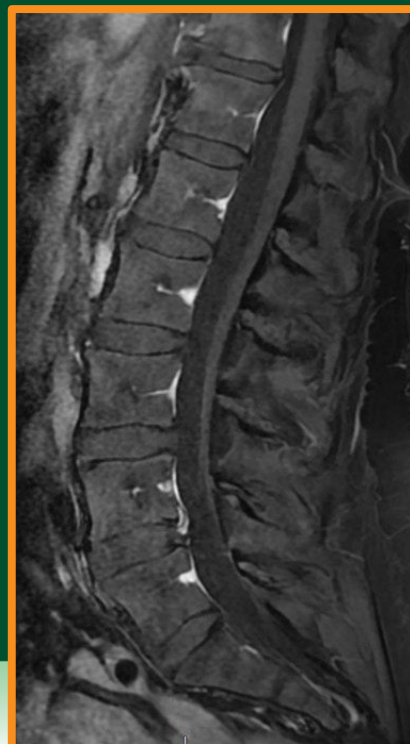
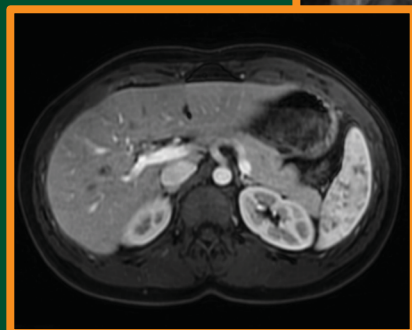
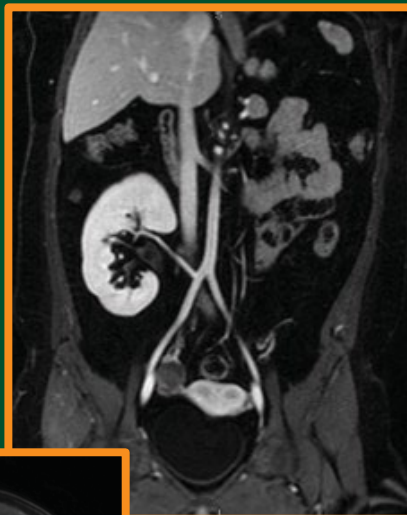
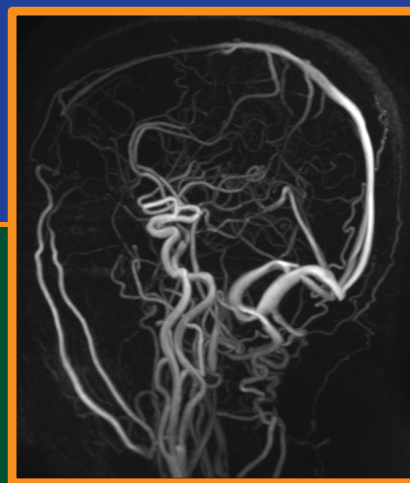
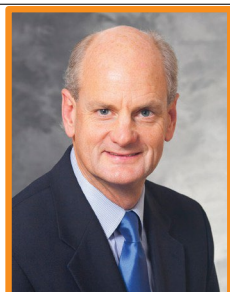


# Advanced MRI Protocols: Optimizing Visualization

1st Edition



Images courtesy of Aaron S. Field, MD, PhD,  
Thomas M. Grist, MD, FACR, and Ali Pirasteh, MD.



## Thomas M. Grist, MD, FACR

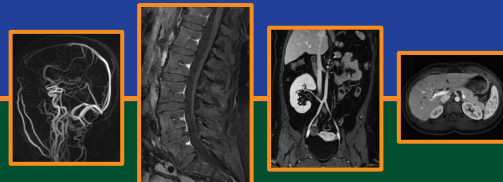
John Juhl Professor of Radiology and Medical Physics  
University of Wisconsin School of Medicine and Public Health  
Madison, Wisconsin

This activity is approved by the International Society for MR Radiographers & Technologists (ISMRT) for 2.25 Category A CE Credits.

