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Effect of High Dose Verapamil on Restenosis After Peripheral Angioplasty

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Objectives. **We sought to determine whether treatment with high dose verapamil prevents restenosis in patients at high risk for reoccurrence after successful percutaneous transluminal coronary angioplasty (PTCA).**

Background. **Restenosis is the major limitation of PTCA. Calcium antagonists have demonstrated some potential as inhibitors of this process.**

Methods. **A total of 98 patients with peripheral occlusive arterial disease (POAD), stable angina pectoris, mild hypertension and at least one additional risk factor increasing the likelihood of restenosis after angioplasty were selected for this placebo-controlled, double-blind, randomized trial. Verapamil (240 mg twice daily) or placebo was taken for 6 months. Efficacy variables assessed before and after angioplasty and at 6 weeks and 6 months after PTCA included thickness of the intima/media complex degree of stenosis, interventricular septal thickness, crurobrachial pressure ratios of dorsalis pedis and posterior tibial arteries, distance to claudication and total vessel diameter.**

Results. **No significant intergroup differences emerged before or immediately after PTCA. Six weeks after angioplasty, a significant thickening of the intima/media complex in the treated vascular segment of 14.3% occurred in the placebo group versus 0% among verapamil patients ($p < 0.01$). At 6 months, the intima/media thickness was 35.7% greater in the placebo group but had decreased by 14.3% in the verapamil group ($p < 0.001$). At 6 months, a marked reduction in septal thickness was observed in the verapamil group versus that in the placebo group ($p < 0.001$). The rate of restenosis was also significantly lower in the verapamil group ($p < 0.001$). Few minor side effects were reported.**

Conclusions. **In patients with POAD at increased risk for restenosis, the administration of high dose verapamil prevented recurrent stenosis for 6 months after successful peripheral angioplasty and was well tolerated.**

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The efficacy and safety of percutaneous transluminal coronary angioplasty (PTCA) in patients with peripheral occlusive arterial disease (POAD) has reached an impressive degree of technical perfection. Depending on the site and complexity of the lesion or lesions involved, primary success rates for this procedure are high. However, the subsequent prognosis of patients who have undergone PTCA for POAD depends to a large extent on the avoidance of restenosis—the major limitation of this procedure.

It is now generally accepted that the proliferation of smooth muscle cells in the media of the vessel walls, and their subsequent migration into the intima, is responsible for the development of restenosis (1). During the past few years, a number of experimental studies (1–8) have demonstrated that calcium antagonists have antiatherogenic properties and could eventually be useful in preventing restenosis. However, initial clinical trials (9–11) failed to show convincing evidence that such agents as diltiazem and nifedipine were able to decrease the restenosis rate after successful PTCA. By contrast, a recent trial (12) using high dose verapamil showed a beneficial effect for patients at high risk of recurrent coronary obstruction. We therefore sought to determine whether such a treatment regimen would also prevent restenosis in patients with POAD after primary successful PTCA.

Methods

Patients. During the recruitment period between January 1993 and September 1995, 98 patients with stage IIb Fontaine POAD (walking distance <200 m on the treadmill at 4 km/h, 10° uphill gradient) and concomitant stable angina pectoris associated with both chronic ischemic heart disease and mild hypertension underwent PTCA at our hospital. The diagnosis of POAD was based on the use of arterial angiography and color-coded duplex ultrasound. Initially all patients had occlusions (diameter ≤5 cm) or subtotal stenoses in the distal superficial femoral artery that were present for >6 months.

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Abbreviations and Acronyms
POAD = peripheral occlusive arterial disease
PTCA = percutaneous transluminal coronary angioplasty
SBP = systolic blood pressure

Chronic ischemic heart disease was diagnosed by coronary angiography and myocardial scintigraphy.

For inclusion in the trial, the following criteria were applied: 1) primary success of PTCA treatment (≥30% reduction of initial lumen constriction); 2) written informed consent; and 3) at least one of six risk factors predictive for restenosis, including diabetes mellitus, hyperlipoproteinemia, initial subtotal or total vascular occlusion of the dilated segmented, eccentric stenosis, residual stenosis of at least 30% or stenosis localized in the distal superficial femoral artery. Patients with a history of pelvic stenoses or occlusions; previous adjuvant therapy with calcium antagonists or with beta-adrenergic blocking agents; age >75 years; earlier revascularization of the same area; serious concomitant diseases; first-, second- or third-degree atrioventricular block; or sinoatrial block were excluded from participation. Other grounds for exclusion were diseases of the supporting or connective tissues, limiting the distance a patient could walk without pain; moderate arterial hypertension with systolic blood pressure >170 mm Hg; and diastolic >95 mm Hg. Finally, patients requiring stent treatment for large anatomic segments or elastic stenoses could not participate in the trial.

