MR Angiography at 3 T of Peripheral Arterial Disease: A Randomized Prospective Comparison of Gadoterate Meglumine and Gadobutrol

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OBJECTIVE. This large-scale randomized study aimed to show the noninferiority in terms of diagnostic performance of gadoterate meglumine–enhanced versus gadobutrol-enhanced 3-T MR angiography (MRA) using digital subtraction angiography (DSA) as the reference standard in patients with peripheral arterial occlusive disease (PAOD).

SUBJECTS AND METHODS. In this prospective international randomized double-blind phase IV trial, 189 patients were enrolled. Of them, 156 could be included in the per-protocol population for on-site assessments and 154 for off-site readings. Subjects underwent peripheral MRA, after injection of 0.1 mmol/kg of either gadoterate meglumine or gadobutrol, and DSA within 30 days. The diagnostic accuracy was evaluated and compared using a noninferiority analysis. Secondary endpoints included sensitivity, specificity, diagnostic confidence, contrast-to-noise ratio, and signal-to-noise ratio evaluations.

RESULTS. The percentage agreement between MRA and DSA for stenosis detection was similar for on-site readings for both groups (mean ± SD, 80.6% ± 16.1% with gadoterate meglumine vs 77.1% ± 19.6% with gadobutrol; 3.5% difference), and the same was true for off-site readings (73.9% ± 16.9% with gadoterate meglumine vs 75.1% ± 13.8% with gadobutrol; 1.1% difference). The noninferiority of gadoterate meglumine to gadobutrol was shown for both on- and off-site readings. Sensitivity in detecting significant stenosis (> 50%) was 72.3% for gadoterate meglumine versus 70.6% for gadobutrol, whereas specificity (92.6% vs 92.3%), diagnostic confidence (87.0% vs 86.0%), signal-to-noise ratio (165.5 vs 161.0), and contrast-to-noise ratio (159.5 vs 155.3) did not differ statistically significantly between the two groups.

CONCLUSION. Gadoterate meglumine was found to be not inferior to gadobutrol in terms of diagnostic performance in patients with PAOD undergoing 3-T contrast-enhanced MRA. No statistically significant differences were detected between the two MRA groups.

The prevalence of peripheral arterial occlusive disease (PAOD) in the general population is as high as 14.5%, and PAOD can affect up to 20% of individuals older than 75 years [1]. The diagnosis of PAOD can be made on the basis of medical history and physical examination. However, for treatment decisions and planning, information about lesion length, distribution, number, and localization is required, whereas pretherapeutic noninvasive imaging of the peripheral vasculature is needed after the clinical diagnosis of PAOD has been made. This information is required to refer the patient to either endovascular treatment or a surgical procedure and to establish a detailed treatment plan (including, for example, access site and distal outflow vessel) [2].

It is the current consensus that this pretreatment imaging should be performed noninvasively with either CT or contrast-enhanced MR angiography (MRA) [3–6]. In clinical practice, contrast-enhanced MRA has some advantages over CT angiography, including the lack of radiation exposure and its negligible risk for contrast-induced renal failure; thus, it is widely used for treatment decision making and treatment planning. The risk for nephrogenic systemic fibrosis is quite low if the existing European Medicines Agency and U.S. Food and Drug Administration guidelines on the classification of contrast media are followed [7]. With an increasing number of whole-body 3-T MRI scanners becoming clinically available, there is the potential to acquire high-spatial-resolution datasets with an almost isotropic resolution of 1 mm^3 or even less.

Some studies have already described the feasibility of peripheral 3-T contrast-en-

hanced MRA [8–10], but, to our knowledge, no prospective randomized trial comparing peripheral 3-T contrast-enhanced MRA to the reference standard, digital subtraction angiography (DSA), has been performed yet in a large population of patients with PAOD. Previous contrast-enhanced MRA studies showed that higher gadolinium concentrations (1.0 M) at 1.5 T are useful, providing high diagnostic accuracy compared with DSA [11, 12]; however, it was also shown that contrast agents with higher gadolinium concentrations provide little difference in relaxivity at 1.5 T over 0.5 M gadolinium chelates, such as gadoterate meglumine [13]. The primary objective of this large-scale study was, therefore, to show the noninferiority of gadoterate meglumine–enhanced versus gadobutrol-enhanced 3-T MRA in terms of diagnostic performance compared with DSA in a large population of patients with PAOD.

Subjects and Methods

Study Design

This study was designed as a prospective phase IV double-blind randomized international trial (Dotarem-Enhanced MRA Compared to Gadovist-Enhanced MRA in the Diagnosis of Clinically Significant Abdominal or Limb Arterial Disease [DALIA]. Institutional review board and regulatory approval were granted from each of the 15 participating European centers (Austria, France, Germany, Italy, and Spain). The study was registered at www.clinicaltrials.gov (registration no. NCT 01026389). Figure 1 summarizes the steps and imaging procedures performed within this study.

Patients

Peripheral contrast-enhanced MRA was performed for 189 patients with PAOD (149 men and 40 women), with a mean (± SD) age of 66.4 ± 10.7 (range, 24–91 years), who were scheduled to undergo peripheral DSA (with or without endovascular therapy) because of PAOD in clinical stages II–IV (according to the classification of Leriche and Fontaine [14]). DSA is still considered the reference standard for arterial imaging [15] and was, consequently, used as a reference standard in this study.

After providing written informed consent, patients were randomized to either of the two MRA groups. Patients' baseline characteristics were well balanced between the two contrast agent groups with respect to demographic data and severity of the disease. Patients underwent peripheral 3-T contrast-enhanced MRA with the administration of either gadoterate meglumine (group A) or gadobutrol (group B) within 1–30 days before the planned DSA, with or without endovascular therapy.

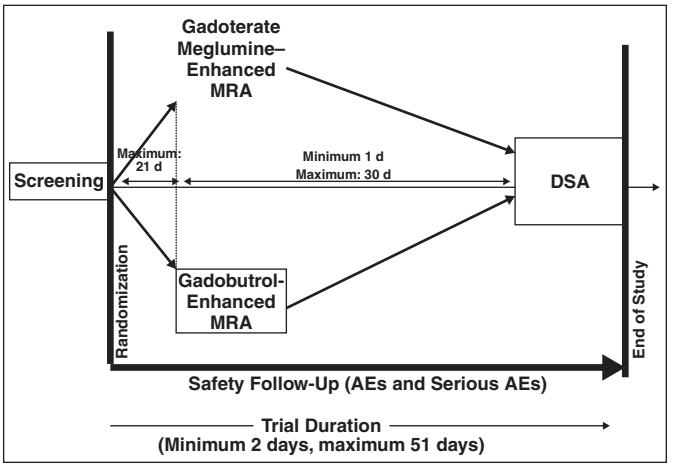

Fig. 1—Schema of trial design. AE = adverse event, DSA = digital subtraction angiography, MRA = MR angiography.

