Safety and Efficacy of Gadofosveset-Enhanced MR Angiography for Evaluation of Pedal Arterial Disease: Multicenter Comparative Phase 3 Study

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OBJECTIVE. The purpose of this study was to evaluate the safety and efficacy of gadofosveset, a gadolinium-based albumin-binding MRI contrast agent, in patients with pedal arterial disease.

SUBJECTS AND METHODS. A total of 185 adult patients with known or suspected pedal arterial disease were randomized in a group receiving 0.03 mmol/kg and a group receiving 0.05 mmol/kg of gadofosveset for MR angiography of the pedal arteries. Gadofosveset-enhanced and unenhanced time-of-flight MR angiograms were compared with conventional angiograms, the standard of reference, for the presence of vascular stenosis. All patients underwent drug safety analysis.

RESULTS. For each of three blinded readers, the specificity (21–35%) of gadofosveset-enhanced MR angiography was a statistically significant (p < 0.01) improvement over that of unenhanced MR angiography in the detection of clinically significant (> 50%) stenosis. The sensitivities of the two techniques were similar. For all blinded readers of MR angiograms, sensitivity, specificity, and accuracy were higher with use of the 0.03-mmol/kg dose of gadofosveset than with the 0.05-mmol/kg dose. In the 0.03-mmol/kg group, 28% of patients reported a total of 55 adverse events, 98% of which were reported as mild or moderate. In the 0.05-mmol/kg group, 28% of patients reported a total of 55 adverse events, 98% of which were reported as mild or moderate. No patients died; one patient left the study because of myocardial infarction considered unrelated to the study drug.

CONCLUSION. Because of markedly better efficacy than no contrast agent and a minimal and transient side-effect profile, 0.03 mmol/kg of gadofosveset was found safe and effective for MR angiography of patients with pedal arterial disease.

Imaging of the pedal vessels in patients with pedal arterial occlusive disease is invaluable for treatment planning. The reference standard is conventional catheter-based angiography. However, preoperative angiography of the foot requires careful acquisition of several views for adequate and reliable visualization of all patent arteries, thus MR angiography, intrinsically 3D, has long attracted interest [1]. Contrast-enhanced MR angiography has gained wide acceptance as an alternative to conventional angiography [2]. Time of flight (an unenhanced technique) and multiphase contrast-enhanced MR angiography of the pedal vessels have been compared [3], and the contrast-enhanced technique was found to depict more vessels in a shorter total imaging time. Multistation MR angiography of the pedal arteries has been evaluated in several studies [4–6], and contrast-enhanced MR angiography has been shown to reveal radiographically occult arteries [7, 8].

Gadofosveset (Vasovist, EPIX Pharmaceuticals) is a gadolinium-based blood-pool contrast agent that reversibly binds to albumin in the blood. Better MR angiographic results in a variety of vascular beds have been reported [9–11] with gadofosveset than with no contrast agent. Results of a previous dose-ranging phase 2 study [10] showed a significant dose response for gadofosveset and that 0.03 mmol/kg was the most clinically appropriate dose for MR angiography of the abdomen.

The objective of this study was to establish the diagnostic value of gadofosveset in MR angiography of the pedal arteries.

Subjects and Methods

Study Design

The study was designed as an open-label multicenter crossover study of the safety and efficacy
of gadofosveset in the evaluation of the pedal arterial territory in patients with known or suspected pedal arterial disease. The primary efficacy end points were the sensitivity, specificity, and accuracy of unenhanced MR angiography and of gadofosveset-enhanced MR angiography in the identification of clinically significant stenosis. An adjudicated blinded reading of conventional angiograms was used as the standard of reference. Clinically significant stenosis was defined as narrowing of 50% or more of the diameter of an artery. Secondary end points included agreement between MR and conventional angiography for location of stenosis, differences between MR and conventional angiography in measured percentage stenosis, the receiver operating characteristics (ROC) of readers’ assessments of likely presence of disease, the proportion of uninterpretable MR angiograms, and diagnostic confidence. The ethical committees of each institution participating in the study approved the protocol, and each enrolled patient gave signed written informed consent.