Study design. On meeting the inclusion criteria, patients were randomly assigned to receive either the active treatment or placebo under double-blind conditions. PTCA was performed using the Seldinger technique with a 5F balloon catheter 4 cm in length and either 5 or 6 mm in diameter (Cordis). The diameter of the balloon was chosen according to the patent upstream or downstream segment of the vessel. As basic medication after angioplasty, patients were administered 300 mg of acetylsalicylic acid, 80 mg of isosorbide dinitrate (one depot tablet for 6 months) and 600 mg of naftidrofuryl (3 × 200 mg, Lipha, Essen, Germany) each day. The latter is a serotonin 5-hydroxytryptamine (HT_2) receptor antagonist agent with vasoactive and rheologic properties. Depending on their randomization, patients were also given identically appearing tablets of either 240 mg of verapamil (480 mg/day) or placebo, to be taken twice daily. The study protocol was approved by the local ethics committee of the University of Dresden. All patients gave their written informed consent to participate.

Efficacy criteria. Various examinations were performed before and immediately after and at 6 weeks and 6 months after PTCA to assess the possible effect of the test medication in preventing restenosis.

Degree of stenosis. To determine the degree of stenosis, angiographic examinations were performed transfemorally using the Seldinger technique with an image intensifier and a closed-circuit television system. Calculation of the degree of stenosis was performed using the following equation: Percent stenosis = $1 - (a/A \times b/B) \times 100$, where a is the greatest constriction of the lumen (mm) in the anteroposterior projection; b is the greatest constriction of the lumen (mm) in the lateral projection; A is the normal diameter of the lumen in the anteroposterior projection; and B is the normal diameter of the lumen in the lateral projection. On the basis of percent stenosis, the vessel was classified according to one of six pathologic stages: I = normal; II = plaques (stenosis 1% to 25%); III = mild (stenosis 26% to 50%); IV = severe (stenosis 51% to 75%); V = very severe (stenosis 76% to 99%); VI = occlusion. The degree of stenosis was also measured using color-coded duplex ultrasound.

Layer thickness. Color-coded duplex ultrasound was used to determine the thickness of the intima/media complex. The equipment used was a Sonos 1000, Hewlett-Packard 7.5/5-MHz linear probe. The examination was evaluated by two independent experts in blinded manner as to which group the patient belonged. The utmost care was taken to perform the ultrasound measurements under identical conditions to achieve the maximal degree of accuracy in the analyses. To reliably sample the same arterial segment over time, the participating investigators consistently measured layer thickness from the midpoint of the popliteal gap. In separate experiments with three observers and four repeated measures of layer thickness for each of 36 patients, we determined intraobserver variability to be 3.1% and interobserver variability 5.9% of total variance. The total diameter of the vessel was measured after electrocardiographic stimulation. Ultrasound imaging of the common and superficial femoral arteries up to the proximal portion of the popliteal artery was performed with the patient in the supine position.

The artery was continuously imaged by pushing the transducer slowly along the course of the vessel in all segments. Occlusions that were shorter than the width of the transducer (<5 cm) were determined directly using the color stop and refilling the arteries, which was recordable with color coding with the aid of freely positioned measuring points integrated into the equipment. Thickness determinations were made just above and below the area of the dilated vessel by means of at least eight individual measurements, which were then averaged.

Septal thickness. Quantitative measurement of the septum was performed using echocardiography (Sonos 1000, Hewlett-Packard, 2.5-MHz sectorial probe) during systole by determining the mean value of at least five echocardiographically triggered individual measurements.

Crurobrachial ratio of dorsalis pedis. Continuous wave Doppler ultrasound was used to measure systolic blood pressure in the arm and in the dorsalis pedis of the leg treated with PTCA. The ankle/arm SBP ratio was then calculated.

Crurobrachial ratio of posterior tibial artery. SBP was measured in the arm and posterior tibial artery by means of continuous wave Doppler ultrasound in the PTCA-treated leg. The ankle/brachial SBP ratio was then calculated.