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## 1. GADOLINIUM-BASED CONTRAST AGENTS

### A. Physicochemical Properties

At present, 8 gadolinium-based contrast agents (GBCAs) are approved by the US Food and Drug Administration (FDA) for use with magnetic resonance imaging (MRI), including (in order of FDA approval) ProHance (gadoteridol), MultiHance (gadobenate dimeglumine), Eovist (gadoxetate disodium), Gadavist (gadobutrol), Dotarem/Clariscan (gadoterate meglumine), and the newest GBCA Vueway/Elucirem (gadopiclenol), which was approved in 2022.<sup>1-8</sup> All of these agents cause T1 shortening based on the presence of a paramagnetic gadolinium (Gd<sup>3+</sup>) ion. However, each agent contains the Gd complexed with a chelate, and the chelates differ in terms of their molecular structures and physicochemical properties, both of which contribute to the safety and efficacy of the resulting contrast agent (**Figure 1; Table 1**).<sup>1-11</sup>

Many of the older linear GBCAs have been withdrawn from the market by their manufacturers because of the lower chelate stability as compared to macrocyclic GBCAs. These include Magnevist (gadopentetate dimeglumine), Omniscan (gadodiamide), and OptiMARK (gadoversetamide). Also, Ablavar (gadofosveset trisodium), a high-relaxivity blood pool agent, was voluntarily withdrawn from the market by its manufacturer in 2016.

**Table 1. Properties of MRI GBCAs<sup>1-9,12</sup>**

	Extracellular Agents				Combined Extracellular/Hepatobiliary Agent	Hepatobiliary Agent
Brand Name	ProHance	Gadavist	Dotarem/Clariscan	Vueway/Elucirem	MultiHance	Eovist
Generic Name	Gadoteridol	Gadobutrol	Gadoterate meglumine	Gadopiclenol	Gadobenate dimeglumine	Gadoxetate disodium
FDA approval (United States)	1992	2011	2013	2022	2004	2008
Molarity (M)	0.5	1.0	0.5	0.5	0.5	0.25
Chemical structure	Macrocyclic	Macrocyclic	Macrocyclic	Macrocyclic	Linear	Linear
Ionicity	Nonionic	Nonionic	Ionic	Nonionic	Ionic	Ionic
Protein binding	None	None	None	Negligible	Weak	Weak
r1 <sup>a</sup> (L · mmol <sup>-1</sup> · sec <sup>-1</sup> )						
0.47T	4.8	6.1	4.3	13.2	9.2	8.7
1.5T	4.1	5.2	3.6	12.8	6.3	6.9
3.0T	3.7	5.0	3.5	11.6	5.5	6.2

FDA = US Food and Drug Administration; GBCAs = gadolinium-based contrast agents; MRI = magnetic resonance imaging.  
<sup>a</sup>r1 measured in plasma/serum at 37° to 40°C.

MultiHance (gadobenate dimeglumine) and Eovist (gadoxetate disodium) are open-chain, linear, ionic agents. MultiHance (gadobenate dimeglumine) is chemically similar to the older, now withdrawn GBCA Magnevist (gadopentetate dimeglumine), but differs with the presence of a lipophilic benzyloxymethyl side chain that extends from the chelate molecule. ProHance (gadoteridol), Gadavist (gadobutrol), Dotarem/Clariscan (gadoterate meglumine), and the new GBCA Vueway/Elucirem (gadopiclenol) are macrocyclic in structure, with Dotarem/Clariscan (gadoterate meglumine) being the only ionic agent in this family. Most agents are formulated at a standard 0.5M concentration; exceptions include Gadavist (gadobutrol; formulated at a double concentration of 1.0M), and Eovist (gadoxetate disodium; formulated at 0.25M). Despite formulation at a higher concentration, the approved dose of Gadavist (gadobutrol; 0.1 mmol/kg) provides the same amount of gadolinium as the approved dose of MultiHance (gadobenate dimeglumine) and the other extracellular fluid (ECF) agents (also 0.1 mmol/kg), only it does so in half the volume.<sup>2,4</sup>

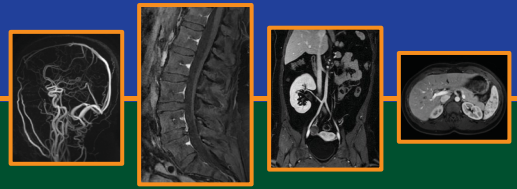
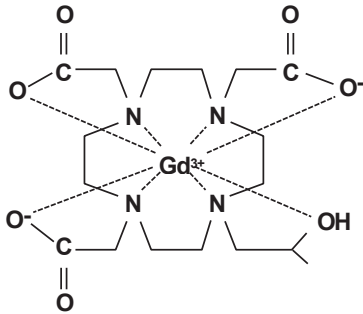
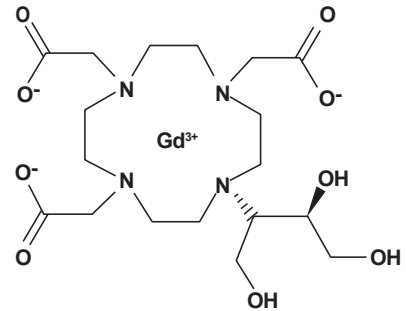