**Patient Selection**

Enrolled in the study were patients 18 years or older with known or suspected pedal arterial disease diagnosed on the basis of physical examination findings or medical history and who were scheduled for an angiographic examination, including pedal evaluation. The MR and conventional angiographic studies were performed within 3–30 days of each other. Patients must not have undergone surgery or percutaneous transluminal angioplasty of the target vessels between enrollment and completion of the imaging studies. No patients with preexisting stents or grafts in the limb to be imaged were included. Patients were excluded from the study if they had had a major cardiovascular event, such as myocardial infarction or stroke, within 30 days before study randomization. To avoid use of the contrast agent in patients with severe renal insufficiency, patients were excluded if they had a serum creatinine concentration greater than 2.0 mg/dL or a history of abnormal renal function, such as renal transplantation or hemodialysis. Pregnant or lactating women were not included. Other exclusion criteria were a history of hemoglobinopathy or any specific MRI exclusion criterion, such as claustrophobia, involuntary motion disorder, and presence of a metallic implant. Patients also were excluded if they had a hypersensitivity to gadolinium-based contrast agents or had previously received gadofosveset. Patients could not have received iodine or other contrast agents within 3 days before or after gadofosveset administration.

**Contrast Agent**

Gadofosveset trisodium is a gadolinium-based small molecule (molecular weight, 975.77 Da) blood-pool contrast agent. It has been shown 88% noncovalently bound to albumin in 4.5% human serum albumin in vitro. The binding sequesters most of the drug in the vascular space, extends the half-life with respect to nonbinding agents, and increases relaxivity to approximately five times that of gadopentetate dimeglumine at 1.5 T [12]. Gadofosveset is primarily renally excreted [13]. IV injection of 0.03–0.05 mmol/kg body weight of gadofosveset was determined to be safe, well tolerated, and effective in phase 1 and 2 clinical trials [10, 14, 15]. In this trial, patients received either 0.03 or 0.05 mmol/kg according to a predetermined randomization scheme. Each patient received an injection of the appropriate volume of drug administered over 25 seconds. The dose was followed by a 30-mL saline flush. Dynamic acquisitions were initiated by an automated timing protocol or by the timing of a bolus of not more than 10% of the specified dose of gadofosveset. If these methods were not available, the imaging delay was determined by the patient’s history or a delay empirically determined in previous studies (65 seconds for < 60 kg body weight, 55 seconds for > 60 kg body weight).

**Imaging**

Digital subtraction angiography was performed according to individual institutional standards. Imaging of the pedal arteries in at least two views was required. Lateral and anteroposterior views included at least from the tibiotalar junction to the metatarsophalangeal junction with an image intensifier matrix of at least 1,024 × 1,024 or cut images. Imaging was to be extended at least 20 seconds beyond the time the contrast agent was expected to arrive in the foot. Additional views were obtained if medically necessary.

MRI was performed with 1.0- to 1.5-T field strength MRI systems with approved and commercially available hardware and software. Before gadofosveset administration, unenhanced (baseline) MR angiograms were obtained according to the standard sequence at each institution or a sequence recommended by the vendor of the MRI system. Approximately one half of the patients in each dose group were imaged with a typical 2D time-of-flight sequence. The other half were imaged with a 3D hybrid or phase-contrast method. Before gadofosveset injection, a subtraction mask was obtained with the imaging parameters specified for the dynamic images.

After gadofosveset injection, dynamic and steady-state imaging was performed with a 3D spoiled gradient-recalled echo technique. Dynamic images were acquired as a sagittal slab, 256 × 320 pixels in plane, 170 × 260 mm field of view with 35–36 partitions interpolated to 70–72 slices set to less than 1.8 mm acquired (< 0.9 mm reconstructed). The contrast parameters were TR/TE, 6–7/minimum with a flip angle of 25°. Reduced-phase field of view gave 167–208 phase steps for an acquisition time of approximately 45 seconds. Two phases (time points) were acquired. The second phase began immediately after the first. One of the allowed timing methods was used to time the start of the dynamic image acquisition.

