Metalloproteinase Inhibition and the Response to Angioplasty and Stenting in Atherosclerotic Primates

Gregory S. Cherr, Stephen J. Motew, Jeffrey A. Travis, Juergen Fingerle, Larry Fisher, Mike Brandl, J. Koudy Williams, Randolph L. Geary

Abstract—Determinants of restenosis after angioplasty include constrictive remodeling and intimal hyperplasia. Both processes require extensive matrix turnover, so matrix metalloproteinases (MMPs) have become potential targets of antirestenosis therapies. We studied the effects of RO113-2908, a broad-spectrum MMP inhibitor (MMPI), on the response to iliac artery angioplasty and stenting in atherosclerotic cynomolgus monkeys. Lumen diameter (LD) was measured angiographically, and artery wall geometry was assessed after perfusion-fixation at 4 weeks. Angiogenesis was measured in subcutaneous polyvinyl alcohol disks. Treatment provided significant, systemic MMP inhibitory activity (97±2.2% inhibition of 25 nmol/L MMP-12 by serum) and inhibited angiogenesis (P=0.007). In contrast, loss of gain in LD (P=0.73) and constrictive remodeling (external elastic lamina area ratio [injured/uninjured×100]: MMPI, 106.3±9.6% vs control, 119.9±7.2%; P=0.27) were not substantially improved 4 weeks after angioplasty. Treatment also failed to reduce intimal hyperplasia after angioplasty (intimal area [mm²]: 1.4±0.3 vs 1.6±0.2, P=0.65) or stenting (2.4±0.2 vs 2.8±0.2, P=0.12). In summary, inhibition of MMP activity reduced angiogenesis but failed to prevent constrictive remodeling or intimal hyperplasia after angioplasty and stenting in atherosclerotic primates. Additional research is needed to define the spectrum of matrix-degrading proteases critical in healing atherosclerotic arteries after angioplasty. (Arterioscler Thromb Vasc Biol. 2002;22:161-166.)

Key Words: restenosis | constrictive remodeling | metalloproteinases | angioplasty | stents

Each year, ≈3 million patients undergo reconstruction of atherosclerotic arteries, and many subsequently develop recurrent stenoses at the sites of repair. Restenosis after angioplasty or stenting is due primarily to constrictive artery wall remodeling or intimal hyperplasia, respectively. These processes involve extensive reorganization of extracellular matrix to facilitate changes in artery wall geometry and accumulation of new intimal mass.

Matrix degradation is tightly regulated in the normal artery wall through a balance between matrix metalloproteinases (MMPs) and their endogenous inhibitors (eg, TIMPs). Atherosclerosis shifts the balance toward degradation, as MMPs are produced by accumulating macrophages and activated smooth muscle cells (SMCs). Angioplasty further increases MMP production, and matrix turnover and maturation continue for months after angioplasty in all layers of the arterial wall, likely contributing to SMC proliferation, migration, and remodeling. These observations have led to speculation that inhibiting MMP activity could limit restenosis. However, experiments with MMP inhibitors to prevent intimal hyperplasia in animal models have shown mixed results, and effects on remodeling have not been well characterized. Whether this approach can improve the response to angioplasty or stenting in human beings with advanced atherosclerosis is yet to be defined.

To extend this approach to a preclinical model, we treated atherosclerotic cynomolgus monkeys with a broad-spectrum MMPI for 4 weeks after angioplasty and stent-angioplasty to determine the impact on restenosis. Treatment provided continuous, systemic MMP inhibitory activity and inhibited angiogenesis, but artery wall remodeling and intimal hyperplasia were not improved. Additional preclinical research is needed to define the spectrum of matrix-degrading proteases critical in constrictive remodeling and intimal hyperplasia of atherosclerotic arteries after angioplasty.

Methods

Animal Model

Thirty-one adult male monkeys (Macaca fascicularis; mean age, 13.5 years) consumed an atherogenic diet (0.28 mg cholesterol/kcal) for 2.5±0.1 years to induce advanced iliac artery lesions. Animals were then randomized into MMPI (n=16) or control (n=15) groups based on diet duration and the ratio of total to HDL cholesterol (HDL-C). Animals received aspirin (5 mg/kg PO) 24 hours before angioplasty and stenting. Anesthesia was induced with ketamine (15 mg/kg IM) and butorphanol (0.05 mg/kg IM), antibiotics (cefazolin, 25 mg/kg IM) were given, and baseline blood chemistry, hematological, and coagulation studies were obtained.