Figure 1. Structural Formulas of Gadolinium-based Contrast Agents<sup>1-9,12</sup>

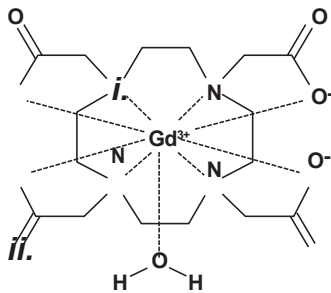
## Macrocyclic



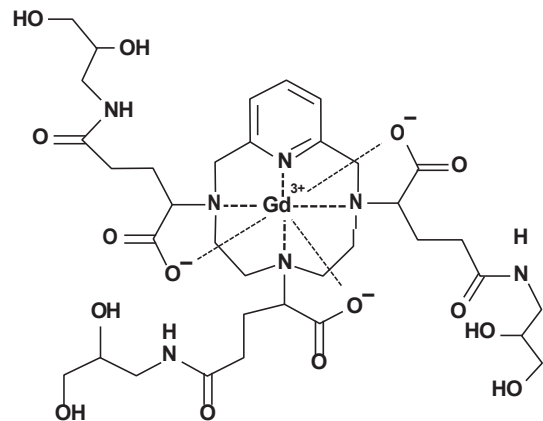
ProHance (gadoteridol)



Gadavist (gadobutrol)

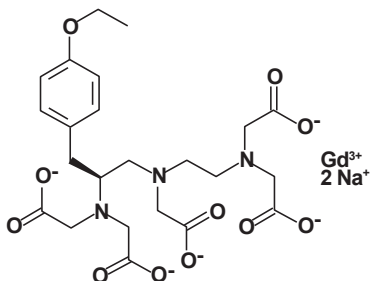


Dotarem/Clariscan (gadoterate meglumine)

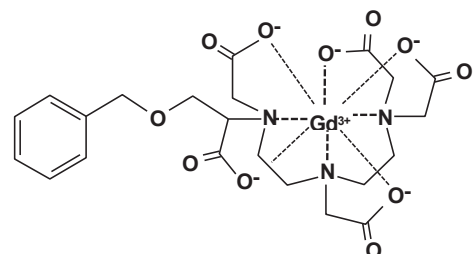


Vueway/Elucirem (gadopiclenol)

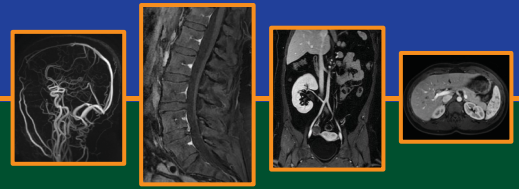
## Open-chain Ionic



Eovist (gadoxetate disodium)



MultiHance (gadobenate dimeglumine)



The 4 nonprotein-binding ECF agents—ProHance (gadoteridol), Gadavist (gadobutrol), Dotarem/Clariscan (gadoterate meglumine), and Vueway/Elucirem (gadopiclenol)—based on their physicochemical properties, have central nervous system (CNS) indications.<sup>1,4-11</sup> The approved indication for Eovist (gadoxetate disodium) is consistent with its physicochemical properties, too; it is approved for liver imaging.<sup>13,14</sup> MultiHance (gadobenate dimeglumine), which was originally approved in 2004 for use in CNS imaging, was granted FDA approval (July 2012) for use during MRA to evaluate adults with known or suspected renal or aorto-ilio-femoral occlusive vascular disease.<sup>15</sup> Gadavist (gadobutrol) was granted additional indications for breast imaging, for evaluation of known or suspected supra-aortic or renal artery disease, and to assess myocardial perfusion (stress and rest) and late gadolinium enhancement in adult patients with known or suspected coronary artery disease.<sup>4</sup>

In 2022, Vueway/Elucirem (gadopiclenol) was approved by the FDA and is indicated for CNS and body imaging in patients 2 years and older<sup>7,8</sup> (**Table 2**).