Steady-state images were acquired as a sagittal slab, 320 × 320 pixels in plane, 280 × 210 field of view, 80 partitions interpolated to 160 slices set to 0.8 mm acquired (0.4 mm reconstructed). The contrast parameters were 18/1.9 with a flip angle of 30°. One fat-suppression pulse per TR and 240 phase steps were used for an acquisition time of approximately 6 minutes. Coursed resolution was used in a few cases in which gradient strength did not allow submillimeter slice thickness. Acquisition of steady-state images began within 15 minutes of gadofosveset administration.

**Safety Monitoring**

After baseline documentation, patients were monitored for at least 72 and up to 96 hours after administration of gadofosveset. Monitoring included physical examination findings, vital signs, pulse oximetry values, ECG, and results of clinical laboratory tests (including hematologic studies, clinical chemistry, coagulation studies, anaphylaxis panel, and urinalysis).

All reports of adverse events (AEs) were recorded according to International Conference on Harmonisation guidelines. The principal investigators at each study site identified AEs regardless of causal relation to the study drug. Onset, duration, severity, and outcome of all AEs were recorded. All AEs were assessed by the principal investigator, who assigned a severity score of mild (did not cause significant discomfort to the patient or change in activities of daily living), moderate (low level of inconvenience to the patient; patient to continue with activities of daily living), or severe (substantially interfered with activities of daily living). Serious (potentially life-threatening) AEs were to be noted and reported. The principal investigator assessed the likelihood (unlikely to be related, possibly related, and probably related) that an AE was related to the administration of gadofosveset. All study monitoring and AE reporting followed good clinical practice guidelines.

**Standard of Reference**

Digital radiographs were transmitted to a central imaging facility. Some institutions provided additional views on film, and these images were digitized for blinded reading. All images were read at a central location by board-certified practicing radiologists. Two independent readers blinded to patient
information aside from the images interpreted the radiographs. The following four vessels were evaluated: distal posterior tibial artery, medial plantar artery, lateral plantar artery, and dorsal plantar artery. The readers identified stenosed regions, noted the location of the most stenosed area on an anatomic diagram, and measured the normal and stenotic diameters using digital calipers. Readers were allowed to deem a vessel uninterpretable if the images were not sufficient to make a determination. For the purposes of the primary analysis, clinically significant disease in each segment was defined as stenosis of 50% or more of the diameter of the vessel. A third blinded reader (the adjudicator) evaluated all vessels on which the first two readers disagreed about either interpretability or presence or absence of clinically significant disease. Each vessel was thus assigned a diagnosis based on the agreement of at least two of the three blinded readers’ interpretations of the conventional angiograms.

MRI Readers
All readers of MR angiograms were board-certified practicing radiologists and were blinded to patient information. Unenhanced and contrast-enhanced images were separately presented and evaluated according to a block randomization scheme that ensured that at least one fourth of all image data sets separated the two data sets representing a given patient. Images were processed and displayed on a workstation (Advantage Windows, GE Healthcare). Readers were provided source images and maximum intensity projections of 3D data sets. For the contrast-enhanced examinations, dynamic contrast-enhanced and steady-state data sets were shown together, as were subtraction images (contrast-enhanced minus unenhanced mask for dynamic contrast-enhanced MR angiography). Readers were allowed to perform further postprocessing, including subvolume maximum intensity projections and oblique reformations, on any data set.

Quantitative image evaluation was performed in the same manner as for the conventional angiographic evaluations. The readers first determined whether the images were interpretable. A patient’s side was considered uninterpretable if two or more vessels were uninterpretable. If the side was interpretable, the readers measured the degree of maximum stenosis in each interpretable vessel to assess the presence or absence of disease in that vessel. Measurements were performed on source or reformatted images with on-screen digital calipers. The blinded readers were not asked to measure stenosis when it was less than 10%. The minimum cross-sectional diameter at the level of stenosis and the diameter of the most normal adjacent arterial segment were measured. After the stenosis measurement, readers rated their overall diagnostic confidence on a per-side basis using a 5-point scale (1, not confident; 2, somewhat not confident; 3, uncertain; 4, somewhat confident; 5, very confident) [16].