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Treated animals then received a loading dose of MMPI (5 mg/kg RO113-2908 in 5% dextrose IV), while control animals received an equal volume of vehicle. Osmotic pumps (Alzet 2 mL, Alza) were then implanted subcutaneously to continuously infuse MMPI (80 mg/mL in polyethylene glycol 400 at \( \sim 75 \mu g \cdot kg^{-1} \cdot h^{-1} \)) or vehicle (polyethylene glycol 400, Sigma) for 4 weeks.

Angioplasty and stenting were performed via the left femoral artery as previously described.14,15 Heparin was administered (100 U/kg IV) and a 4F catheter with inserted sterilely into the femoral artery. Nitroglycerin was administered intra-arterially to minimize vasospasm (1.25 \( \mu g \) in 3 mL saline, \( \sim 0.3 \mu g/kg \)), and baseline arteriography of the distal abdominal aorta and iliac arteries was performed. A 3F Fogarty embolectomy catheter (Baxter) was then inserted into the distal aorta, inflated with sterile saline and contrast, and retrieved across the common iliac segment 3 times by using moderate tension under fluoroscopic guidance.14,16,17 A Palmaz coronary stent (Cordis) was then deployed in the external iliac artery on a 3.5-mm angioplasty catheter (SciMed) inflated to 6 atm for 30 seconds. Arteriography was repeated after the procedure and the sheath was removed. Animals were allowed to recover and returned to social housing, and the atherogenic diet was continued throughout the study. Animal care and procedures were approved by the Animal Care and Use Committee and performed at the Comparative Medicine Clinical Research Center of the Wake Forest University School of Medicine. Protocols conformed to standards set forth in the Guide for the Care and Use of Laboratory Animals (7th ed, 1996).

**Drug Levels and MMP Inhibitory Activity**

RO113-2908 (molecular weight, 406.89) is a hydroxamic acid analogue, MMP active-site inhibitor, with a broad spectrum of activity (IC50 in mmol/L): MMP-1, 360; MMP-2, 0.44; MMP-3, 12; MMP-7, 800; MMP-8, 0.15; MMP-9, 0.41; MMP-12, 0.12; and MMP-13, 0.23. RO113-2908 does not inhibit tumor necrosis factor-\( \alpha \)-converting enzyme. Drug delivery was confirmed by measuring plasma levels prebolus, 30 minutes postbolus, and at 14 and 28 days by a chromatographic assay (F. Hoffmann-La Roche). In brief, 100 \( \mu L \) plasma was mixed with 50 \( \mu L \) of 0.1N HCl and 2500 \( \mu L \) ethyl acetate and shaken for 10 minutes before centrifugation at 2000g for 10 minutes at room temperature. Supernatant (2000 \( \mu L \)) was then evaporated under \( N_2 \) at 40\( ^\circ \)C, the residue was dissolved in 100 \( \mu L \) of the mobile phase, and 50 \( \mu L \) was injected into a Novapak phenyl column (150X3.9-mm ID; particle size, 4 \( \mu m \); Waters Corp). The column was eluted at 1 mL/min with 35% acetonitrile in 0.05 mol/L H3PO4, and then washed with 65% acetonitrile in 0.05 mol/L H3PO4; the drug was detected at 223 nm.

Steady-state circulating MMP-inhibitory activity was measured in each animal at the end of the 4-week treatment period. The fluorescent substrate M1895 (2 mmol/L in 100% dimethyl sulfoxide, Bachem) was added to 200 \( \mu L \) serum from treated and control animals at a final concentration of 48 \( \mu L/mL \). Samples were incubated at 37\( ^\circ \)C with and without 25 mmol/L exogenous MMP-12 (2 \( \mu L/mL \) in 50 mmol/L Tris, pH 7.4, 200 mmol/L NaCl, 10 mmol/L CaCl2, and 0.005% Brij). Substrate cleavage was then measured continuously over the linear part of the reaction (5 minutes) as the change in fluorescence intensity (excitation 334 nm, emission 390 nm) with the use of a GeminiXS plate reader ( Molecular Devices). Net MMP-12 activity was determined by subtracting endogenous activity in paired samples without MMP-12. Net activity for 15 treated animals was then compared with the average activity of 14 controls to determine percent inhibition.