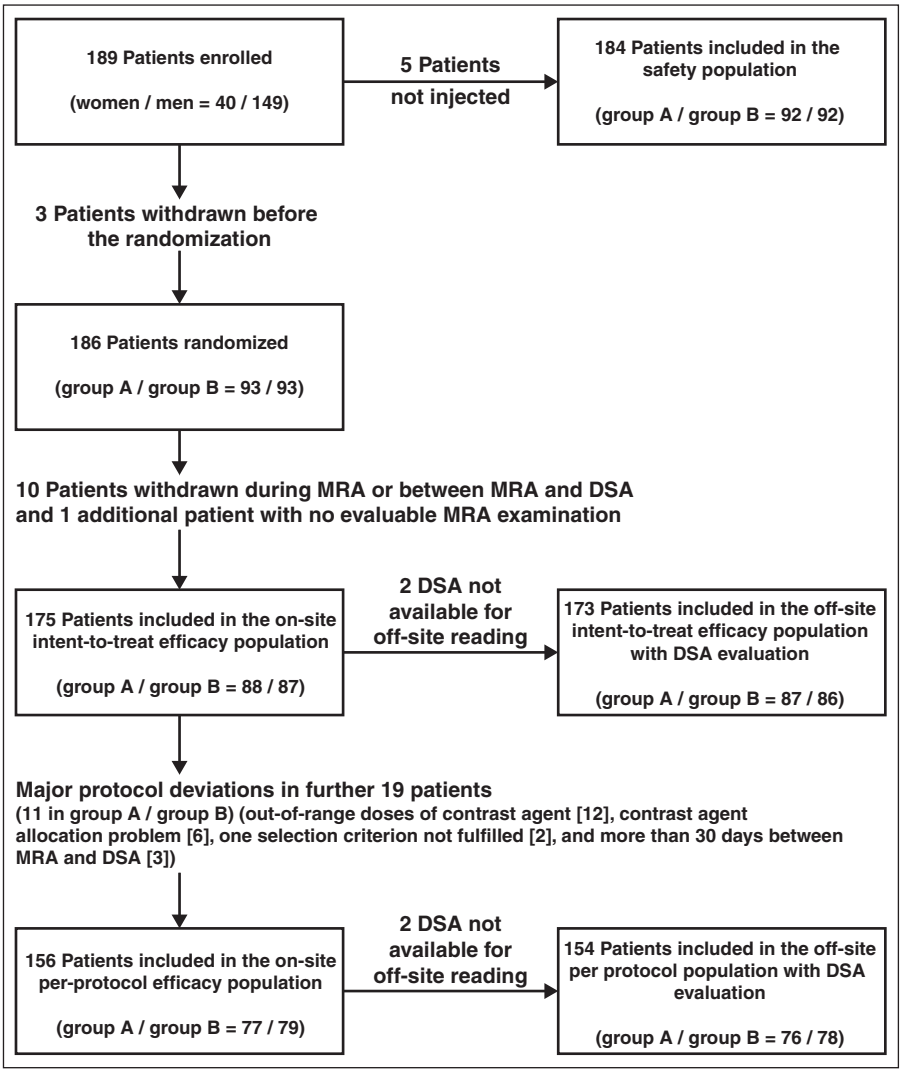

Fig. 2—Flowchart for patient inclusion (group A received gadoterate meglumine, and group B received gadobutrol). DSA = digital subtraction angiography, MRA = MR angiography.

To be eligible, patients had to be older than 18 years. Inclusion criteria were no history of allergic reaction to MRI contrast media and no contraindication to MRI because of pacemakers, implanted metallic devices, aneurysm clips, severe claustrophobia, or metallic joint replacement. Exclusion criteria were abdominal aortic or iliac grafts or stents, or a history of a major cardiovascular event within 30 days before the screening. Chronic renal failure was not mentioned as an exclusion criterion by definition. European Medicines Agency guidelines [7] suggest that patients at risk are those with severe renal insufficiency (glomerular filtration rate < 30 mL/min/1.73 m^2), but gadoterate meglumine and gadobutrol are classified as low-risk gadolinium-based contrast agents and are not contraindicated in this at-risk population [6].

MRI Technique

All examinations were performed on either Siemens Healthcare $n = 80$; 45.7%; 40 in each group), Philips Healthcare $n = 72$; 41.1%; 34 in group A and 38 in group B), or GE Healthcare $n = 23$; 13.1%; 14 in group A and nine in group B) 3-T whole-body systems. For all patients, a bolus-triggering technique in the coronal plane was applied to ensure exact timing of contrast agent injection for the pelvic region. No dedicated timing was performed for the thigh or calf. The scan was initiated after visual detection of the bolus arrival in the ROI. A centric k-space sample order was used. The sequence protocol comprised vessel localizers and 3D T1-weighted spoiled gradient-echo sequences in a coronal orientation in a stepping-table technique that included three steps. A mask sequence before the administration of contrast agent was acquired in three FOVs, covering the complete vascular tree from the abdominal aorta to the level of the feet, which was subsequently subtracted from the contrast-enhanced images to reduce background signal. For examinations on the Siemens Healthcare scanner, TR/TE ranged from 2.5/0.9 to 4.1/1.3 (mean, 3.1/1.1). The mean slice thickness was 1.3 mm (range, 1–1.6 mm), and the mean flip angle was 24° (range, 9–40°). For the Philips Healthcare scanner, TR/TE values ranged from 3.5/1.3 to 4.2/1.5 (mean, 3.9/1.3). The mean slice thickness was 1.6 mm (range, 0.9–3.4 mm), and the flip angle for all examinations was 20°. For the GE Healthcare scanner, TR/TE values ranged from 3.3/1.1 to 5.2/1.8 (mean, 4.1/1.4). The mean slice thickness was 3.25 mm (range, 2.8–3.4 mm), and the mean flip angle was 26° (range, 18–40°).