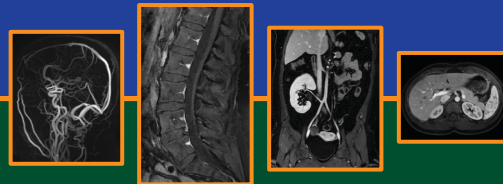
**Table 2. Currently Available Gadolinium-based Magnetic Resonance Contrast Agents<sup>1-8</sup>**

Brand Name	Generic Name	Company	Indications	Approved Dose
ProHance	Gadoteridol	Bracco Diagnostics	CNS, adults & pediatrics (including term neonates); Head and neck, adults	Adults: 0.1 mmol/kg + 2nd dose of 0.2 mmol/kg up to 30 min after 1st dose; pediatrics: 0.1 mmol/kg
Gadavist	Gadobutrol	Bayer Healthcare	CNS, adults & pediatrics (including term neonates); Assess presence and extent of malignant breast disease; MRA to evaluate known or suspected supra-aortic or renal artery disease in adult and pediatrics (including term neonates)	0.1 mmol/kg
Dotarem/ Clariscan	Gadoterate meglumine	Guerbet/ GE HealthCare	CNS, adults & pediatrics (including term neonates)	0.1 mmol/kg
Vueway/ Elucirem	Gadopiclenol	Bracco Diagnostics/ Guerbet	Adults & pediatrics ≥2 years: CNS (brain, spine, and associated tissues), body (head and neck, thorax, abdomen, pelvis, and musculoskeletal system)	0.05 mmol/kg
MultiHance	Gadobenate dimeglumine	Bracco Diagnostics	CNS, adults & pediatrics (including term neonates); MRA in adults, to evaluate known or suspected renal or aorto-ilio-femoral occlusive vascular disease	Adults & pediatrics ≥2 years of age: 0.1 mmol/kg; pediatrics <2 years of age: 0.05-0.1 mmol/kg (ie, 0.1-0.2 mL/kg) (CNS)
Eovist	Gadoxetate disodium	Bayer Healthcare	Liver imaging in adults	0.025 mmol/kg

CNS = central nervous system; MRA = magnetic resonance angiography.

In terms of biodistribution, most of the agents approved in the United States (with the exception of MultiHance [gadobenate dimeglumine] and Eovist [gadoxetate disodium]) distribute solely to the ECF space and are eliminated almost exclusively by glomerular filtration via the kidneys. MultiHance (gadobenate dimeglumine) differs in that 0.6% to 4% of the injected dose is excreted through the biliary tract.<sup>2</sup> Thus, in addition to its use as an ECF agent, it is also suitable for delayed hepatobiliary phase imaging.<sup>16</sup> The injected dose of Eovist (gadoxetate disodium) is eliminated from the kidneys and liver on a 50:50 basis; therefore, this agent is useful primarily as a liver-specific imaging agent.<sup>3</sup>

All ECF GBCAs have an elimination half-life of approximately 1.5 hours; however, the half-lives of MultiHance (gadobenate dimeglumine) and Eovist (gadoxetate disodium) are 1.17±0.26 to 2.02±0.6 hours and 0.91 to 0.95 hours, respectively (**Table 3**).<sup>1-8</sup>



**Table 3. Mean Elimination Half-life for Available GBCAs Agents<sup>1-8</sup>**

Brand Name	Generic Name	Mean Elimination Half-life (Hours)
ProHance	Gadoteridol	1.57 ± 0.08
Gadavist	Gadobutrol	1.81 (1.33 to 2.13)
Dotarem/Clariscan	Gadoterate meglumine	1.4 ± 0.2 to 2.0 ± 0.7
Vueway/Elucirem	Gadopiclesol	1.5
MultiHance	Gadobenate dimeglumine	1.17 ± 0.26 to 2.02 ± 0.60
Eovist	Gadoxetate disodium	0.91 to 0.95

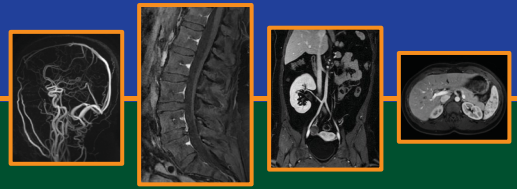
GBCAs = gadolinium-based contrast agents.