**Angiogenesis Assay**

Angiogenesis depends in part on MMP activity, and the inhibition of MMP activity reduces angiogenesis.18 Therefore, the impact of the MMPI on microvessel ingrowth into polyvinyl alcohol disks was also assessed. Three disks (10-mm diameter, M-Pact Corp) were placed subcutaneously on the upper back. The disks were removed at 2 weeks, fixed in formalin, and embedded in paraffin, and perpendicularly cut sections were cut from the disk center for immunohistochemistry. Endothelial cells were localized with anti-\( \alpha \)-von Willebrand factor antibody (1:500, Dako) as described,8,14 and microvessels were counted in nonoverlapping fields with an eyepiece reticule at \( \times 400 \). Microvessel number was expressed per section and per square millimeter, and mean values were determined for each animal and group.

**Laboratory and Tissue Analyses**

Lipid profiles were measured twice before randomization (total cholesterol, HDL-C, LDL-C, triglycerides, and lipoprotein(a)). Baseline blood chemistry, hematology, and coagulation studies were measured the day of angioplasty and repeated at 2 and 4 weeks. Bleeding time was measured at 4 weeks (Surgicut, ITC Inc.). Animals were then anesthetized and heparinized (100 U/kg IV), and arteriography was repeated via a right femoral sheath. At necropsy deep anesthesia was induced with pentobarbital, and the vasculature was rinsed free of blood with saline. The distal abdominal aorta and iliac arteries were fixed in situ with 10% formalin at 100 mm Hg for 15 minutes, then removed en bloc, and immersed in formalin for 48 hours. Injured and uninjured common iliac arteries were divided into 5 equal rings for paraffin embedding. Stented external iliac arteries were embedded in methacrylate, and 4 sections were cut and polished with the stent in place (Exakt System).14-17 Cross sections were stained for elastin to aid in computer-assisted morphometry.14-17 Areas bounded by the external elastic lamina (EEL), internal elastic lamina (IEL), and lumen were measured, and medial and intimal areas were calculated by subtraction. Depth of injury was graded in each ring as previously described (0, no fracture; 1, plaque fragmented; 2, IEL disrupted; 3, media fractured; 4, EEL disrupted; and 5, artery rupture).16,17 Change in common iliac artery size (remodeling) was estimated by calculating the EEL area ratio (percent) between the injured and contralateral uninjured reference artery in each animal, as previously described.14-17 Stented external iliac artery cross sections were similarly analyzed with stent and lumen areas measured and neointimal area calculated by subtraction.15 Mean neointimal thickness (mm) was calculated by dividing neointimal area by stent perimeter.15 Mean values were determined for each artery by averaging results from individual rings.

**Quantitative Arteriography**

Arteriography obtained preintervention, postintervention, and after 28 days was recorded in DICOM format at 60 frames per second (series 9600, OEC Medical Systems). A guidewire with a 30-mm radiopaque tip (SciMed) was inserted into the iliac artery for calibration of each image. Mean lumen diameter (LD, mm) was measured in each common iliac artery segment by using a computer-assisted edge-detection program (custom modification of Image software, National Institutes of Health) by a single observer blinded to treatment group. With intervention, postintervention, and day 28 common iliac LDs, acute gain (\( \text{LD}_{\text{final}}-\text{LD}_{\text{acute}} \)), percent gain (\( \text{LD}_{\text{final}}-\text{LD}_{\text{acute}}/\text{LD}_{\text{initial}} \times 100 \)), late loss (\( \text{LD}_{\text{final}}-\text{LD}_{\text{acute}} \)), and percent loss of gain (late loss/acute gain \times 100) were determined at the site of balloon injury.

**Statistical Analysis**

Paired comparisons were made within treatment groups and unpaired comparisons between groups with a 2-tailed, Student’s \( t \) test. Significance was assigned at \( P<0.05 \) and values reported as mean±SEM.

**Results**

All procedures were completed without complication, and all arteries were patent at the end of the protocol. Animal weight remained stable throughout the experiment, and no adverse treatment effects were observed. One control animal died 23 days after angioplasty without obvious pathology at necropsy. One treated animal died 14 days after angioplasty of an enteric infection. Data from these animals were excluded from subsequent analyses, leaving \( n=15 \) MMPI animals and \( n=14 \) controls.
Plasma Lipids and Extent of Preexisting Atherosclerosis

The atherogenic diet increased lipid levels significantly and similarly in both groups (Table 1). After 2.5 years, complex lesions had developed in common iliac arteries (Figure 1), as previously established in this model.8,14–17 Atherosclerosis extent (plaque area/IEL area×100) was measured in the uninjured iliac artery opposite the site of angioplasty and was similar in treated and control animals (25.5±4.1% vs 20.1±4.8%, P=0.40).