Contrast Agents

Of 189 patients included, five did not receive contrast agent (for reasons described later), resulting in 184 contrast agent administrations performed, 92 in each group. Patients underwent contrast-enhanced stepping-table MRA during the administration of either gadoterate meglumine (0.5 mmol gadolinium/mL; Dotarem, Guerbet; group A) or gadobutrol (1.0 mmol gadolinium/mL; Gadovist, Bayer HealthCare; group B). All contrast agent injections were performed via an antecubital venous access using a power injector. All patients received 0.1 mmol gadolinium/kg of body weight, independently of contrast agent injected. Given the difference in the gadolinium concentration between the agents used in this trial, different injection parameters were used for the two different groups: Gadoterate meglumine was administered at a flow rate of 1.0 mL/s, followed by 25–30 mL of saline flush (1.0 mL/s) in group A. Gadobutrol was given at a flow rate of 0.5 mL/s, followed by 25–30 mL of saline flush (0.5 mL/s) in group B. Half the flow rate was used for the gadobutrol injection to compensate for the double gadolinium concentration (1.0 M) and to reach the same injection duration to cover the entire multistep acquisition and to reach comparability between the two groups.

Digital Subtraction Angiography

All DSAs were performed within 1–30 days after the study MRA (at least 24 hours after contrast agent injection during MRA). DSA examinations were performed as part of the standard medical treatment, and patients underwent DSA independently of MRA. In cases where endovascular treatment was required for the PAOD, the diagnostic angiograms obtained before the intervention were used for comparison with contrast-enhanced MRA.

Image Analysis

Evaluation of the study images obtained was performed in two steps, consisting of on- and off-site readings.

On-site reading—For on-site reading, all available MRA data, including source data, subtracted images, and maximum intensity projections, were interpreted by one experienced reader from each site. The reader was blinded to the contrast agent used. Another reader, who was not involved in MRA acquisition or reading and was unaware of contrast-enhanced MRA findings, assessed the DSA images.

Off-site reading—For the centralized blinded reading, images were transferred anonymously to a core laboratory. Two independent readers, who had 10 and 4 years of experience and who were blinded to the type of contrast agent used, assessed the MRAs. No consensus reading was performed. All readings were performed in a random order, with the readers blinded to patient data. One experienced reader, also blinded to the clinical history of patients, assessed the DSAs.

Study Endpoints

Efficacy endpoints were evaluated by on- and off-site readers, separately. For analysis purposes, the arterial vascular system was divided into 21 segments per patient: aorta, common iliac, external iliac and common femoral (counted as one segment), superficial femoral, deep femoral, popliteal, anterior tibial, posterior tibial, peroneal, dorsal pedal, and media pedal. For each vascular segment, the degree of arterial stenosis was assessed. Stenoses were quantified according to diameter measurements and were calculated as follows: percentage stenosis = 100 × (1 − [narrowest diameter / normal diameter]). According to this calculation, each lesion was graded as follows: 0, no significant stenosis (0–50%); 1, moderate stenosis (51–69%); 2, severe stenosis (70–99%); and 3, occlusion (100%).

The primary efficacy endpoint was the agreement between MRA and the DSA used as the reference standard for stenosis detection. This percentage of agreement was assessed on a per-patient level and was compared for the two groups. Secondary endpoints included additional quantitative and qualitative efficacy and safety assessments and were evaluated either on site, off site, or both.

For efficacy endpoints, sensitivity and specificity values in stenosis evaluation, as well as positive predictive values (PPVs) and negative predictive values (NPVs), were assessed on a per-segment level. Diagnostic confidence was rated on a per-patient level using a 5-point scale (5, excellent; 4, high; 3, moderate; 2, poor; and 1, not assessable). Visualization of arterial segments and collateral circulation was assessed on and off site by means of a 4-point scale, as follows: 1, providing the expected information (totally satisfactory); 2, providing sufficient information (satisfactory); 3, not providing all the expected information (not satisfactory, may need further investigation); and 4, not providing enough information (not satisfactory, further investigation recommended). In addition, venous overlap that interfered with artery visualization was also graded using a 4-point scale (4, not seen; 3, partially seen; 2, seen; and 1, not assessable). Contrast enhancement was assessed from signal intensity (SI) measurements obtained at predefined ROIs (i.e., the iliac, popliteal, and calf territories). For all measurements, source data were used. Contrast-to-noise ratio (CNR) and signal-to-noise ratio (SNR) were derived from the following equations: $SNR = SI_a / NO$ and $CNR = (SI_a - SI_m) / NO$, where SI_a is the SI measured in the ROI positioned in the common iliac artery, the popliteal artery, and the calf artery; SI_m is the signal intensity measured only once in the psoas muscle; and NO is noise defined as the SD of SI_m measured in the subtraction image at the same location as the SI_m to be measured.

For safety endpoints, vital signs (blood pressure and heart rate) were monitored just before and 15 and 30 minutes after each MRA procedure. Injection-site tolerance was assessed and, in case of pain, a questionnaire (visual analog scale) was to be filled in by the patients 30 minutes after the procedure. Furthermore, all patients were monitored for adverse events (AEs) and serious AEs throughout the study. In brief, AEs were defined as all untoward medical occurrences with a possible, but not necessarily causal, relationship to the administered drug. Per definition, serious AEs were all untoward medical events that led to death, were life threatening, required hospitalization, resulted in persistent or significant disability or incapacity, or were related to congenital anomaly. The on-site radiologist rated the event's severity (mild, moderate, or severe) and its causal relationship (possible, doubtful, and not related) to the contrast agent, as well as the outcome of AEs (resolved with or without sequelae, persisting at the time of follow-up, or death).

Sample Size Calculation and Statistical Analysis

All statistical analyses were conducted using SAS software (version 9.2, SAS Institute). For sample size calculation, it was hypothesized that the within-patient agreement for gadoterate meglumine–enhanced MRA with the reference standard would be around 85%. With a 2.5% one-sided type I error and 80% power, a sample size of 170 patients was considered sufficient to show the noninferiority of gadoterate meglumine–enhanced to gadobutrol-enhanced MRA. Noninferiority was statistically shown if the lower bound of the 95% CI between agreements was above −6.5%, set as the clinical noninferiority limit (minimum clinically relevant difference). Considering a 10% drop-out rate during the study, a sample size consisting of 188 patients was calculated to be sufficient to achieve the study objectives. Secondary efficacy endpoints were investigated using a logistic regression model with adjustment for centers.

Results

Patients Eligible for Analysis

A total of 189 patients were enrolled in 15 centers in five European countries, hereafter referred to as the all-included population (Fig. 2). From this all-included population were defined the safety population and several efficacy populations (on-site and off-site intent to treat and on-site and off-site per protocol). Results are presented for this per-protocol population (156 patients for on-site reading and 154 patients for off-site reading). As shown in Table 1, there were no demographic differences between the two groups of patients. The mean total volume of contrast material administered was double in group A (gadoterate meglumine: 15.4 ± 3.1 mL; range, 8.0–28.0 mL) than in group B (gadobutrol: 7.6 ± 1.3 mL; range, 4.5–11.5 mL), whereas the total amount of gadolinium was the same in both groups. The most common stenosis locations were femoral (49.2% left, 51.3% right) and popliteal (34.9% left, 38.1% right). A history of diabetes was found in 37.6% of the study population (34.4% in group A and 40.9% in group B).