Analysis and Statistical Methods
The primary analysis was performed to determine sensitivity, specificity, and overall accuracy in the detection of clinically significant stenosis in the pedal arteries on gadofosveset-enhanced MR angiography and unenhanced MR angiography in comparison with the adjudicated conventional angiographic standard. Sensitivity was defined as the number of correctly identified diseased vessels divided by the total number of diseased vessels. Specificity was defined as the number of correctly identified normal vessels divided by the total number of normal vessels. Accuracy was defined as the number of correctly identified vessels (abnormal or normal) divided by the total number of vessels with a reference diagnosis. All MR angiograms on which vessels were uninterpretable were considered inaccurate for the purposes of determining sensitivity, specificity, and accuracy. That is, if a vessel was deemed uninterpretable by a blinded reader of an MR angiogram and was diagnosed as diseased with conventional angiography, the MR angiographic finding for the vessel was counted as false negative. However, if the vessel was considered not clinically significant with conventional angiography, the MR angiographic finding for the vessel was counted as false positive. Statistical comparisons between gadofosveset-enhanced MR angiography and unenhanced MR angiography were performed with sensitivity, specificity, and accuracy for each reader. Statistical significance was assessed with a cluster-corrected McNemar’s test, which is used to account for correlations within the vessels of each subject [17].

The 0.05- and 0.03-mmol/kg groups were considered separately in all analyses, and the groups were compared with respect to the primary analysis. The 95% CIs for the difference between contrast-enhanced results were calculated. This calculation involved a cluster correction on the variance estimates before estimation of the differences between the unpaired groups. The secondary analyses were performed on the dose group that had superior performance or on the lower dose if the performances were similar.

The agreement between readers of conventional angiograms was assessed by computation of the sensitivity (agreement for the presence of ≥50% stenosis), specificity (agreement for the absence of ≥50% stenosis), and accuracy (overall agreement) of interpretation of each reader versus the other. The two readers thus were evaluated in reference to the other’s diagnosis.

ROC curves were constructed with the qualitative diagnoses. The five qualitative measures of disease state were separately considered the positive diagnostic threshold, and sensitivity versus 1 minus specificity was plotted for each reader MR angiograms. The average and SD of the numeric confidence of diagnosis metric were computed for each MR angiography reader. Mean confidence scores and 95% CIs were calculated using the t statistic for each reader and each MR angiographic technique.

Counts and percentages of adverse events were tabulated. Also noted were changes in vital signs, laboratory results, physical examination findings, and ECG measurements. For ECG recordings, changes from baseline for the PR interval, QRS complex, QT interval, QTc interval, and ST segment were summarized with descriptive statistics and interpreted by an independent cardiologist. Any out-of-range results were noted as adverse events, according to International Conference on Harmonisation reporting standards.

Results
Demographics
One hundred eighty-five subjects (135 men, 50 women; mean age, 67.8 years; range, 42–91 years) were enrolled in the study (i.e., signed consent forms) between April 2002 and February 2003. All of them received the study agent. The patient demographics are summarized in Table 1.