Blood Chemistry, Hematology, and Drug Levels

No differences were identified in baseline blood chemistry, hematology, or coagulation parameters between the 2 groups (P=NS). Modest differences were noted 4 weeks after angioplasty between treated and control animals for serum sodium, glucose, and creatinine (please see online Table I at http://atvb.ahajournals.org). Serum glucose was slightly higher in both groups at 28 days compared with baseline, reflecting a shorter period of fasting before necropsy (data not shown). Treatment did not significantly alter coagulation parameters or bleeding times, and no bleeding complications occurred in either group. Plasma MMPI levels were significantly elevated 30 minutes after loading and remained well above the IC50 for MMP-2, -3, -9, -12, and others (see above) at 14 and 28 days (Table 1). Consistent with high circulating drug levels, sera from treated animals completely inhibited the activity of 25 nmol/L exogenous MMP-12 (97.4±2.2% inhibition vs control serum).

Angiogenesis

Control disks healed, with ingrowth of a rich plexus of microvessels, as previously described (Figure 2).19 MMPI significantly inhibited angiogenesis with fewer and smaller microvessels penetrating disk interstices (Figure 2). Treatment reduced microvessel number per disk cross section by 37% (73.2±10.2 vs 115.9±9.6, P=0.007) and microvessel density by 21% (9.6±1.0 vs 12.2±0.8/mm², P<0.05).

Angioplasty and Stenting

Angiographic analysis demonstrated that the baseline preangioplasty LD of common iliac arteries was slightly smaller in treated animals (Table 2). This accounted for a slightly smaller LD immediately after angioplasty and less acute gain (Table 2), but the gain as a percentage of baseline LD was comparable for each group (27.2±5.1% vs 29.4±3.9%, P=0.73). After 4 weeks, common iliac artery LD was similar between groups, and treatment did not reduce the percent loss of gain (Table 2).

Morphometric analysis of perfusion-fixed iliac artery cross sections showed that balloon injury had fractured preexisting atherosclerotic plaques, injured the overlying media and adventitia, and led to a significant intimal hyperplasia response (Figure 1). The depth of injury (ie, injury grade) was slightly less in treated animals (2.5±0.3 vs 3.3±0.3, P=0.08), but intimal hyperplasia and the resulting intimal mass were similar (P=0.65) in treated and control arteries (Figure 3). Moreover, treatment did not prevent constrictive artery wall remodeling. Lumen area (P=0.47) and artery wall size (P=0.63) were similar in both groups (Figure 3). We have previously documented a strong correlation between right and left common iliac artery size (IEL area) within individual atherosclerotic monkeys14,16 and that balloon injury acutely increases EEL area ~160%.14,15 To further estimate the extent of artery wall shrinkage, we determined the EEL area ratio (injured/uninjured×100) in common iliac arteries at 4 weeks. Treatment did not increase the EEL area ratio (ie, reduce constrictive remodeling) compared with controls (106.3±9.5% vs 116.9±7.3%, P=0.39).

Stent deployment was successful in each animal, and all stents were patent at the end of the study protocol. Angiographic LD within the stented external iliac artery was similar for treated and control animals in the short term (3.0±0.1 vs 3.1±0.1) and after 4 weeks (2.3±0.1 vs 2.2±0.1). Morphometric analysis documented a similar depth of stent strut injury in each group (P=0.96), resulting in significant intimal hyperplasia at 4 weeks (Figures 1 and 4). However, lumen area (P=0.38), neointimal area (P=0.12), and neointimal

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>MMPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipids, mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>11.1±0.7</td>
<td>10.3±0.6</td>
</tr>
<tr>
<td>HDL-C</td>
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<td>1.0±0.1</td>
</tr>
<tr>
<td>LDL-C</td>
<td>9.9±0.8</td>
<td>9.1±0.6</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.5±0.1</td>
<td>0.3±0.03</td>
</tr>
<tr>
<td>Lipoprotein(a)</td>
<td>1.0±0.2</td>
<td>1.1±0.2</td>
</tr>
<tr>
<td>MMPI, mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postbolus</td>
<td>ND</td>
<td>6850±386*</td>
</tr>
<tr>
<td>Week 2</td>
<td>ND</td>
<td>627±95*</td>
</tr>
<tr>
<td>Week 4</td>
<td>ND</td>
<td>966±205*</td>
</tr>
</tbody>
</table>

ND indicates not detected. Shown are mean lipid levels while consuming an atherogenic diet before randomization.