Primary Efficacy Endpoint

In the per-protocol population, the number of assessable arterial segments taken into account in the analysis was dependent on the reader (1940 for off-site reader 1, 2036 for off-site reader 2, and 2145 for the on-site reader). Within-patient agreement between MRA and DSA was similar and did not differ statistically significantly between groups A and B for on-site readings (80.6% ± 16.1% vs 77.1% ± 19.6%; $p = 0.23$; Table 2). The mean difference in percentage agreement (groups A minus group B) was 3.5% (95% CI, −2.2% to 9.1%) for the on-site reader. Pooled data from off-site readers showed a mean percentage agreement in group A of 73.9% ± 16.9% versus 75.1% ± 13.8% in group B, resulting in a mean difference of −1.1% (95% CI, −5.3% to 3.1%). On- and off-site readings showed the noninferiority of gadoterate meglumine–enhanced versus gadobutrol-enhanced MRA in patients with PAOD, because the lower limits of 95% CI (−2.2% and −5.3%) were superior to the noninferiority margin (−6.5%) (Figs. 3 and 4). The results of primary endpoint according to vascular territories are described in Table 3.

Secondary Quantitative and Qualitative Efficacy Endpoints

Sensitivity, specificity, positive predictive value, and negative predictive value—Stenoses with 50% or more luminal narrowing were considered relevant. Applying this cutoff for clinical significance, 502 relevant stenoses greater than 50% were identified by DSA (264 in group A and 238 in group B), out of 2145 assessable segments. The percentage of relevant stenoses did not differ statistically significantly between the two groups ($p = 0.79$). Significant stenoses were correctly diagnosed by MRA in 191 of 264 patients in group A and in 168 of 238 patients in group B. Conversely, 763 of 824 nonsignificant stenoses were correctly diagnosed by MRA in group A versus 756 of 819 in group B. Sensitivity and specificity values (72.3% vs 70.6% and 92.6% vs 92.3%, respectively) showed no statistically significant difference between groups for the detection of relevant stenosis ($p = 0.79$ and $p = 0.98$, respectively) (Fig. 5).

PPVs and NPVs for the diagnosis of significant stenosis were similar in both groups (PPV, 75.8% in group A vs 72.7% in group B; NPV, 91.3% in group A vs 91.5% in group B) in the per-protocol population (Fig. 5). Off-site reading results were comparable and are displayed in Figure 6.

Diagnostic confidence—No difference was found between the two groups, even for on-site readings, with respect to diagnostic confi-

TABLE 1: Demographic and Other Baseline Characteristics for the Per-Protocol Population

Baseline Characteristics	Group A, Gadoterate Meglumine ($n = 77$)	Group B, Gadobutrol ($n = 79$)	Total ($n = 156$)	Test
Age (y), mean ± SD (minimum/maximum)	66.7 ± 10.5 (43/85)	66.3 ± 10.7 (42/89)	66.5 ± 10.5 (42/89)	Student *t* test ($p = 0.803$)
Sex, no. (%) of patients				Chi-square test ($p = 0.602$)
Male	63 (81.8)	62 (78.5)	125 (80.1)	
Female	14 (18.2)	17 (21.5)	31 (19.9)	
BMI, mean ± SD (minimum/maximum)	27.2 ± 4.6 (17.6/39.9)	26.6 ± 3.5 (20.0/38.2)	26.9 ± 4.1 (17.6/39.9)	Student *t* test ($p = 0.366$)
Relevant stenosis > 50% narrowing by DSA (vascular segments)	264	238	502	Chi-square test ($p = 0.339$)

Note—BMI = body mass index (weight in kilograms divided by the square of height in meters), DSA = digital subtraction angiography.

TABLE 2: Primary Efficacy Endpoint: Percentage Agreement Between MR Angiography (MRA) and Digital Subtraction Angiography (DSA) on a Per-Patient Level in the Per-Protocol Population

Reading Site	Percentage Agreement Between MRA and DSA		Percentage Difference Between Group A and Group B (95% CI)	*p*
	Group A, Gadoterate Meglumine	Group B, Gadobutrol		
On-site reading (*n* = 77 for group A and *n* = 79 for group B)			3.5 (–2.2 to 9.1)	0.23
Mean ± SD	80.6 ± 16.1	77.1 ± 19.6		
Minimum/maximum	0/100	0/100		
Off-site readings pooled (*n* = 152 for group A and *n* = 156 for group B)			–1.1 (–5.3 to 3.1)	0.60
Mean ± SD	73.9 ± 16.9	75.1 ± 13.8		
Minimum/maximum	16.7/100	31.6/100		

TABLE 3: Primary Efficacy Endpoint: Percentage Agreement Between MR Angiography (MRA) and Digital Subtraction Angiography (DSA) on a Per-Patient Level According to Vascular Territories in the Per-Protocol Population (On-Site Reading)

Vascular Territory	Percentage Agreement Between MRA and DSA	
	Group A, Gadoterate Meglumine	Group B, Gadobutrol
Aorta (*n* = 65 for group A; *n* = 61 for group B)		
Mean ± SD	90.8 ± 29.2	88.5 ± 32.1
Minimum/maximum	0.0/100	0.0/100
Iliac (*n* = 69 for group A; *n* = 69 for group B)		
Mean ± SD	77.9 ± 25.9	81.2 ± 27.3
Minimum/maximum	0.0/100	0.0/100
Femoral (*n* = 76 for group A; *n* = 77 for group B)		
Mean ± SD	81.9 ± 24.7	80.1 ± 27.0
Minimum/maximum	0.0/100	0.0/100
Popliteal (*n* = 74 for group A; *n* = 77 for group B)		
Mean ± SD	75.0 ± 37.2	72.1 ± 38.5
Minimum/maximum	0.0/100	0.0/100
Calf (*n* = 72 for group A; *n* = 75 for group B)		
Mean ± SD	70.5 ± 29.0	60.9 ± 35.1
Minimum/maximum	0.0/100	0.0/100

dence, which was rated high or excellent in 67 (87.0%) patients in group A versus 68 (86.0%) in group B (Table 4). Results from off-site readings are displayed in Table 5.

Visualization of arterial segments and collateral circulation—Visualization of arteries was assessed on site from a total of 3154 artery segments (1558 in group A vs 1596 in group B). In 80.9% of segments (*n* = 1261) for group A versus 80.2% of segments (*n* = 1279) for group B, expected or sufficient information could be obtained (Fig. 7). Image quality was adequate to excellent for pedal or foot vessels in 33.9% (*n* = 62) of group A patients, compared with 32.8% (*n* = 67) of group B patients.