TABLE 1: Subject Demographics (n = 185)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>0.02 mmol/kg</th>
<th>0.05 mmol/kg</th>
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<tr>
<td>n</td>
<td>96</td>
<td>89</td>
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<tr>
<td>Age (y)</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
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<tr>
<td></td>
<td>68.1 ± 10.7</td>
<td>67.4 ± 10.2</td>
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<td></td>
<td>Range</td>
<td>43–91</td>
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<tr>
<td></td>
<td>42–88</td>
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<tr>
<td>Sex (n)</td>
<td>Men</td>
<td>Women</td>
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<tr>
<td></td>
<td>67 (69.8)</td>
<td>68 (76.4)</td>
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<tr>
<td></td>
<td>29 (30.2)</td>
<td>21 (23.6)</td>
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<tr>
<td>Race (n)</td>
<td>White</td>
<td>Black</td>
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<tr>
<td></td>
<td>63 (65.6)</td>
<td>0 (0)</td>
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<tr>
<td></td>
<td>54 (60.7)</td>
<td>1 (1.1)</td>
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<tr>
<td></td>
<td>Hispanic</td>
<td>Other</td>
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<tr>
<td></td>
<td>33 (34.4)</td>
<td>0 (0)</td>
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<tr>
<td></td>
<td>34 (38.2)</td>
<td>0 (0)</td>
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<tr>
<td></td>
<td>Height (cm)</td>
<td>Mean ± SD</td>
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<tr>
<td></td>
<td>168.5 ± 10.2</td>
<td>169.1 ± 8.4</td>
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<td></td>
<td>Range</td>
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<td></td>
<td>149–194</td>
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<tr>
<td>Weight (kg)</td>
<td>Mean ± SD</td>
<td>76.7 ± 7.1</td>
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<td></td>
<td>Range</td>
<td>75.6 ± 15.2</td>
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<td></td>
<td>43–127</td>
<td>46–114</td>
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Note—Values in parentheses are percentages. "n = 182 because height was not recorded in three cases."
Efficacy

One hundred eighty patients completed the study, that is, underwent gadofosveset-enhanced MR angiography and conventional angiography and thus were included in the evaluation of efficacy. Their demographic statistics did not differ notably from those of the whole population who received gadofosveset. Among the 180 patients, 93 were in the 0.03-mmol/kg dose group and 87 were in the 0.05-mmol/kg dose group. Both dose groups were similar with respect to demographic characteristics.

Fourteen patients in each dose group were imaged with 1-T magnets, and performance was similar to those of the whole population.

Of the 93 patients in the 0.03-mmol/kg dose group, the images of nine were randomly selected for blinded reader training and testing. In four other cases, readers did not agree about the interpretability of the data on conventional angiograms, so no standard of reference was established. Therefore, the efficacy analysis was based on data on 80 patients. Of the 87 patients in the 0.05-mmol/kg dose group, the images of six were randomly selected for blinded reader training and testing, and no standard of reference was established in five cases. The efficacy analysis thus was based on data on 76 patients.

In the primary efficacy analysis, the results were similar in the two dose groups. Accuracy and specificity increased over those for unenhanced MR angiography for all readers for both dose groups. Except for the accuracy of reader B at the 0.03-mmol/kg dose, these increases were statistically significant ($p \leq 0.011$). The changes in sensitivity were generally inconsistent and not statistically significant. At the 0.03-mmol/kg dose, reader A had a strongly significant increase in sensitivity at the cost of a smaller increase in specificity compared with the other two readers. The primary results are summarized in Table 2.

Each of the two readers of conventional angiograms were evaluated for sensitivity, specificity, and accuracy of diagnosis with the other held to be the standard of reference. This analysis was used to evaluate the correspondence between readers of conventional angiograms in a diagnostic task equivalent to the primary MR angiography end point. These results are summarized in Table 3.