Distance to claudication. The pain-free walking distance was measured on the treadmill under standardized conditions (12° uphill, 4 km/h).

Laboratory tests. These tests included measurement of serum electrolytes, creatinine, transaminases, total cholesterol and triglycerides and hematologic examinations that were carried out before and after PTCA and 6 weeks and 6 months after the procedure.

Statistical analysis. Simple comparisons between mean values were calculated using *t* tests: unpaired for group comparisons or paired for time point comparisons; *U* tests were used for simple between-group comparisons of the degree of stenosis. Comparison of mean values versus initial values with a Bonferroni adjustment were performed using repeated measures covariance analysis and multiple procedures according to Winer et al. (13). Probabilities were considered statistically significant for two-tailed tests at the 0.05 level. Unless otherwise indicated, results are reported as mean value ± SD.

For a decrease >50% in the rate of restenosis to be clinically relevant, we estimated that at least 80 patients would have to be studied. Because high risk patients were selected, the restenosis rate in the placebo group was expected to exceed 45%. With a presumed dropout rate of 20%, it was necessary that at least 98 patients enter the study to achieve sufficient statistical power of at least 90% for a relative effect equal to 60% of the standard deviation of the variables tested.

Table 1. Patient, Clinical and Angiographic Characteristics

Characteristic	Placebo Group	Verapamil Group
Patient related		
Age (yr)	64.7 ± 5.6	63.3 ± 6.9
Men/Women	35/14	26/23
Risk factors		
Diabetes	22	23
Hyperlipoproteinimia	36	38
Subtotal/total occlusion	42	40
Eccentric stenosis	6	8
Residual stenosis (≥30%)	43	41
Clinical		
SBP (mm Hg)	152 ± 5.2	150 ± 5.6
DBP (mm Hg)	91 ± 2.5	90 ± 3.9
Smoking	28	30
Distance to claudication (m)	110 ± 34.0	100 ± 38.5
Duration of POAD (mo)	52 ± 14	45 ± 18
Concomitant CAD	33	35
Angiographic		
No. of lesions treated	49	49
% DS before PTCA	96.7 ± 2.1	96.8 ± 2.5
% DS after PTCA	39.2 ± 7.5	38.5 ± 6.9

Data presented are mean value ± SD or number of patients. CAD = coronary artery disease; DBP = diastolic blood pressure; DS = diameter stenosis; POAD = peripheral occlusive arterial disease; PTCA = percutaneous transluminal coronary artery disease; SBP = systolic blood pressure.

Results

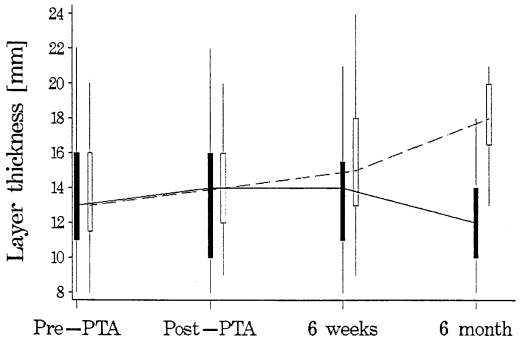
Baseline characteristics. Table 1 summarizes patient, clinical and angiographic characteristics for each treatment group. No significant differences emerged between groups at baseline for any of these characteristics. The mean number of risk factors for restenosis was 2.7 ± 0.6 and 2.5 ± 0.9 in the verapamil and placebo groups, respectively. Baseline values for layer and septal thickness were also similar in both groups, as shown in Figures 1 and 2, respectively.

Adherence to study protocol. A total of 48 patients in the verapamil group and 47 in the placebo group completed the trial and could be analyzed (Table 2). One verapamil group and two placebo group patients were placed on other medication by their physicians during the trial and were therefore excluded from the efficacy analysis.

In two verapamil group patients, laboratory tests showed a threefold increase in transaminases above normal baseline values. However, during further treatment with verapamil, the elevated transaminases returned to normal levels within 4 weeks, so that these patients were not excluded from the study. Verapamil-related side effects were limited to one patient who transiently complained of constipation and dizziness; two placebo group patients also reported nausea and constipation.