Expected or sufficient information was obtained for on-site visualization of the collateral circulation in 65 of 77 patients (84.4%) who underwent gadoterate meglumine–enhanced MRA, versus 66 of 79 patients (83.5%) who underwent gadobutrol-enhanced MRA (Table 4).

As shown in Figure 8 and Table 5, off-site results for the quality of visualization of artery segments and collateral circulation were similar to those found for on-site readings.

Venous overlap—Venous overlap was partially or not seen in 31 (40.3%) and 36 (46.8%) patients, respectively, from group A versus 27 (34.2%) and 37 (46.8%) patients, respectively, from group B (Table 4) for on-site reading. Off-site reading results are displayed in Table 5.

Signal intensity, Contrast-to-Noise Ratio, and Signal-to-Noise Ratio measurements—MRA parameters were site and brand dependent and ranged within routine limits. Under these conditions, contrast enhancement was measured in specified ROIs (i.e., the iliac, popliteal, and calf territories) for gadoterate meglumine and gadobutrol. Pooling all territories, mean artery SI values did not differ statistically significantly between groups A and B (1167 ± 930 vs 1243 ± 964; $p = 0.19$). No statistically significant differences were detected between groups A and B for SNR (165.5 ± 200.2 vs 161.0 ± 201.6; $p = 0.72$) and CNR (159.5 ± 198.0 vs 155.3 ± 198.8; $p = 0.73$).

Overall, both contrast agents did not appear to differ quantitatively with regard to arterial enhancement despite different gadolinium concentrations.

Safety Endpoints

No clinically significant change in vital signs compared with baseline was observed in either group. In two patients from group A (2.2%), four AEs occurred after gadoterate meglumine injection. The reported event in one patient was a burning sensation (mild and possibly contrast related). In addition, one 51-year-old man from group A developed three events, including folliculitis (mild unrelated event), severe acute coronary syndrome for 14 days, and severe carotid artery stenosis for 90 days, but these two last serious AEs were considered by the investigator to be unrelated to gadoterate meglumine. This patient with a body mass index (weight in kilograms divided by the square of height in meters) of 20.6 had an ongoing history of dyslipidemia, hypertension, lower limb arteriopathy, and alcohol and tobacco abuse. In two patients from group B (2.2%), two AEs developed after gadobutrol injection. These events included an injection site extravasation (mild and unrelated) and a hot flush (mild and possibly contrast related).

Discussion

Within a medical environment with rapid technologic developments, the benefit of contrast media always remains to be investigated. This study was designed to assess

TABLE 4: Secondary Efficacy Endpoints, On-Site Reading, Per-Protocol Population

Category	Group A, Gadoterate Meglumine (*n* = 77)	Group B, Gadobutrol (*n* = 79)
Visualization of collateral circulation		
Providing the expected information	29 (37.7)	28 (35.4)
Providing sufficient information	36 (46.8)	38 (48.1)
Not applicable or not providing enough or all the expected information	12 (15.6)	13 (16.5)
Venous overlap		
Not seen	36 (46.8)	37 (46.8)
Partially seen	31 (40.3)	27 (34.2)
Seen	8 (10.4)	13 (16.5)
Not assessable	2 (2.6)	2 (2.5)
Diagnostic confidence		
Excellent	28 (36.4)	31 (39.2)
High	39 (50.6)	37 (46.8)
Moderate	9 (11.7)	11 (13.9)
Poor or nil	1 (1.3)	0 (0.0)

Note—Data are number (%) of patients. Not all percentages total 100 because of rounding.

the clinical equivalence of gadoterate meglumine–enhanced and gadobutrol-enhanced peripheral 3-T MRA, using DSA as the reference standard, in patients with abdominal or lower limb arterial diseases during a large prospective randomized blinded trial. The results provided here for diagnostic accuracy in the detection of relevant stenosis substantiate the clinical usefulness of contrast-enhanced MRA of the peripheral arteries at 3 T. Sensitivity, specificity, NPVs, and PPVs obtained from a large study population are clear proof-of-concept that peripheral 3-T MRA can be performed in the clinical routine.

Actually, because of the increasing current availability of clinical 3-T whole-body MRI scanners, the advantages of 3 T can now be used even for peripheral vascular imaging purposes. These advantages are manifold, including the ability to acquire high-spatial-resolution datasets with an almost isotropic resolution of 1 mm^3 or even less. Especially for vascular imaging by means of contrast-enhanced MRA, 3 T offers increased SNR and higher CNR values compared with 1.5 T. The prolongation of the longitudinal tissue relaxation time (T1) in background tissue, which leads to increased CNR between contrast-enhanced vascular structures and the surrounding background tissue, reflects one of the most important benefits of contrast-enhanced high-field MRA [16, 17]. However, because of limitations in the homogeneity of the magnetic field, the smaller FOV of 3-T scanners was once a drawback when imaging the peripheral arterial tree. Recent improvements in scanner technologies, including new whole-body coils, now enable imaging of the peripheral arterial tree within three FOVs, even at 3 T [18]. These advantages of 3 T over 1.5 T for contrast-enhanced MRA have already been evaluated and proven [8–10, 16]. However, despite promising results, a large prospective PAOD trial comparing the diagnostic performance of peripheral 3 T MRA with the refer-

TABLE 5: Secondary Efficacy Endpoints, Off-Site Reading, Per-Protocol Population

	Reader 1		Reader 2	
Category	Group A, Gadoterate Meglumine (*n* = 77)	Group B, Gadobutrol (*n* = 79)	Group A, Gadoterate Meglumine (*n* = 77)	Group B, Gadobutrol (*n* = 79)
Visualization of collateral circulation[a]				
Providing the expected information	22 (28.6)	27 (34.2)	27 (35.1)	21 (26.6)
Providing sufficient information	43 (55.8)	41 (51.9)	38 (49.4)	42 (53.2)
Not applicable or not providing enough or all the expected information	12 (15.6)	11 (13.9)	12 (15.6)	16 (20.3)
Venous overlap[b]				
Not seen	26 (33.8)	31 (39.2)	8 (10.4)	14 (17.7)
Partially seen	37 (48.1)	29 (36.7)	50 (64.9)	47 (59.5)
Seen	11 (14.3)	18 (22.8)	17 (22.1)	16 (20.3)
Not assessable	3 (3.9)	1 (1.3)	2 (2.6)	2 (2.5)
Diagnostic confidence[c]				
Excellent	14 (18.2)	18 (22.8)	27 (35.1)	26 (32.9)
High	37 (48.1)	38 (48.1)	27 (35.1)	28 (35.4)
Moderate	17 (22.1)	19 (24.1)	13 (16.9)	20 (25.3)
Poor or nil	9 (11.7)	4 (5.1)	10 (13.0)	5 (6.4)

Note—Data are number (%) of patients. Not all percentages total 100 because of rounding.
[a] $p = 0.795$ for reader 1; $p = 0.477$ for reader 2.
[b] $p = 0.281$ for reader 1; $p = 0.656$ for reader 2.
[c] $p = 0.475$ for reader 1; $p = 0.377$ for reader 2.

