Clinical Investigation and Reports

Effects of Probucol on Vascular Remodeling After Coronary Angioplasty

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Background—We have shown that probucol reduces restenosis after balloon angioplasty. Whether probucol acted via prevention of neointimal formation or improvement in vascular remodeling could not be addressed by angiography and required the use of intravascular ultrasound (IVUS).

Methods and Results—Beginning 30 days before angioplasty, 317 patients were randomly assigned to receive probucol, multivitamins, combined treatment, or placebo. Patients were then treated for 6 months after angioplasty. IVUS examination was performed immediately after angioplasty and at follow-up in 94 patients (111 segments). The cross section selected for serial analysis was the one at the angioplasty site with the smallest lumen area at follow-up. In the placebo group, lumen area decreased by $-1.21 \pm 1.88 \text{ mm}^2$ at follow-up, and wall area and external elastic membrane (EEM) area increased by $1.50 \pm 2.50$ and $0.29 \pm 2.93 \text{ mm}^2$, respectively. Change in lumen area, however, correlated more strongly with the change in EEM area ($r = 0.53$, $P = 0.002$) than with the change in wall area ($r = -0.13$, $P = 0.49$). Lumen loss was $-1.21 \pm 1.88 \text{ mm}^2$ for placebo, $-0.83 \pm 1.22 \text{ mm}^2$ for vitamins, $-0.25 \pm 1.17 \text{ mm}^2$ for combined treatment, and $-0.15 \pm 1.70 \text{ mm}^2$ for probucol alone ($P = 0.002$ for probucol, $P = 0.84$ for vitamins). Change in wall area was similar for all groups. EEM area increased by $0.29 \pm 2.93 \text{ mm}^2$ for placebo, $0.09 \pm 2.33 \text{ mm}^2$ for vitamins only, $1.17 \pm 1.61 \text{ mm}^2$ for combined treatment, and $1.74 \pm 1.80 \text{ mm}^2$ for probucol only ($P = 0.005$ for probucol).

Conclusions—Lumen loss after balloon angioplasty is due to inadequate vessel remodeling in response to neointimal formation. Probucol exerts its antirestenotic effects by improving vascular remodeling after angioplasty. (Circulation. 1999;99:30-35.)

Key Words: antioxidants, coronary disease, restenosis, angioplasty, ultrasonics, remodeling

Numerous pharmacological approaches have failed to modify the high incidence of restenosis after balloon coronary angioplasty. This inability to alter the restenosis process was caused in part by our incomplete understanding of its pathophysiology. Conflicting data exist concerning the relative role of neointimal formation and vascular remodeling in lumen loss after angioplasty. Most of the patients included in the largest study that attempted to answer this question and that identified vascular remodeling (modification in the area circumscribed by the external elastic membrane [EEM]) as the predominant mechanism of restenosis underwent interventions other than balloon angioplasty.7 Most of these patients also underwent follow-up examinations because of recurrence of symptoms, and the study involved a mix of primary and restenotic lesions. Interestingly, data from the Serial Ultrasound Restenosis study show that most lumen loss after balloon angioplasty may be caused by an increase in wall area (WA).8 Small clinical studies have suggested that probucol started before angioplasty may prevent restenosis.9–11 Recently, we have shown in the Multivitamins and Probucol (MVP) study that the antioxidant probucol reduced angiographic lumen loss by 68%, restenosis rate by 47%, and the need for repeated angioplasty by 58%.12 It was not possible to determine with angiography alone whether probucol acted via inhibition of neointimal formation or improvement in vascular remodeling. We have performed serial intravascular ultrasound (IVUS) examinations in a consecutive series of patients involved in the MVP trial. By providing tomographic views of coronary arteries with high resolution, IVUS allows quantitative assessment of changes in lumen and wall dimensions. Therefore, the objectives of this study were to determine (1) the pathophysiology of coronary restenosis after balloon angioplasty in patients systematically undergoing follow-up IVUS examination and (2) the effect of probucol on neointimal formation and vascular remodeling after coronary angioplasty.