*P<0.05 vs controls.
thickness (P=0.14) were similar in treated and control animals, thus documenting a lack of inhibition of in-stent intimal hyperplasia by the MMPI (Figure 4).

**Discussion**

Key observations in the present study were that a continuous, 4-week infusion of a broad-spectrum MMPI provided consistently high systemic drug levels and circulating MMP-inhibitory activity that significantly reduced angiogenesis without apparent toxicity. Despite the duration and intensity of treatment, the MMPI failed to alter the arterial response to injury in atherosclerotic primates. Intimal hyperplasia and constrictive remodeling were similar in treated and control animals 4 weeks after angioplasty. To our knowledge, this is the first report to also address the role of MMPs in stent intimal hyperplasia, and treatment did not limit in-stent lesion formation. These results contrast with the prevailing view that MMP activity contributes to the pathogenesis of restenosis. However, this hypothesis has not been previously tested in atherosclerotic primates.

MMPs are expressed in normal arteries (eg, MMP-2), but their activity is low because they are produced in the pro-form and, once cleaved, are inactivated by TIMPs. Atherosclerosis results in increased MMP activity due to increased production by invading leukocytes and activated plaque SMCs and reduced expression of endogenous inhibitors. Angioplasty further increases MMP activity, but the functional impact on artery wall structure has yet to be resolved. In particular, balloon injury has consistently increased MMP-2 and MMP-9 expression in arteries of rats, rabbits, and swine. Restenosis after angioplasty is due to artery wall remodeling and intimal hyperplasia. Strategies to prevent restenosis have thus focused on reorganization of cells and matrix and on SMC replication, migration, and new matrix synthesis, respectively. MMPIs block smooth muscle migration in vitro and in vivo and thus limit neointima formation. In separate studies, Bendek et al treated rats with high doses of the MMP antagonist GM-6001 and batimastat and found reduced smooth muscle migration at 4 days and reduced intimal thickening at 7 days after injury. Follow-up studies by Bendek et al and Prescott et al, however, found no reduction in intimal hyperplasia from 14 days through 6 months, suggesting that “catch-up” intimal

**TABLE 2. Quantitative Angiography**

<table>
<thead>
<tr>
<th>Lumen Diameter, mm</th>
<th>Control</th>
<th>MMPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>2.9±0.2</td>
<td>2.5±0.1*</td>
</tr>
<tr>
<td>Acute gain</td>
<td>0.8±0.1</td>
<td>0.6±0.1*</td>
</tr>
<tr>
<td>Acute gain, % of baseline</td>
<td>29.4±3.9</td>
<td>27.2±5.1</td>
</tr>
<tr>
<td>4 Weeks</td>
<td>2.6±0.1</td>
<td>2.4±0.1</td>
</tr>
<tr>
<td>Late loss</td>
<td>1.0±0.1</td>
<td>0.9±0.2</td>
</tr>
<tr>
<td>Loss of gain, % of acute gain</td>
<td>154.5±22.9</td>
<td>142.7±24.9</td>
</tr>
</tbody>
</table>

*P<0.05 vs controls.

Figure 3. Bar chart compares EEL, media, intima, and lumen areas 4 weeks after angioplasty of common iliac arteries from control and MMPI-treated animals. No significant treatment effects were noted.

Figure 4. Bar charts compare lumen and intimal areas (A) and intimal thickness (B) within Palmaz stents of control and MMPI-treated animals. Intimal thickness was used to normalize data for variations in baseline artery size. No significant treatment effects were noted.
growth had occurred. Our data and a recent study in miniature swine by de Smet et al13 are consistent, in that intimal hyperplasia was not reduced by MMPIs 4 to 6 weeks after angioplasty. Clowes and others14 have recently explored the effects of endogenous MMPIs on the response to arterial injury in the rat. Forough et al31 expressed TIMP-1 in injured rat carotid arteries by seeding SMCs transduced with a retroviral TIMP-1 vector. This resulted in a 40% decrease in intimal hyperplasia compared with arteries seeded with control cells. Dollery et al12 reported a similar effect in the rat model with an adenoviral TIMP-1 vector. These data are consistent with the effects of pharmacological MMPIs outlined above. Whether TIMP overexpression can provide durable results remains to be seen, because these effects have not been reported beyond 2 weeks.

