>60.7±32.6</td>
<td>&lt;.001</td>
<td>.905</td>
</tr>
<tr>
<td>Follow-up</td>
<td>0.00±0.00</td>
<td>0.00±0.00</td>
<td>59.8±24.9</td>
<td>69.6±40.8</td>
<td>&lt;.001</td>
<td>.270</td>
</tr>
</tbody>
</table>

Plus-minus values are mean±SD. PTCA denotes percutaneous transluminal coronary angioplasty.
Probability values are based on two-way ANOVA (probucol×vitamins).

Prevention of Restenosis in Small Arteries With Probucol

and neutrophils at the angioplasty site can induce chain reactions which result in endothelial dysfunction and LDL oxidation. Activation of macrophages by oxidized LDL and dysfunction of the endothelium can result in the release of growth factors promoting tissue proliferation. Secretion of metalloproteinases by endothelial and smooth muscle cells and of new extracellular matrix also occurs as part of the unaltered remodeling process, with collagen cross-linking presumably causing arterial constriction and endothelial dysfunction possibly limiting positive chronic flow-dependent changes in vessel dimensions. Thus the antioxidant probucol may prevent endothelial dysfunction and LDL oxidation and in turn modify neointimal formation and vascular remodeling involved in restenosis. Probucol also has weak lipid-lowering properties, which probably cannot account for its antirestenotic effect especially in light of the fact that the more potent lovastatin failed to prevent restenosis in one large clinical trial. On the other hand, it has been demonstrated that probucol also inhibits the secretion of interleukin-1 by macrophages. This effect may be clinically important, since inhibition of interleukin-1 secretion may result in a decreased production of matrix metalloproteinases by smooth muscle cells and thus modify remodeling of the extracellular matrix.

There was a tendency for probucol to have better results when given alone than when it was combined with vitamins. The interaction between probucol and vitamins for late lumen loss in coronary arteries <3.0 mm was not significant (P=.19), but the power to detect such an interaction was low in this substudy (39%). The possible pro-oxidant effects of the very high doses of vitamins used in the MVP study may explain this observation.

Limitations

The MVP trial was not specifically designed to address the issue of balloon angioplasty in small coronary arteries. Nevertheless, this analysis of 189 subjects well distributed in each of the four study groups offers strong evidence that the positive overall results obtained in the main trial also apply to this clinically important subgroup of patients.

Clinical Implications

Percutaneous revascularization of small coronary arteries presents major shortcomings. Our study demonstrates a significant
reduction in restenosis with the use of the antioxidant probucol when started 1 month before balloon angioplasty in stable angina patients with coronary arteries <3.0 mm in diameter. It remains to be determined if the high restenosis rate after balloon angioplasty can also be reduced by stenting such vessels. Further research addressing this question will help to determine the respective roles of stenting and of an effective pharmacological agent such as probucol for the prevention of restenosis in patients with small coronary arteries.

Acknowledgments
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