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30
Methods

Study Design and Population

This is the IVUS substudy from the MVP trial. The protocol was approved by our institutional review board. Patients referred for elective coronary angioplasty were evaluated ≥30 days before their scheduled procedures. Eligible patients were asked to provide written informed consent. Patients were eligible if they were scheduled to undergo standard balloon angioplasty on ≥1 native artery and had ≥1 de novo target lesion with luminal narrowing ≥50% by caliper measurements.

Beginning 30 days before scheduled angioplasty, patients were randomly assigned to receive probucol alone, multivitamins alone, probucol plus multivitamins, or placebo. Probucol 500 mg or matched placebo was administered twice daily. The multivitamin complex (vitamin E 700 IU, vitamin C 500 mg, β-carotene 30 000 IU) or matched placebo was also administered twice daily. All patients received an extra dose of probucol 1000 mg and/or vitamin E 2000 IU and/or matched placebos 12 hours before angioplasty, according to randomization assignment. After angioplasty, all successfully dilated patients who did not present a periprocedural complication were maintained on their assigned study regimen until follow-up angiography was performed. Balloon angioplasty was performed according to standard techniques. Nitroglycerin (0.3 mg IC) was given for each target artery for predilatation and postdilatation angiography and at follow-up. Patients were readmitted for follow-up coronary angiography at 5 to 7 months. Patients in whom arteriography was performed for clinical reasons before the fifth month returned for repeated angiographic examination at 5 to 7 months if no definite restenosis was present on ≥1 dilated site.

The MVP study was stopped prematurely by an independent monitoring board after 317 patients had entered the trial because probucol had a significant effect on the primary angiographic efficacy end point. A total of 161 patients could not have IVUS analysis because the substudy was initiated later than the main trial. In addition, 49 patients did not undergo baseline IVUS examination of the angioplasty site after final angioplasty for various reasons: Vessels were too small, diffusely diseased, or markedly bent in 14 patients; stents were deployed in 10 patients; the presence of extensive dissection, thrombus or significant recoil represented a contraindication in 7 patients; no angioplasty was performed in 6 patients; IVUS was done after angioplasty for various reasons: Vessels were too small, diffusely diseased, or markedly bent in 14 patients; stents were deployed in 10 patients; the presence of extensive dissection, thrombus or significant recoil represented a contraindication in 7 patients; the dilated site was not crossed with the IVUS catheter in 6 patients; no angioplasty was performed in 6 patients; IVUS was done during the procedure but not after final balloon inflation in 4 patients; 1 patient had a failed angioplasty; and 1 patient had not taken any of the medications in the pretreatment period. Thus, 107 patients underwent IVUS examination of the angioplasty site after final balloon inflation at baseline and constituted the population for the IVUS substudy.

IVUS Examinations

IVUS examinations were performed with 30-MHz, 3.5F mechanical ultrasound catheters (Boston Scientific) and a dedicated imaging console (Hewlett-Packard). In 6 patients, both examinations were performed with 20-MHz, 3.5F, 64-element IVUS catheters (Endosonics). IVUS studies were first performed after angioplasty (after final balloon inflation) and then after follow-up angiography (before any subsequent intervention) and were always preceded by administration of nitroglycerin (0.3 mg IC). IVUS imaging was monitored by an experienced cardiologist, but the angioplasty operator was blinded to ultrasound results to avoid altering standard balloon angioplasty practice. The IVUS catheter was advanced distal to the dilated site to an easily recognizable landmark, most often a side branch, which was noted and used for follow-up examination. One angiographic view was recorded on videotape before pullback of the IVUS catheter was begun. Slow manual pullbacks (~0.5 mm/s) were performed up to the guiding catheter, and the ultrasound images were recorded onto 0.5-inch super-VHS videotape for off-line analysis, with a detailed running audio commentary describing the location of the ongoing IVUS interrogation, including the angioplasty site. Simultaneous high-resolution fluoroscopic images were recorded on the IVUS imaging screen during pullbacks so that the location of the arc of calcification at the selected site did not shadow extrapolation of the EEM level was performed directly when each arc of calcification at the selected site did not shadow ≥60° of the adventitial circumference. In addition, study of the anatomic slices just proximal and distal to a selected calcified site was performed when necessary to escape the shadowing and to identify the EEM correctly.