### ***i. Concentration vs Relaxivity***

Unlike contrast-enhanced (CE) computed tomography (CT), which relies on contrast agent concentration in tissues, CE-MRI depends on contrast agent relaxivity and dose for achieving optimal enhancement.<sup>17</sup> The higher the r1 relaxivity of an agent, the greater its ability to provide contrast enhancement. The r1 relaxivity values of the ECF-only “conventional” GBCAs (ie, ProHance [gadoteridol] and Dotarem/Clariscan [gadoterate meglumine]) are very similar despite differences in molecular structure (see Table 1).<sup>9,13,15</sup> Due to the presence of the lipophilic side chain, MultiHance (gadobenate dimeglumine) interacts with serum proteins, greatly increasing the apparent size of the molecule and reducing its tumbling rate.<sup>10</sup> As a result, MultiHance (gadobenate dimeglumine) has almost twice the r1 and r2 relaxivities in plasma compared with the older ECF agents, and this higher relaxivity has been shown to persist at all commercially available magnetic field strengths (ie, 0.2T-3T).<sup>9,10,13,15</sup>

Most importantly, higher relaxivity has been shown in parallel and intraindividual crossover studies to provide diagnostic benefit for a wide variety of clinical applications, including the CNS, breast and liver imaging, and MRA.<sup>18-32</sup> Specifically, these studies show that MultiHance (gadobenate dimeglumine) generates greater signal enhancement at the same molar dose or equivalent signal enhancement at a lower dose.<sup>18-32</sup> In addition, the greater r2 relaxivity of MultiHance (gadobenate dimeglumine) may have advantages for perfusion imaging and applications for which greater T2-weighting is required.<sup>33</sup>

The higher-concentration ECF agent Gadavist (gadobutrol) does not interact with serum proteins and, therefore, does not show the enhanced relaxivity in the presence of serum proteins seen with MultiHance (gadobenate dimeglumine).<sup>9,15,34</sup> A slight increase in relaxivity over the conventional agents has been noted with Gadavist (gadobutrol)<sup>9,15,34</sup>; however, as demonstrated in a study in patients with brain metastases, Gadavist (gadobutrol) at 0.1 and 0.2 mmol/kg doses performs similarly to a 0.2 mmol/kg dose of the conventional ECF agent ProHance (gadoteridol).<sup>35</sup> Most recently, equivalent 0.1 mmol/kg doses of MultiHance (gadobenate dimeglumine) and Gadavist (gadobutrol) were directly compared in an intraindividual crossover comparison for qualitative and quantitative evaluation of brain tumors in 114 adult patients.<sup>36</sup> All 3 blinded readers demonstrated a significant preference for MultiHance (gadobenate dimeglumine) for all qualitative endpoints. In addition, significantly superior contrast-to-noise and lesion-to-brain ratios were observed with MultiHance (gadobenate dimeglumine).<sup>36</sup> These studies demonstrate that, when administered at the same dose, a higher-concentration agent does not provide the same benefit for visualization of CNS lesions as a higher-relaxivity agent. Eovist (gadoxetate disodium) is formulated at lower concentration (0.25M) but does have a higher r1 relaxivity (6.9 L • mmol<sup>-1</sup> • sec<sup>-1</sup> at 1.5T) compared with conventional contrast agents.<sup>3,9</sup> Eovist (gadoxetate disodium) has been approved for T1-weighted MRI of the liver to detect and characterize lesions in adults with known or suspected focal liver disease.<sup>3</sup>