### Table 2: Diagnostic Sensitivity, Specificity, and Accuracy of MR Angiography by Reader

| Reader | No. of Patients | No. of Vessels | No Contrast Enhancement (%) | Gadofosveset Enhancement (%) | Difference (%) | $p^a$ | No. of Patients | No. of Vessels | No Contrast Enhancement (%) | Gadofosveset Enhancement (%) | Difference (%) | $p^a$
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<tbody>
<tr>
<td>Sensitivity</td>
<td>72</td>
<td>200</td>
<td>77.0</td>
<td>93.0</td>
<td>16.0</td>
<td>&lt; 0.001</td>
<td>74.6</td>
<td>181</td>
<td>79.6</td>
<td>5.0</td>
<td>0.328</td>
<td></td>
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<tr>
<td>A</td>
<td>86.5</td>
<td>77.5</td>
<td>-9.0</td>
<td>0.062</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>B</td>
<td>78.0</td>
<td>78.5</td>
<td>0.5</td>
<td>0.919</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>C</td>
<td>53</td>
<td>116</td>
<td>38.8</td>
<td>59.5</td>
<td>20.7</td>
<td>0.010</td>
<td>29.5</td>
<td>122</td>
<td>48.4</td>
<td>18.9</td>
<td>0.006</td>
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<tr>
<td>Specificity</td>
<td>66</td>
<td>181</td>
<td>28.4</td>
<td>62.9</td>
<td>34.5</td>
<td>&lt; 0.001</td>
<td>27.8</td>
<td>122</td>
<td>58.2</td>
<td>29.5</td>
<td>&lt; 0.001</td>
<td></td>
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<tr>
<td>A</td>
<td>63.0</td>
<td>80.7</td>
<td>17.7</td>
<td>&lt; 0.001</td>
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<tr>
<td>B</td>
<td>66.5</td>
<td>73.4</td>
<td>7.0</td>
<td>0.126</td>
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<td></td>
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<tr>
<td>C</td>
<td>59.8</td>
<td>72.8</td>
<td>13.0</td>
<td>0.004</td>
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<td></td>
<td></td>
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<tr>
<td>Accuracy</td>
<td>80</td>
<td>316</td>
<td>56.4</td>
<td>67.0</td>
<td>10.6</td>
<td>0.011</td>
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<tr>
<td>A</td>
<td>66.5</td>
<td>73.4</td>
<td>7.0</td>
<td>0.126</td>
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<tr>
<td>B</td>
<td>58.1</td>
<td>70.0</td>
<td>11.9</td>
<td>0.006</td>
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<td>56.4</td>
<td>67.7</td>
<td>11.2</td>
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<td></td>
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</table>

Note—Sensitivity, specificity, accuracy, and difference are percentages. Sensitivity population is the number of patients or vessels with the determination of abnormal findings on conventional angiography. Specificity population is the number of patients or vessels with the determination of normal findings on conventional angiography. Patients may have contributed vessels to both sensitivity and specificity. Accuracy population is the total number of patients or vessels with interpretable conventional angiograms. Uninterpretable MR angiogram values were considered inaccurate for this analysis. Clinically significant disease is defined as 50% or greater stenosis.

$^a$From modified McNemar’s test.

![Fig. 1A](image1.png)  
A, Graph shows ROC curves for 0.03-mmol/kg dose group.  
B, Graph shows ROC curves for 0.05-mmol/kg dose group.
MR Angiography of Pedal Artery Disease

ROC curves of the five qualitative diagnostic scores were constructed separately for the two dose groups. The results are shown in Figure 1. Uninterpretable vessels for each reader were excluded from this analysis. The increased diagnostic power of the contrast-enhanced images is apparent in both groups, but neither dose was clearly superior to the other.

Because the primary results did not show an increase in accuracy at the higher dose, the results at the 0.03-mmol/kg dose were considered further. Example images of a patient in the 0.03-mmol/kg specificity population are depicted in Figure 2. In this dose group, the standard of reference accounted for 316 vessels; 200 vessels were identified with clinically significant disease, and 116 (63%) of these vessels were deemed totally occluded.

Also in the 0.03-mmol/kg dose group, the number of examinations with uninterpretable segments decreased with the use of contrast material. For two of the three readers of MR angiograms, this rate was lower than for either reader of conventional angiograms (Table 4). Furthermore, the confidence expressed in diagnoses of interpreted segments was significantly higher for readers A and B using contrast-enhanced MR angiography as opposed to unenhanced MR angiography (Table 5). Reader C had equivalent confidence in both MR angiographic techniques but chose to interpret the percentage stenosis in the fewest segments.

Safety

One hundred eighty-five patients were enrolled in the study. Of these, 96 received 0.03 mmol/kg of gadofosveset, and 89 were given 0.05 mmol/kg of gadofosveset. There were no notable differences in the safety profiles of the two dose groups.