Statistical Analysis

Statistical analysis was performed for all patients who underwent both postangioplasty and follow-up examinations. The same analyses were performed for compliant patients only. Measurements are reported as mean±SD. Groups were compared on postangioplasty measurements with multiple regressions. The relations between changes in LA, WA, and EEM within study groups were studied with Pearson’s correlation coefficients. Because we were interested in the

Figure 1. IVUS measurements. Inner and outer white oval lines indicate lumen and EEM areas, respectively.

IVUS transducer would be constantly known. The operator was allowed to pause at sites of interest (angioplasty site, side branches), and contrast injections were performed when necessary to identify major and selected minor side branches, to accurately define the position of the IVUS catheter in relation to the angioplasty site, and to improve delineation of the lumen-intimal interface. Gain settings were carefully optimized during initial assessment and changed only if required because of suboptimal image quality.

Quantitative IVUS Measurements

All the IVUS images were interpreted by experienced technicians supervised by a cardiologist blinded to treatment assignment. The postangioplasty and follow-up studies were analyzed side by side. Great care was taken to ensure that the same and correct anatomic slice was measured in both IVUS studies. The fluoroscopic and angiographic images and audio commentary were used to determine the axial location of the ultrasound transducer and of IVUS landmarks relative to the angioplasty site and side branches. IVUS landmarks (side branches, veins, calcifications, fibrotic deposits) were used to allow matching of the anatomic slice in both studies by use of frame-by-frame review of the images. The anatomic cross section selected for serial analysis was the one at the angioplasty site with the smallest lumen area (LA) at follow-up. The corresponding anatomic slice was then identified on the postangioplasty study. The images were digitized, and quantitative analysis was performed with custom-developed software for geometric computations (NIH Image). Quantitative analysis consisted of measurements of LA and the area within the EEM (Figure 1). EEM was defined as the border between the hypoechoic media zone and the surrounding echo-bright adventitia. WA was calculated as the difference between EEM and LA. When the plaque encompassed the IVUS catheter, LA was assumed to be the size of the catheter. Reference segments were not evaluated in this analysis because the data required to meet our study objectives consisted of measurements of the LA, WA, and EEM at the injured site. These data were provided on the same cross section on IVUS.

Measurement of the EEM area can be difficult in the presence of extensive calcifications because of acoustic shadowing of deeper structures. Two strategies were used to circumvent this problem.

Considering that coronary cross sections are relatively circular, extrapolation of the EEM level was performed directly when each arc of calcification at the selected site did not shadow ≥60° of the adventitial circumference. In addition, study of the anatomic slices just proximal and distal to a selected calcified site was performed when necessary to escape the shadowing and to identify the EEM correctly.

Figure 1. IVUS measurements. Inner and outer white oval lines indicate lumen and EEM areas, respectively.
changes in areas between the 2 examinations after angioplasty. IVUS measurements were analyzed between groups with a 2-way ANCOVA on follow-up areas, controlling for postangioplasty area and potential prognostic factors. IVUS measurements at both examinations were analyzed per segment by the generalized estimating equations technique,14 which takes into account potential dependence between segments in the same patient.

**Results**

Of the 107 patients who underwent IVUS examination of the angioplasty site immediately after intervention, 11 were not studied at follow-up for various reasons: 4 patients had total or subtotal occlusion; the previously dilated site was not crossed in 2 patients; 2 patients had bypass surgery; 1 patient died during the study; 1 patient withdrew from the trial; and 1 patient did not have IVUS images for administrative reasons. In addition, 2 patients underwent both IVUS studies, but extensive calcifications precluded quantitative analysis at the selected angioplasty site. Thus, 94 patients constituted our study population and were distributed into the 4 groups as follows: 21 received probucol alone; 25, multivitamins alone; 20, probucol plus multivitamins; and 28, placebo alone.

Selected demographic, clinical, and angiographic characteristics of the 4 groups are shown in Table 1. There were no statistically significant baseline differences between groups except for a smaller number of patients with hypertension in the probucol group. This variable was not associated with efficacy end points. Six patients were not adequately compliant to study medications (1, 2, 2, and 1 in the probucol, vitamins, combined treatment, and placebo groups, respectively).