Restenosis. Table 2 shows the changes in mean values for the two treatment groups over time for percent stenosis, intima/media thickness, vessel diameter, septal thickness, arterial pressure and the crurobrachial ratios of the dorsalis pedis and posterior tibial arteries. For these variables, as well as for the distance to claudication and laboratory tests (data not shown), no significant intergroup differences were observed on the side of the treated leg either before or immediately after PTCA. By contrast, significant differences between verapamil and placebo emerged (Fig. 1 and 2, Table 2) after 6 weeks of treatment with regard to intima/media and septal thickness (both $p < 0.01$). At 6 months after PTCA, the differences between verapamil- and placebo-treated patients for these variables (both $p < 0.001$), as well as the degree of stenosis ($p < 0.001$) and the crurobrachial ratio of the posterior tibial artery ($p < 0.01$), became even more apparent. The divergence

Figure 1. Changes in median layer thickness during the trial in placebo and verapamil group patients. Median values are shown by **solid** (verapamil) or **dashed lines** (placebo); box and whisker plots indicate the interquartile range (**box**) as well as the 10th and 90th percentiles (**whiskers**).



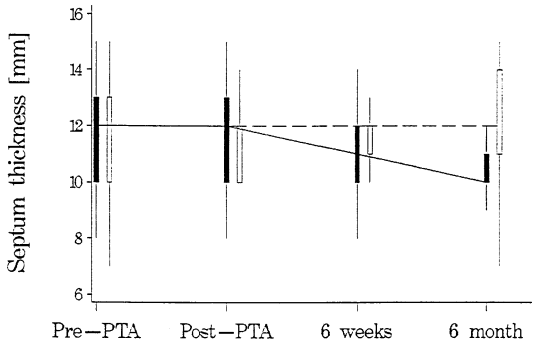


Figure 2. Changes in median septal thickness during the trial in placebo and verapamil group patients. Symbols as in Figure 1.

between groups tended toward significance for the crurobrachial ratio of the dorsalis pedis ($p = 0.06$). Laboratory variables were unaffected after 6 months.

The decrease in septal thickness was also related to a mean decrease in arterial blood pressure (Table 2). After 6 months, a positive correlation emerged in the verapamil group between septal chamber geometry and mean arterial pressure ($r = 0.85$, $p = 0.01$). As seen in Table 2, measurements of total vessel diameter indicated important post-PTCA enlargements in both groups, followed by a gradual but diverging decrease between placebo and verapamil group patients (Table 2). This difference in vessel diameter became significant at month 6 ($p < 0.001$). Furthermore, a positive correlation was found between restenosis and total vessel diameter after 6 months among placebo patients ($r = 0.93$, $p = 0.01$) (Table 3).

With regard to disease stage (Table 3), the generally successful results of PTCA were maintained in the verapamil group at 6 weeks and at 6 months, with only one patient showing a regression to occlusion. By contrast, although all 49 placebo group patients were classified as having stage I or II disease after PTCA, this number decreased to 34 after 6 weeks and then to 22 after 6 months of placebo treatment.

Discussion

Limits of PTCA. In patients with POAD, PTCA is an effective procedure, with high initial success rates. Previous studies have indicated that the primary success rate of peripheral arterial dilation of the distal superficial femoral artery is 91%. After PTCA, ~48% of patients have no remaining stenosis; a further 17% show stenosis <30%, whereas 34% have residual stenoses in excess of 30% in the region of the dilated area (14–16). Thereafter, lumen renarrowing is ob-