In the 0.03-mmol/kg dose group no patient died, experienced serious AEs, or withdrew from the study because of AEs. Twenty-seven (28%) of the patients in this group reported 50 AEs during the study, and 19 (20%) reported 30 AEs the investigator considered possibly or probably related to the study drug. Fifty-four (98%) of the AEs reported for this group were mild or moderate in severity. One patient reported one AE that was severe and led to the patient’s withdrawal from the study, but the AE was not considered treatment related. This severe event (myocardial infarction) was the only TABLE 3: Interobserver Sensitivity, Specificity, and Accuracy for Readers of Conventional Angiograms (0.03 mmol/kg Dose Group)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reader A vs Reader B</th>
<th>Reader B vs Reader A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>79.8 (154/193)</td>
<td>81.5 (154/189)</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>88.8 (95/107)</td>
<td>68.8 (95/138)</td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>83.0 (249/300)</td>
<td>76.1 (249/327)</td>
</tr>
</tbody>
</table>

Note—Values are percentages with raw numbers in parentheses.

The second reader is considered the reference standard.

Fig. 2—49-year-old man with left-sided claudication and gangrenous left great toe. A–D, Angiogram (A) and maximum intensity projections from unenhanced 2D time-of-flight MR angiogram (B) and gadofosveset-enhanced MR angiograms in dynamic (C) and steady (D) states show comparable findings.
AEs reported to be serious, and no patient died. The most common treatment-related AEs were nausea, burning sensation, and paresthesia (4% each) and pruritus and vasodilatation (3% each). Taken together, the overall AE profile was similar to that previously reported for gadofosveset [9, 11].

Two (2%) of the patients in the 0.03-mmol/kg group had blood chemistry, hematologic, and urinalysis values during the MR angiography monitoring period that were considered AEs, although none of these AEs was judged serious. The two patients had a total of three clinically significant laboratory values. Increased neutrophil count and increased WBC count occurred in the same patient, and hypoglycemia was reported for the other patient. There were no clinically concerning trends in any of these values over time. Three (3%) of the patients in the 0.05-mmol/kg group had blood chemistry, hematologic, and urinalysis values during the MR angiography monitoring period that were considered AEs, although none of the events was judged serious. These three patients had a total of eight clinically significant laboratory values, and no single event was reported by more than one patient.

For both dose groups, no individual changes in vital signs were considered serious or related to gadofosveset. Isolated patients had abnormal ECG readings. In the 0.03-mmol/kg group, one (1%) of the patients reported one clinically significant event of ventricular extrasystole unlikely related to the study drug. In the 0.05-mmol/kg group, four patients reported a total of four clinically significant events, none of them considered related to the study drug. No clinically significant trends in ECG results were discerned.

**Discussion**

The results of this study showed that in the pedal arteries, the primary benefit of gadofosveset was to improve the specificity of MR angiography compared with unenhanced MR angiography. One reader had a statistically significant improvement in sensitivity, but the other readers had equivocal results, including one reader with better, though not statistically significantly so, results interpreting unenhanced images. Clinically and statistically significant improvement in specificity (range, 21–35%), however, occurred for all three blinded readers interpreting contrast-enhanced MR angiograms. The efficacy of gadofosveset was further confirmed in the analyses of secondary efficacy end points. Of particular importance, the mean frequency of uninterpretable images decreased from 16% for unenhanced MR angiography to 2% for contrast-enhanced MR angiography.

The two doses of gadofosveset had similar advantages over no contrast agent. Higher sensitivity, specificity, and accuracy were observed in the 0.03-mmol/kg dose group, but the differences between diagnoses with and without contrast enhancement were similar in the two dose groups. Because the dose groups had independent patient populations, the trend may be systematic, but it may also be due to increased extravasation at the higher dose. Phase 2 studies showed a decrease in contrast efficacy beyond 0.05 mmol/kg [10] in the aortoiliac vessel bed, presumably because the albumin in plasma becomes saturated and more gadofosveset leaks into the extravascular space. In either case, there does not appear to be an advantage to the higher dose.