### Natural History of Restenosis: IVUS Results in the Placebo Group

Table 2 summarizes IVUS results for the placebo group and for the 3 active treatment groups. Immediately after angioplasty in the placebo group, LA, WA, and EEM were $4.52 \pm 1.39$, $8.85 \pm 3.01$, and $13.37 \pm 3.45$ mm$^2$, respectively. At follow-up, LA decreased by $-1.21 \pm 1.88$ mm$^2$, and WA and EEM increased by $1.50 \pm 2.50$ and $0.29 \pm 2.93$ mm$^2$ (Table 3). The change in LA correlated more strongly with the change in EEM ($r=0.53$, $P=0.002$) than with the change in WA ($r=-0.13$, $P=0.49$).
TABLE 2. Descriptive Results of Serial IVUS Examinations

<table>
<thead>
<tr>
<th></th>
<th>Placebo Alone (n=31)</th>
<th>Vitamins Alone (n=30)</th>
<th>Probucol Plus Vitamins (n=25)</th>
<th>Probucol Alone (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>After angioplasty</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LA</td>
<td>4.52±1.39</td>
<td>4.08±1.41</td>
<td>4.10±0.95</td>
<td>4.62±1.59</td>
</tr>
<tr>
<td>WA</td>
<td>8.85±3.01</td>
<td>9.09±3.28</td>
<td>7.11±2.75</td>
<td>7.57±3.98</td>
</tr>
<tr>
<td>Follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LA</td>
<td>3.31±1.44</td>
<td>3.24±1.58</td>
<td>3.85±1.39</td>
<td>4.47±1.93</td>
</tr>
<tr>
<td>WA</td>
<td>10.35±3.95</td>
<td>10.02±3.40</td>
<td>8.52±3.49</td>
<td>9.46±4.36</td>
</tr>
<tr>
<td>EEM area</td>
<td>13.66±4.18</td>
<td>13.26±3.80</td>
<td>12.37±3.70</td>
<td>13.93±4.74</td>
</tr>
</tbody>
</table>

n=111 target vessels. All values are mm² (mean±SD).

Effects of Probucol and Vitamins on Neointimal Formation and Vascular Remodeling: IVUS Results in the Four Study Groups

As shown in Tables 2 and 3, LA at follow-up was 3.31±1.44 mm² for placebo, 3.24±1.58 mm² for vitamins only, 3.85±1.39 mm² for combined treatment, and 4.47±1.93 mm² for probucol alone, representing lumen losses of −1.21±1.88 mm² for placebo, −0.83±1.22 mm² for vitamins alone, −0.25±1.17 mm² for combined treatment, and −0.15±1.70 mm² for probucol alone (P=0.002 for probucol versus no probucol, P=0.84 for vitamins versus no vitamins). The change in LA was 1.50±2.50, 0.93±2.26, 1.41±1.45, and 1.89±1.87 mm², respectively (P=NS). EEM increased at follow-up by 0.29±2.93 mm² in the placebo group, 0.09±2.33 mm² in the vitamins only group, 1.17±1.61 mm² in the combined treatment group, and 1.74±1.80 mm² in the probucol alone group (P=0.005 for probucol versus no probucol, P=0.36 for vitamins versus no vitamins). An increase in EEM ≥1 mm² at follow-up occurred in 38.7% of patients given placebo alone, in 23.3% in those given vitamins alone, in 44.0% in those given combined treatment, and in 72.0% of patients taking probucol (Figure 2). Table 2 shows the changes in LA, WA, and EEM for compliant patients only.

Although probucol did not affect LA immediately after angioplasty (0.14 mm², P=0.55), there were differences in WA and EEM between groups at this initial examination. Multiple regressions showed that probucol therapy was associated with a reduction in WA (−1.33 mm², P=0.01) and in EEM (−1.20 mm², P=0.06) immediately after angioplasty, after controlling for sex and type of dilated vessels. Left circumflex arteries also had smaller WA (−1.69 mm², P=0.02) and EEM (−2.27 mm², P=0.005) after angioplasty. In contrast, patients in whom the right coronary artery was dilated had larger WA (1.10 mm², P=0.10) and EEM (1.74 mm², P=0.02); similar findings were observed in men (WA, 2.53 mm², P<0.001; EEM, 3.32 mm², P<0.001).