## ii. Minimizing Gadolinium Exposure

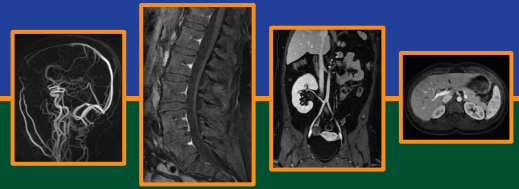
In 2022, a new GBCA—gadopiclenol—was approved for clinical use by the FDA. It is marketed under the brand names Vueway (Bracco Diagnostics, Inc) and Elucirem (Guerbet, LLC). Gadopiclenol represents the first high-relaxivity macrocyclic GBCA to enter clinical practice.<sup>7,8</sup> This agent possesses both very high relaxivity and extremely high kinetic stability.<sup>12</sup> Vueway (gadopiclenol) provides a  $r_1$  relaxivity of 12.8 at 1.5 T and 11.6 at 3T in human serum.<sup>12</sup> This agent demonstrates extremely high kinetic stability in acidic conditions with a dissociation half-life of  $20 \pm 3$  days as compared to Clariscan/Dotarem (gadoterate meglumine)  $4 \pm 0.5$  days, Gadavist (gadobutrol) 18 hours, and ProHance (gadoteridol) 4 hours.<sup>12</sup> Unlike other extracellular agents (Clariscan/Dotarem [gadoterate meglumine], Gadavist [gadobutrol], and ProHance [gadoteridol]) and the combined extracellular/hepatobiliary agent MultiHance (gadobenate dimeglumine), Vueway (gadopiclenol) is approved at 0.05 mmol/kg instead of 0.1 mmol/kg, thereby reducing gadolinium exposure by half as compared to other GBCAs. Vueway/Elucirem (gadopiclenol) is currently indicated to detect and visualize lesions with abnormal vascularity in the CNS (brain, spine, and associated tissues) and the body (head and neck, thorax, abdomen, pelvis, and musculoskeletal system) in patients  $\geq 2$  years.<sup>7,8</sup>

In an era in which serial MR imaging is becoming more common, having the ability to reduce gadolinium exposure by using lower doses of GBCAs is extremely compelling. Vueway (gadopiclenol) provides clinicians with the ability to halve the gadolinium dose while maintaining equal diagnostic performance.<sup>37–39</sup> Moreover, as higher magnet strengths are increasingly being used in MR imaging, Vueway (gadopiclenol) overcomes the limitations of other GBCAs at higher magnet strengths because it consistently retains its high relaxivity at 3T (**Table 1**).<sup>12</sup>

A phase IIb international, multicenter, double-blind, randomized, controlled, parallel-dose crossover study of Vueway (gadopiclenol) vs MultiHance (gadobenate dimeglumine) was conducted by Bendszus and colleagues.<sup>37</sup> A total of 272 adult patients with known or highly suspected lesions with disrupted blood-brain barrier were enrolled. Patients received 1 scan with Vueway (gadopiclenol) and another with MultiHance (gadobenate dimeglumine) or vice versa. For Vueway (gadopiclenol), patients were randomized to 4 different doses (0.025, 0.05, 0.1, or 0.2 mmol/kg) and MultiHance (gadobenate dimeglumine) was administered at its indicated dose of 0.1 mmol/kg. Qualitative and quantitative efficacy evaluations were performed by 3 independent off-site blinded readers. Adverse events were monitored up to 1 day after the second scan.

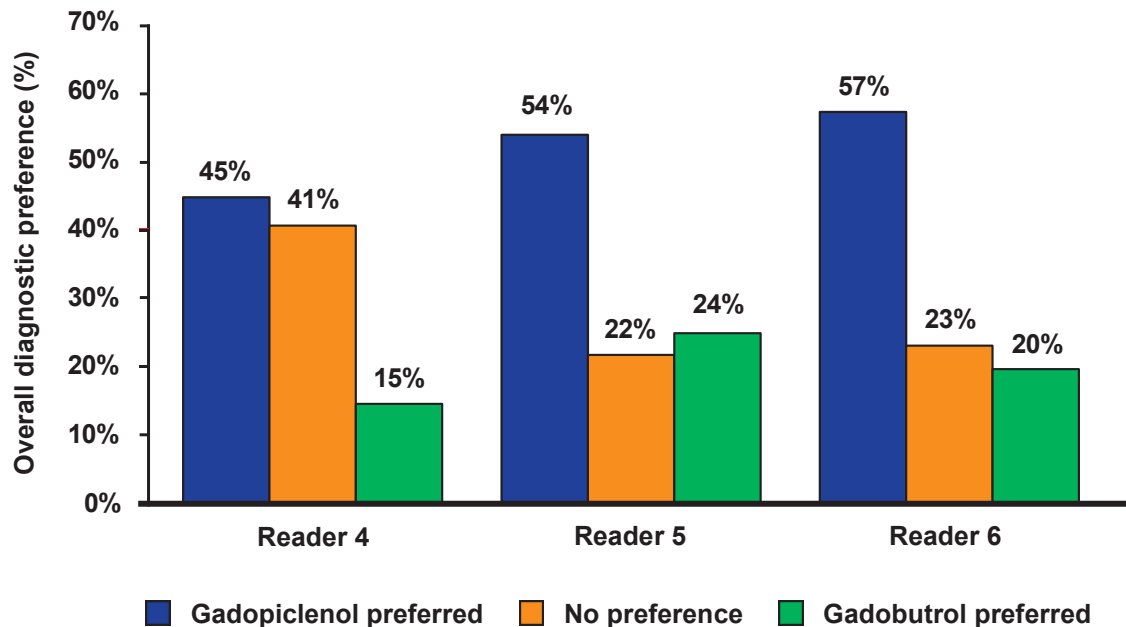
The superiority of Vueway (gadopiclenol) vs MultiHance (gadobenate dimeglumine) was demonstrated at both 0.2 and 0.1 mmol/kg for all readers with an increase in contrast-to-noise ratio (CNR) of more than 30% ( $P \leq 0.0007$ ). More importantly, at 0.05 mmol/kg, Vueway (gadopiclenol) had a similar CNR to MultiHance (gadobenate dimeglumine) dosed at 0.1 mmol/kg, with no statistically significant difference. The investigators concluded that Vueway (gadopiclenol) dosed at 0.05 mmol/kg demonstrated equivalent contrast enhancement to MultiHance (gadobenate dimeglumine) dosed at 0.1 mmol/kg while reducing gadolinium exposure by half.<sup>37</sup>