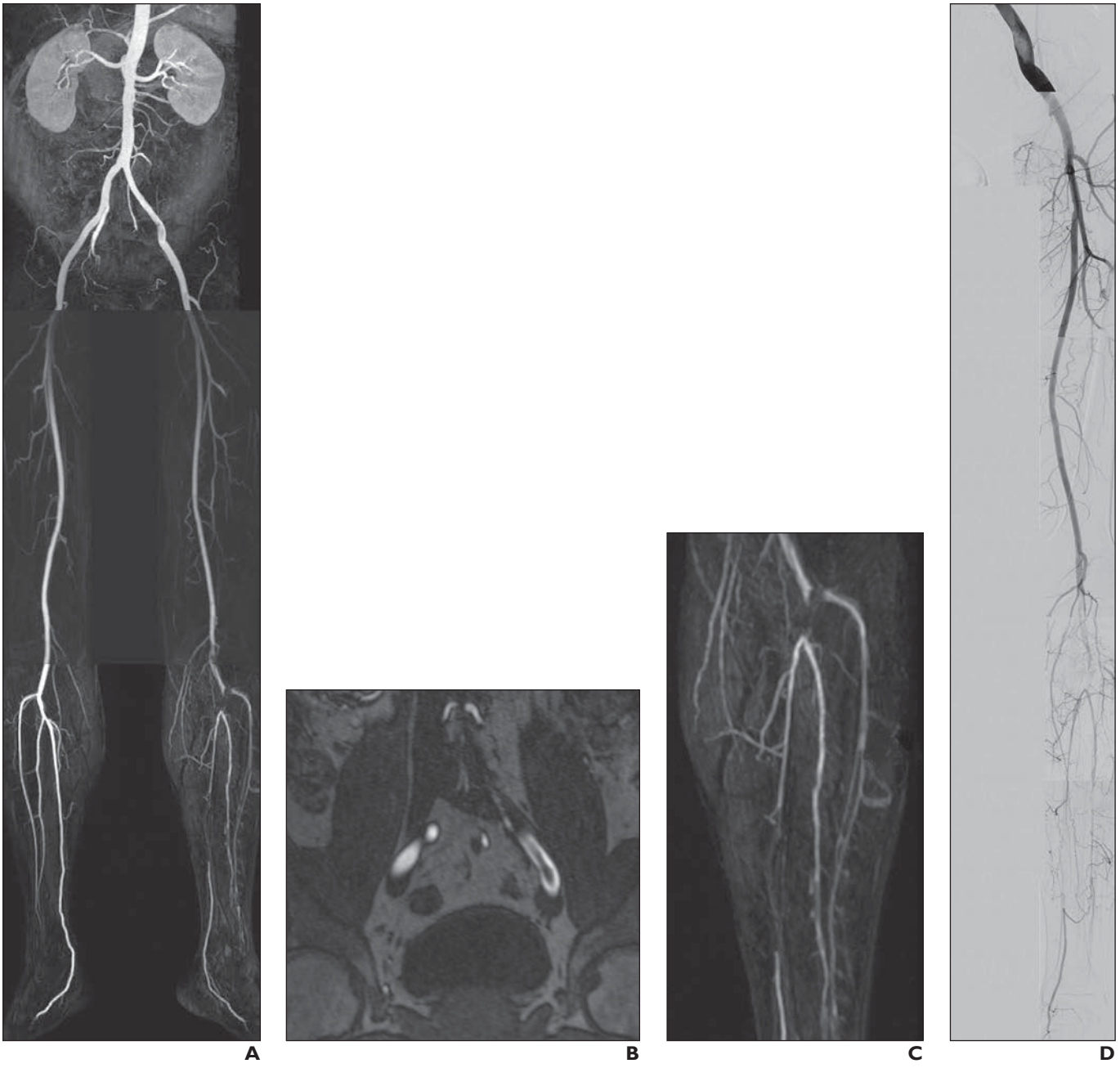

Fig. 3—51-year-old man with pain in left leg at rest for 3 days (peripheral arterial occlusive disease stage III).
A–C, Maximum intensity projections of gadobutrol-enhanced MR angiograms are shown. Image of peripheral arteries (**A**) shows occlusion of tibiofibular trunk and of left posterior tibial artery. Magnification of pelvic region (**B**) shows thromboembolic material within left external iliac artery. Magnification of calf region (**C**) shows thromboembolic occlusion of left tibiofibular trunk and left posterior tibial artery.
D, Digital subtraction angiography performed during endovascular treatment confirms thromboembolic occlusion of left tibiofibular trunk and left posterior tibial artery.

ence standard, DSA, had not been published. This is important because, in addition to improved diagnostic image quality, there are more beneficial effects of MRA at 3 T. However, specific artifacts may interfere with the diagnostic accuracy at 3 T. For example, the B1 inhomogeneity represents a well-known artifact problem for MRI at 3 T [19], possibly influencing the diagnostic accuracy.

Our study shows the noninferiority of 0.5 M gadoterate meglumine compared with 1.0 M gadobutrol in peripheral MRA at 3 T and shows the robustness of this technique in a multipractice environment. Furthermore, the fact that results from the on-site evaluation could be confirmed by off-site readers further shows the reliability of peripheral MRA at 3 T for diagnosis and treatment planning in PAOD. The lower levels of accuracy reached within this trial, compared with those recently published [20], may be attributable to several different factors. First, this study was performed as a double-blind multicenter trial with a predefined examination protocol. It is well known that such an approach provides less-homogeneous results compared with single-center studies. Second, additional dedi-