The blinded reading and analysis of image data were prospectively designed to extract the diagnostically relevant information from the images. The blinded readings were conducted by three independent readers of MR angiograms to compare contrast-enhanced and unenhanced techniques and by two separate readers of conventional angiograms to establish the standard of reference with a third reader, the adjudicator, to resolve diagnostic disagreements. All image readers were blinded to clinical information about the patients and therefore provided an assessment of the diagnostic imaging procedure alone. Because two readers of conventional angiograms interpreted all angiograms, a comparison between the two readers was also available. This condition allowed comparison of the primary end points with the conventional angiographic agreement, which necessarily limited the accuracy of the standard of reference.

Gadofosveset-enhanced MR angiography was clinically and statistically superior to unenhanced MR angiography, primarily because of a large increase in specificity. Generating clinically useful MR images in low-flow blood vessels is a well-recognized problem of unenhanced time-of-flight MR angiography. For example, Pipe [18] estimated that flow slower than a few centimeters per second can produce loss of signal intensity of a vessel that can be confused with stenosis or occlusion. The very low specificity of unenhanced MR angiography in this study (average, 33% for the 0.03-mmol/kg dose) most likely reflects an increased tendency to deem disease present owing to the absence of apparent signal intensity of vessels on unenhanced MR angiograms. Because contrast-enhanced MR angiography does not depend on blood velocity for signal intensity, contrast-enhanced imaging overcame this problem in slow-flow vessels.

For our patient population, specificity, which reflects the probability of correctly identifying nondiseased vessels, is particu-
the accuracy and specificity of the conventional angiography standard was a limitation of our study design. As a result, the specificity of both unenhanced and contrast-enhanced MR angiography may have been underestimated. The difference in specificity is among vessels visualized on conventional angiography, but the success rate of MR angiography among patent vessels that are radiographically occult cannot be directly determined. Furthermore, this limitation may give an apparent sensitivity advantage to the inferior technique, and this advantage may be the reason for the inability to discriminate a sensitivity difference. Perhaps only a follow-up study such as the aforementioned [7] can resolve such a difference.

This study was limited in two important respects. First, we did not compare gadofosveset with extracellular contrast agents for MR angiography. Second, we did not separately evaluate the advantage of imaging in the steady state. Contrast-enhanced MR angiography with extracellular agents in the pedal vessels has been shown effective, but concerns about extravasation and venous contamination make single-station high-resolution imaging difficult [20]. Pedal MR angiography therefore has been studied with careful bolus timing and various bolus chase techniques [4]. These techniques cannot extend the time window available for imaging the vasculature. Gadofosveset, however, remains in the blood with minimal extravasation for a period of time that allows higher-resolution imaging, enabling discrimination of arteries and vessels depicted with computerized image segmentation [21, 22]. Because high-resolution steady-state images were provided, this advantage was partly available to the readers in this study, but the relative advantage of these images and computerized segmentation methods that may increase their utility remains to be studied.

Gadofosveset continued to have only mild and transient side effects. Among treatment-related adverse events, none was severe, and the most common was paresthesia. Nephrogenic systemic fibrosis has been associated with high-dose MR angiography in renally compromised patients, and we excluded such patients from the study. Although no cases of nephrogenic systemic fibrosis associated with gadofosveset have been reported, we recommend the usual caution in imaging of renally compromised patients.

The study was a benchmark comparison of gadofosveset MR angiography of the pedal arteries with conventional and MR angiography without contrast enhancement. The amount of diagnostically relevant information greatly improved with the use of gadofosveset. This finding is apparent in the diagnostic specificity, the rate of interpretable examinations, the ROC curves of qualitative diagnosis among interpretable images, and the overall diagnostic confidence. The efficacy results of this study coupled with the acceptable and transient side-effect profile indicate that MR angiography with a single IV bolus injection of 0.03 mmol/kg of gadofosveset is safe, more effective than unenhanced MR angiography alone, and similar to conventional angiography in terms of utility in the diagnosis of clinically important vascular lesions in the pedal arterial region.

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