Discussion

Probucol is 1 of the first pharmacological agents shown to reduce coronary restenosis after balloon angioplasty.9–12 Whether probucol acted in the MVP study via prevention of neointimal formation, improvement in vascular remodeling, or both could not be adequately addressed by angiography and thus required the use of IVUS. Answering this fundamental question may lead to the development of better strategies to prevent restenosis.

Before determining how probucol acted in the MVP study, it was necessary to clarify the mechanisms of lumen loss and restenosis after balloon angioplasty in the placebo group. In these control patients, the increase in WA (mean, 1.50 mm²) was greater than the decrease in LA (−1.21 mm²), with a slight increase in EEM (0.29 mm²). However, the change in LA correlated better with the change in EEM than it did with the change in WA. Taken together, these results indicate that the direction (enlargement or constriction) and extent (inadequate or adequate compensatory enlargement) of vascular remodeling in response to the neointimal formation that occurs after balloon angioplasty determine the magnitude of lumen loss at follow-up. Animal studies have yielded various results on the relative importance of remodeling and neointimal formation in the pathogenesis of restenosis.1–5 Animal models, however, have different proliferative and thrombogenic responses to arterial trauma, and plaque content is often

TABLE 3. Changes in Areas on Serial IVUS Examinations

<table>
<thead>
<tr>
<th></th>
<th>Placebo Alone (n=31)</th>
<th>Vitamins Alone (n=30)</th>
<th>Probucol Plus Vitamins (n=25)</th>
<th>Probucol Alone (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up – post-PTCA, mm²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Δ LA</td>
<td>−1.21±1.88</td>
<td>−0.83±1.22</td>
<td>−0.25±1.17</td>
<td>−0.15±1.70</td>
</tr>
<tr>
<td>Δ WA</td>
<td>1.50±2.50</td>
<td>0.93±2.26</td>
<td>1.41±1.45</td>
<td>1.89±1.87</td>
</tr>
<tr>
<td>ΔEEM area</td>
<td>0.29±2.93</td>
<td>0.09±2.33</td>
<td>1.17±1.61</td>
<td>1.74±1.80</td>
</tr>
</tbody>
</table>

Per-segment analysis with the generalized estimating equations technique. n=111 target vessels.
Probucol and Vascular Remodeling

Different than what is found in human atherosclerotic stenoses requiring angioplasty. One additional limitation is that WA and EEM were never measured serially with the same method in a given animal artery.

Although clinical studies have revealed that remodeling occurs in humans after different interventions, relative changes in WA and EEM have varied. Mintz et al. observed that 73% of late lumen loss after intervention was explained by a decrease in EEM. As acknowledged by the authors, their study involved a mix of primary and restenotic lesions on which different interventions were performed. Balloon angioplasty was performed alone in only a minority of patients, and follow-up examination was driven largely by the presence of symptoms. Underestimation of the increase in WA may also have occurred in that study because of the larger acoustic size of the catheters used. Data from another study now appear to show that most of the lumen loss after balloon angioplasty is not caused by a decrease in EEM but by probucol.16,17

Whereas data from this and other studies support the conclusion that lumen loss after balloon angioplasty is caused by the combination of inadequate or deleterious vessel remodeling and neointimal formation, probucol in the MVP study significantly reduced lumen loss chiefly by improving vascular remodeling and neointimal formation, probucol in the MVP study now appear to show that most of the lumen loss after angioplasty is caused by probucol24 may also have favored axial redistribution of plaque away from the dilated site toward the noninjured regions during angioplasty. EEM was also smaller immediately after angioplasty in patients treated with probucol.16,17

The positive results obtained with probucol suggest that the restenosis process is associated with oxidative stress. The powerful antioxidant effects of probucol may have prevented endothelial dysfunction, LDL oxidation, and macrophage and metalloproteinase activation. This could have limited smooth muscle cell activation, migration, and proliferation; matrix degradation; and deposition of new collagen fibers. By ultimately limiting smooth muscle cell contraction, collagen formation and cross-linking, and endothelial dysfunction, probucol may have modified vascular remodeling and allowed greater vessel enlargement. Specific inhibition by probucol of the secretion of interleukin-1 may also have decreased secretion of metalloproteinases and modified matrix remodeling.