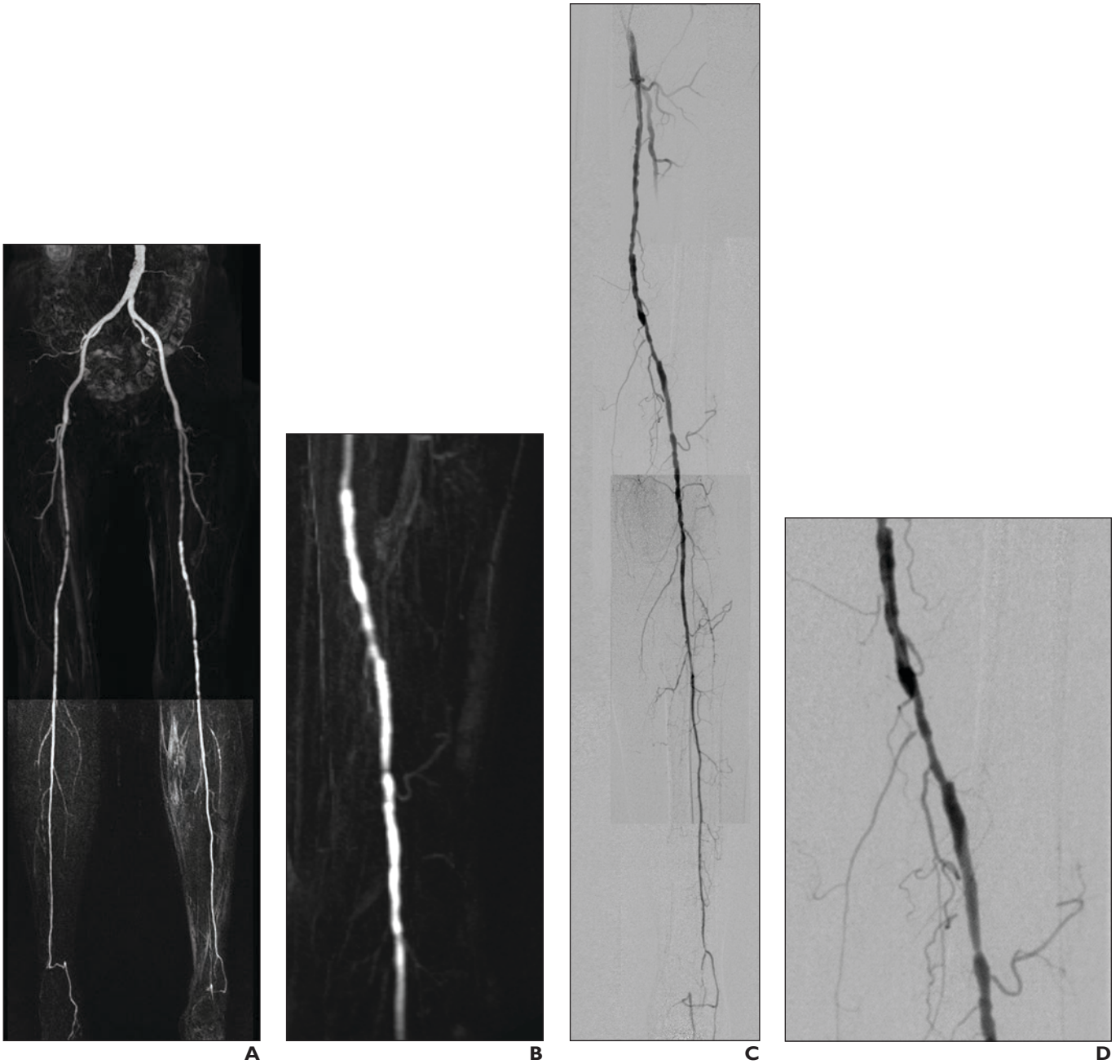

Fig. 4—86-year-old woman with tissue loss at left forefoot (peripheral arterial occlusive disease stage IV).
A and **B,** Maximum intensity projections of gadoterate dimeglumine–enhanced MR angiograms are shown. Image of peripheral arteries (**A**) shows multiple high-grade stenoses of superficial femoral arteries on both legs. There is also occlusion of anterior and posterior tibial arteries on both legs. Magnification image of left superficial femoral artery (**B**) shows multiple high-grade stenoses.
C, Digital subtraction angiography (DSA) of left leg shows multiple high-grade stenoses of left superficial femoral arteries. There is also occlusion of left anterior and left posterior tibial arteries.
D, DSA of left superficial femoral artery (magnification) confirms MR angiography findings of multiple high-grade stenoses.

cated or time-resolved scans for calf vessels (i.e., hybrid scans) were not allowed to ensure comparability between the two macrocyclic contrast agents, although the combination of a moving-table MRA technique with dynamic single-station MRA of the calf has been shown to improve diagnostic accuracy [21–25]. Injection parameters and bolus timing for the thigh and calf areas could not be adjusted individually to the patients' requirements to allow comparability between the two groups in this multicenter trial. Diagnostic confidence could be further improved by adding dedicated scans for the calf arteries, even at 3 T. Finally, the use of a single dose of gadolinium for the entire peripheral MRA in all patients could also explain the slightly poorer results than those reported previously.

The influence of gadolinium concentrations of both contrast agents was also assessed for diagnostic performance. Apart

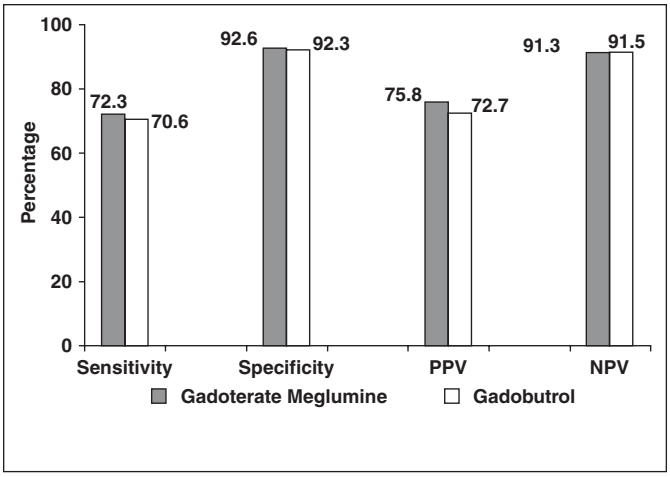

Fig. 5—Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) assessment for on-site reading, per-protocol population.