Table 2. Intergroup Differences in Efficacy Criteria During Six-Month Trial

	Before PTCA	After PTCA	At 6 wk	At 6 mo
No. of patients				
Placebo	49	49	48	47
Verapamil	49	49	49	48
% DS				
Placebo	96.7 ± 2.1	39.2 ± 7.5	55.5 ± 10.0	69.6 ± 12.2
Verapamil	96.8 ± 2.5	38.5 ± 6.9	46.8 ± 14.1	48.0 ± 11.5*
Intima/media thickness (mm)				
Placebo	1.4 ± 0.38	1.4 ± 0.42	1.6 ± 0.43	1.9 ± 0.47
Verapamil	1.4 ± 0.35	1.4 ± 0.38	1.4 ± 0.33*	1.2 ± 0.31†
Septal thickness (mm)				
Placebo	11.6 ± 1.8	11.0 ± 1.7	11.9 ± 1.8	11.9 ± 2.3
Verapamil	11.5 ± 1.9	11.6 ± 1.7	11.0 ± 1.5*	10.2 ± 1.1†
Crurobrachial ratio				
Dorsalis pedis				
Placebo	0.68 ± 0.10	0.77 ± 0.10	0.75 ± 0.09	0.72 ± 0.08
Verapamil	0.68 ± 0.09	0.77 ± 0.09	0.76 ± 0.08	0.76 ± 0.10
Posterior tibial artery				
Placebo	0.67 ± 0.10	0.78 ± 0.10	0.76 ± 0.10	0.70 ± 0.10
Verapamil	0.65 ± 0.09	0.77 ± 0.09	0.77 ± 0.11	0.76 ± 0.09*
Arterial pressure (mm Hg)				
Placebo				
SBP	168 ± 5.2	170 ± 6.3	163 ± 6.3	165 ± 6.5
DBP	101 ± 2.5	98 ± 3.1	98 ± 3.1	97 ± 4.4
Verapamil				
SBP	170 ± 5.6	150 ± 5.5†	135 ± 5.5†	134 ± 5.2†
DBP	100 ± 3.9	92 ± 4.0†	86 ± 4.1†	87 ± 4.2†
Total vessel diam (mm)				
Placebo	7.1 ± 0.5	9.3 ± 0.4	8.2 ± 0.6	7.5 ± 0.3
Verapamil	7.1 ± 0.4	9.4 ± 0.3	8.5 ± 0.6	8.3 ± 0.3†

*$p < 0.01$. †$p < 0.001$. Data presented are mean value ± SD, unless otherwise indicated. Abbreviations as in Table 1.

Table 3. Change in Degree of Stenosis During Six-Month Trial

	Verapamil				Placebo			
Disease Stage*	Before PTCA (n = 49)	After PTCA (n = 49)	At 6 wk (n = 49)	At 6 mo (n = 48)	Before PTCA (n = 49)	After PTCA (n = 49)	At 6 wk (n = 48)	At 6 mo (n = 47)
I		22	20	18		26	17	7
II		23	24	24		20	17	15
III		4	5	5		3	13	19
IV	16				25		1	4
V	33				24			
VI				1				2

*I = normal; II = plaques (stenosis 1% to 25%); III = mild (stenosis 26% to 50%); IV = severe (stenosis 51% to 75%); PTCA = percutaneous transluminal coronary angioplasty. V = very severe (stenosis 76% to 99%); VI = occlusion. Data presented are number of patients.

served in a substantial number of patients. According to Strunk et al. (16), the proportion of open lumens falls to some 77% at 6 months after PTCA and further decreases to 67% after 1 year. The crucial deleterious changes in the vascular wall generally seem to occur within the first 6 months (16). The amount and rate of restenosis is also more likely to occur when such factors as diabetes mellitus, excessive smoking, hypercholesterolemia and a high degree of postoperative residual stenosis are present (16).

Previous studies with verapamil. In our patients (at increased risk for recurrent obstruction), administration of high dose verapamil significantly reduced the degree of stenosis and related variables 6 months after angioplasty compared with placebo. This result was not unexpected because calcium antagonists have been shown to possess antiatherogenic properties both in vitro (1,4) and in vivo (3). The selection of verapamil for use in the present trial was based on the results of cell culture experiments that demonstrated stronger antiproliferative effects than diltiazem and nifedipine on vascular smooth muscle cells (1,4) and on intimal cells derived from early atherosclerotic lesions (17). Administration of a relatively high dose of verapamil was indicated because data from studies in a rabbit model (18) had shown that larger doses of calcium antagonists were required to markedly decrease atherogenic lesion development. Nevertheless, administration of 240 mg of verapamil twice daily for 6 months proved safe, with only a few, mild side effects reported in the active treatment group.

To our knowledge, the present study is the first to evaluate the use of calcium antagonists for the prevention of restenosis after PTCA. The vascular protective effect of verapamil observed in this trial was similar to the beneficial effects documented by Hoberg et al. (12) in which 196 patients at high risk of coronary obstruction after primary successful coronary angioplasty were given high dose verapamil for 6 months. Our results therefore extend the potential efficacy of verapamil beyond the subgroup of patients undergoing PTCA to those with POAD as well. However, additional studies are warranted to ascertain whether the possible benefits of verapamil treatment pertain to patients at a lower risk for restenosis after PTCA.