We have chosen to compare the changes in EEM and WA between the postangioplasty and follow-up examinations, because we wanted to learn the effects of probucol on vascular remodeling and neointimal formation after angioplasty. However, the smaller WA found immediately after angioplasty in patients treated with probucol deserves comment. It may have been caused by early regression of plaque at the target lesion site induced by the month of treatment with probucol before angioplasty. Changes in plaque content caused by probucol may also have favored axial redistribution of plaque away from the dilated site toward the noninjured regions during angioplasty. EEM was also smaller immediately after angioplasty in patients treated with probucol. A greater amount of axial redistribution of plaque during angioplasty would have resulted in the requirement of less stretching of the EEM to obtain the same angiographic results. This smaller EEM could also represent a manifestation of the inverse Glagov phenomenon (a reduction in EEM secondary to a reduction in WA). We also observed the expected differences in areas associated with sex and type of vessel dilated. However, the association between probucol therapy and reduction in WA and EEM immediately after angioplasty persisted after adjustment for these potentially confounding variables.

Similar to what we observed angiographically, multivitamins had no significant effect on IVUS end points. It is not clear why multivitamins did not prevent restenosis whereas probucol did. Dietary intervention and smoking habits were similar in all groups. Probucol may simply be a more

Table 4. Efficacy Analysis in Compliant Patients

<table>
<thead>
<tr>
<th>Follow-up – post-PTCA, mm²</th>
<th>Placebo Alone (n=30)</th>
<th>Vitamins Alone (n=28)</th>
<th>Probucol &amp; Vitamins (n=23)</th>
<th>Probucol Alone (n=24)</th>
<th>P, Probucol vs No Probucol</th>
<th>P, Vitamins vs No Vitamins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ LA</td>
<td>-1.04±1.67</td>
<td>-0.78±1.25</td>
<td>-0.25±1.20</td>
<td>-0.07±1.69</td>
<td>0.0020</td>
<td>0.5605</td>
</tr>
<tr>
<td>Δ WA</td>
<td>1.52±2.54</td>
<td>0.89±2.15</td>
<td>1.40±1.31</td>
<td>1.95±1.88</td>
<td>0.2179</td>
<td>0.1345</td>
</tr>
<tr>
<td>ΔEEM area</td>
<td>0.48±2.77</td>
<td>0.10±2.23</td>
<td>1.15±1.60</td>
<td>1.88±1.69</td>
<td>0.0034</td>
<td>0.1989</td>
</tr>
</tbody>
</table>

Per-segment analysis with the generalized estimating equations technique. n=105 target vessels.
powerful antioxidant than multivitamins, or its effect on interleukin-1 may have contributed to this result. The improvement in vascular remodeling after angioplasty observed with the combination of vitamins C and E in 1 animal study, contrasts with the lack of effect of multivitamins on the EEM in the MVP trial. The possible prooxidant effects of the higher doses of vitamins C and E used in our patients and the addition of β-carotene to the combination may explain the discrepant results. Two other studies have shown that α-tocopherol reduces neointimal formation in animal models. Although the difference was not significant, it is interesting to note that the smallest increase in WA after angioplasty in our study occurred in the vitamins alone group.

There are limitations to this study. This IVUS study was relatively small, but the results were nevertheless statistically highly significant. In addition, reference segments were not analyzed in the study. Although interesting, this analysis was not strictly necessary to determine the pathophysiology of restenosis after balloon angioplasty and the effect of probucol on remodeling and neointimal formation. In conclusion, lumen loss after balloon angioplasty is due to the inadequate response to neointimal formation. We have shown using IVUS that probucol exerts its antirestenotic effects in humans by improving vascular remodeling after angioplasty.

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