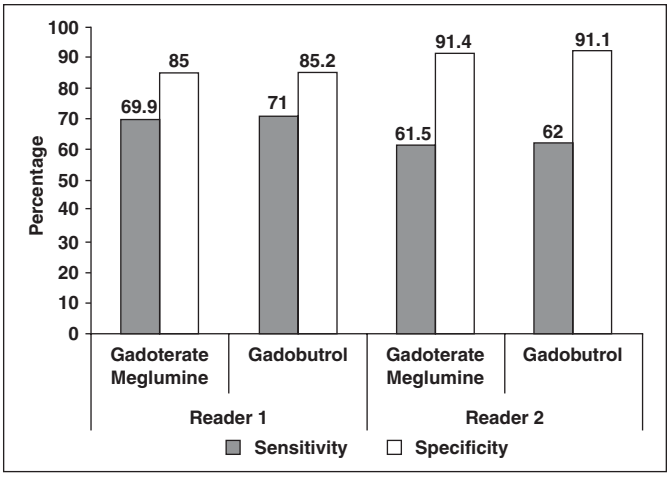

Fig. 6—Sensitivity and specificity assessment for off-site reading, per-protocol population.

from gadolinium concentration, relaxivity is a key factor in determining the SNR and CNR and, ultimately, image quality, knowing that gadoterate meglumine and gadobutrol are not high-relaxivity molecules. Early MRA studies found higher SNRs with 1.0 M gadobutrol compared with conventional 0.5 M gadolinium chelates at 1.5 T, but smaller differences in SNR between 1.0 M gadobutrol and 0.5 M contrast agents, such as gadoterate meglumine, could be expected at 3 T [26]. Because of the better background suppression of unenhanced tissues at 3 T, vessel conspicuity is usually higher than at 1.5 T. To test this assumption in subjects with PAOD, we randomized patients to two groups who underwent peripheral 3-T MRA, during the administration of either a 0.5 M (gadoterate meglumine, group A) or 1.0 M (gadobutrol, group B) concentration of contrast agent. This study showed the lack of a clinically relevant difference between the two contrast agents when evaluating diagnostic performance in the assessment of patients with PAOD at 3 T.

The results presented in this article show the clinical equivalence of gadoterate meglumine–enhanced and gadobutrol-enhanced MRA for the detection of relevant stenoses in the peripheral vasculature, as previously reported for smaller sample sizes [13, 26]. In addition, the comparability of both agents was shown with regard to other findings in patients with PAOD: no differences were found between groups, particularly for the visualization of collateral arteries and the presence of venous overlap. So that comparability of examination protocols in the two groups could be ensured, injection parameters were adjusted to the injection of gadolinium per second. Half the volume of gadobutrol, compared with gadoterate meglumine, was injected at half the injection speed, which resulted in the same gadolinium flow per second in all patients. Thus, it can assumed that the injection was not optimized for each contrast agent and that the use of gadobutrol at the same injection speed and volume could have increased the CNR, but this would have led to doubling the total gadolinium dose, which leads to increased risk for nephrogenic systemic fibrosis as well as increased costs.

Our study has limitations. Because of the different techniques used, some artery segments were not available for evaluation, because they were not visualized by DSA if an anterograde arterial access was used. However, these were mostly proximal segments, where no relevant problems for noninvasive imaging usually occur. Thus, results should not be influenced by this factor. Another limitation of the study might be the fact that different MRI scanner types and imaging techniques were used as a result of the multicenter design. However, we strongly think that the advantages of a multicenter design, combined with centralized reading, overcome the limitations due to mild inhomogeneity of data and wide SI variations among magnet brands. Theoretically, a higher gadolinium concentration should provide a higher intravascular signal, thus maximizing vessel conspicuity and image quality, because the same amount of gadolinium is injected in a shorter time. However, in this study, no statistically significant difference was found between gadoterate meglumine and gadobutrol for SI, SNR, CNR, or image quality, if all vascular territories were pooled. Comparison with a true reference standard (DSA) was made in this trial, resulting in a robust methodologic approach, and the sample size was large enough to show clinically reliable and significant results. Finally, a single contrast material injection was allowed by the study

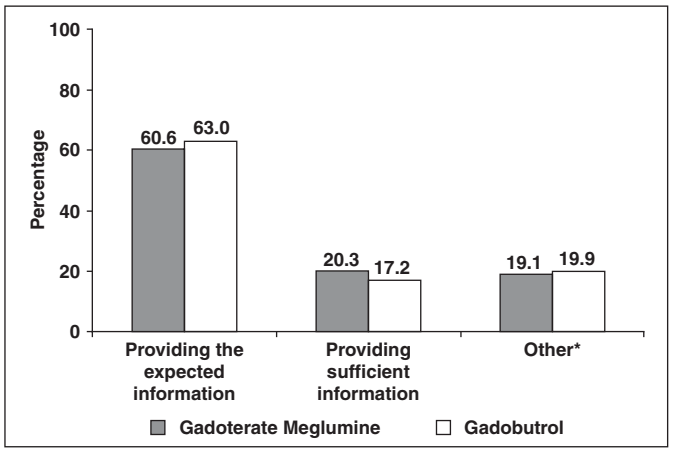

Fig. 7—Visualization of patients' arteries, on-site reading, per-protocol population. Asterisk denotes not providing all the expected information, not providing enough information, or not applicable.

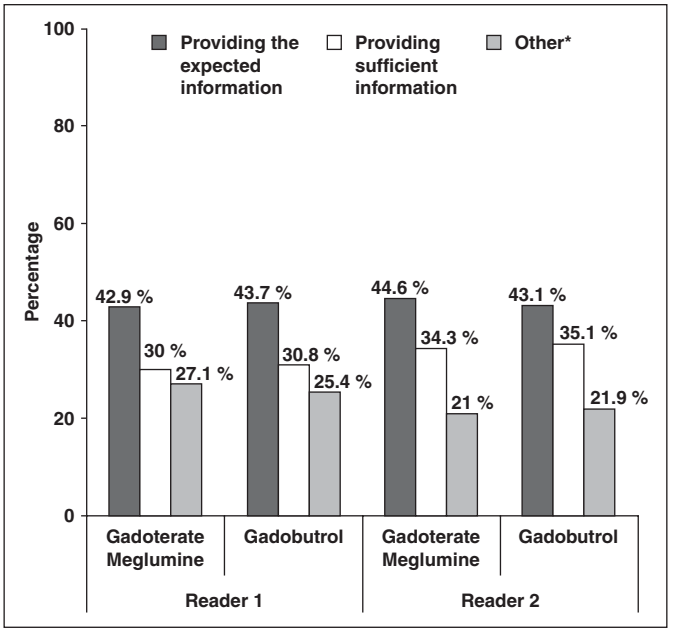

Fig. 8—Visualization of patients' arteries, off-site reading, per-protocol population. Asterisk denotes not providing all the expected information, not providing enough information, or not applicable.

protocol to ensure comparability between the two groups, although it has been shown that a time-resolved MRA, or the acquisition of an additional high-resolution static MRA with a second contrast material bolus, could further improve the results of 3-T MRA below the knee. Even without the acquisition of such additional scans, the level of diagnostic confidence achieved by MRA in this study was high compared with DSA, and no difference was found between the two groups.

Conclusion

Gadoterate meglumine was found to be not inferior to gadobutrol in terms of diagnostic performance in this large population of patients with PAOD undergoing 3-T contrast-enhanced MRA. No statistically significant differences were detected between the two MRA groups.

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