Remodeling after PTCA. Various studies (19–21) have suggested that arterial remodeling in coronary arteries after balloon angioplasty may contribute substantially to the development of restenosis. On measuring total vessel diameter, we observed a general pattern of vessel enlargement at 6 weeks after PTCA, followed by a decrease in vessel diameter at 6 months. Late lumen loss was significantly greater among placebo group patients than verapamil group patients. Our results parallel the recent observations of Kimura et al. (22) who found that remodeling after coronary angioplasty was characterized by early adaptive vessel enlargement, followed by late constriction. The positive correlation between restenosis and remodeling of total vessel diameter after 6 months extends the phenomenon of remodeling after coronary angioplasty to peripheral arterial vessels as well.

Value of ultrasound measurement. The development of high resolution 7.5-MHz probes and the use of these B-mode image intensifiers in Doppler ultrasound equipment have made it possible to transcutaneously record and structurally depict the intima and media of large arteries (23–26). The arterial wall can be visualized on ultrasound as a double contour, with two hyperechoic lines around a hypoechoic one. The limits of ultrasound diagnosis are reached in the presence of large-vessel wall calcifications, where it is difficult to investigate layer thickness and degree of stenosis because of acoustic shadow. A comparison of ultrasound and histologic measurements of arterial wall structures of the common carotid artery in humans (26) showed good concurrence between the total thickness of the inner hyperechoic and middle hypoechoic lines and the actual thickness of the histologically determined intima/media complex. Similar findings were reported in vitro in normal and arteriosclerotically altered human aorta preparations using an 8-MHz ultrasound probe (27).

The good imaging quality of the new ultrasound systems allows high reproducibility of transcutaneous ultrasound measurements of the intima/media complex (26). For this reason, it has proven useful to apply ultrasound to determine thickening of the intima/media complex in the region of the carotid arteries in studies of hypertension. Using such a technique, Mayet (28) demonstrated that the use of angiotensin-

converting enzyme inhibitors led to a regression of this thickening, even if lipid levels and body mass remained unchanged.

Although restenosis after peripheral arterial dilatation is significantly associated with endothelial proliferation, these endothelial changes can only be established angiographically when the vascular lumen is constricted by at least 30%. To date, evaluation of early endothelial changes in the region of the peripheral vessels has only been possible, with difficulty, by means of intravascular 6F endoultrasound catheters (24). This limitation has prevented controlled studies from being carried out to evaluate early endothelial proliferation after angioplasty. However, by means of color-coded duplex ultrasound, the thickness of the layers in this pathologic process can be measured noninvasively at a significantly earlier stage. In the present study, staging of stenosis was performed simultaneously with angiography and (color duplex) ultrasound because only limited experience with grading stenosis using (color duplex) ultrasound has been reported (23,26). Our investigations showed the ultrasound and angiographic results to be similar in determining the degree of stenosis (results not shown).

Other means for preventing restenosis. Early occlusions after vascular surgery (within the first week) are primarily due to arterial thromboses in dissections that have occurred after dilation (14), whereas progressive stenosis is linked to endothelial proliferation (16). In addition to refining dilation techniques, which are currently also being combined with stent treatment in the peripheral vessels, drugs that can inhibit endothelial proliferation have been studied (29). However, the prevention of restenosis by means of systemically administered substances, such as antithrombotic, anticoagulant and thrombolytics agents; corticosteroids; lipid-reducing drugs; and cytostatics agents, could not be shown convincingly to date either for the coronary arteries or peripheral vessels. More recently, Voisard et al. (30) observed that the proliferation of the endothelium in cell cultures was significantly reduced when the calcium antagonist Trapidil was used. Comparative investigations of available interventional techniques, such as atherectomy, rotablation or stent implantation, which were all performed in the coronary system, showed that although the problem of restenosis can be reduced by means of optimal recanalization techniques, it cannot be eliminated (31).

Conclusions. In patients with POAD who are at increased risk for restenosis after angioplasty, the administration of 240 mg twice daily of verapamil prevents significant thickening of the intima/media complex of the treated vascular segment and appears to limit vessel remodeling. Further trials with larger numbers of patients are needed to confirm these results and to determine whether the vascular protective effect of verapamil extends beyond the 6-month period investigated in the present study.

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