Constrictive artery wall remodeling has emerged as the dominant structural determinant of lumen narrowing after angioplasty.16,32,33 Although the molecular basis of artery wall shrinkage has not been defined, changes in artery wall geometry must involve reorganization of the extracellular matrix because it accounts for >60% of the artery wall mass.8 Thus, MMPIs are logical candidates for the regulation of artery wall remodeling, but few studies have addressed this issue directly. Data linking MMPIs to changes in artery wall geometry come primarily from studies of human aortic aneurysms, where proteolytic activity is increased compared with that in the normal aorta,9,34–36 and from animal models in which MMPIs limit aneurysm formation.37–39 Recently, Mason et al39 seeded injured rat carotid arteries with SMCs overexpressing MMP-9 and documented a significant increase in artery size. In contrast, Dollery et al12 reported no change in the size of injured rat carotid arteries expressing an adenoviral TIMP-1 vector. Therefore, although excess MMP activity promoted outward remodeling after arterial injury,39 MMP inhibition had no effect.12 These data are consistent with the present study and suggest that cellular and molecular events governing outward and inward remodeling may be distinct rather than opposite ends of a spectrum.

At odds with our findings are those of a recent study by de Smet et al.,13 who found reduced inward remodeling after iliac angioplasty in miniswine treated with batimastat. Although the arteries were not significantly larger in treated animals 6 weeks after angioplasty, the extent of artery shrinkage measured by intravascular ultrasound was reduced. Key differences in experimental design could explain our contrasting results. de Smet et al used a double-injury technique after a brief period of cholesterol feeding in contrast to our protocol of a single injury in primates with advanced atherosclerosis. Single- and double-injury techniques have been shown to elicit distinct cellular responses,40,41 and treatments effective at inhibiting the injury response in lower species (eg, hepatic and angiotensin-converting enzyme inhibitors) have generally failed in nonhuman primates.42–45 Another important difference was the inhibitor used and the route of delivery. In contrast to batimastat, RO113-2908 lacks activity against tumor necrosis factor-α–converting enzyme. Thus, batimastat may have inhibited leukocyte recruitment and activation in response to angioplasty, thereby indirectly reducing MMP activity or other unrelated effects of inflammation on remodeling. Batimastat is also more active against MMP-1, and drug concentrations in the present study were only 2- to 3-fold the IC50 for MMP-1. On the other hand, we infused RO113-2908 continuously in contrast to the intermittent injections used by de Smet et al. Further studies with different inhibitors and dosing strategies will be necessary to resolve these differences.

Despite failing to alter the response to angioplasty and stenting, we are confident that MMP inhibition was achieved within tissues, since circulating MMPI concentrations and activity were quite high and angiogenesis was substantially reduced in subcutaneous disks. MMPIs have been implicated in both normal and pathological angiogenesis.18,46,47 MMP-2 and MMP-9 are associated with angiogenesis during wound healing and tumor growth, and deletion of either gene results in impaired angiogenesis in mice.47 By significantly inhibiting angiogenesis, we have strengthened our conclusion that gelatinases (MMP-2 and MMP-9) specifically have a limited role in the pathogenesis of restenosis. However, because the arteries in our study were fixed in situ to preserve wall geometry, MMP activity could not be measured directly, so we cannot entirely exclude the possibility that, in contrast to other species, these and other MMPIs were not induced by angioplasty in the monkey model. Furthermore, an antiangiogenic effect does not address the possibility that MMPIs incompletely inhibited by RO113-2908, or perhaps tumor necrosis factor-α–converting enzyme, are major determinants of the remodeling response.

In summary, these data demonstrate that inhibiting MMP activity does not reduce constrictive remodeling or prevent intimal hyperplasia after angioplasty and stenting in primates with preexisting atherosclerotic lesions. Although the literature is not entirely consistent13 and confirmatory studies are needed, we suggest that MMPIs presently do not have a clear role in the prevention of restenosis after angioplasty or stenting.

Acknowledgments
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References


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