The PICTURE Trial was a phase III multicenter, prospective, randomized, double-blinded, controlled crossover study conducted at 33 medical centers in 11 countries.<sup>38</sup> A total of 256 adult patients with CNS lesions were randomized to undergo 2 MRIs (interval, 2–14 days) with Vueway (gadopiclenol) dosed at 0.05 mmol/kg and Gadavist (gadobutrol) dosed at 0.1 mmol/kg. The primary endpoint was lesion visualization based on 3 parameters (border delineation, internal morphology, and contrast enhancement) assessed by 3 off-site blinded readers. Secondary endpoints included lesion-to-background ratio, enhancement percentage, CNR, overall diagnostic preference, and adverse events.



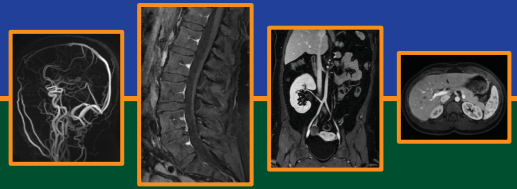
The PICTURE Trial demonstrated statistical noninferiority of Vueway (gadopiclenol) vs Gadavist (gadobutrol) in all imaging parameters by all 3 readers (n=236, lower limit 95% confidence interval [CI] of the difference  $\geq -0.06$ , above the noninferiority margin  $[-0.35]$ ,  $P < 0.0001$ ). In addition, enhancement percentage and lesion-to-background ratio were significantly higher with Vueway (gadopiclenol) for all readers ( $P < 0.0001$ ). The readers preferred images with Vueway (gadopiclenol) for 44.8%, 54.4%, and 57.3% of exams, reported no preference for 40.7%, 21.6%, and 23.2% of exams, and preferred images with Gadavist (gadobutrol) for 14.5%, 24.1%, and 19.5% of exams ( $P < 0.001$ ) (**Figure 2**). Forty-nine adverse events (AEs) were reported in 36 patients (14.6%) with Vueway (gadopiclenol) and 55 AEs in 43 patients (17.6%) with Gadavist (gadobutrol). Most AEs were mild (48/49 [98%] with Vueway [gadopiclenol] and 50/55 [91%] with Gadavist [gadobutrol]).<sup>38</sup>

**Figure 2. Noninferiority and Superiority Analyses for Lesion Visualization<sup>38</sup>**



The investigators concluded that Vueway (gadopiclenol) dosed at 0.05 mmol/kg is noninferior to Gadavist (gadobutrol) dosed at 0.1 mmol/kg for MRI of the CNS, confirming that Vueway (gadopiclenol) can be used at half the gadolinium dose than other GBCAs while providing similar diagnostic efficacy.<sup>38</sup>

The PROMISE Trial was a phase III multicenter, prospective, randomized, double-blinded, controlled crossover study conducted at 33 centers in 11 countries.<sup>39</sup> A total of 300 adult patients with at least 1 suspected focal lesion in 1 of 3 different body regions (1–head and neck; 2–breast, thorax, abdomen, or pelvis; or 3–musculoskeletal system) were randomized to undergo 2 MRI scans: 1 with Vueway (gadopiclenol) dosed at 0.05 mmol/kg followed by 1 with Gadavist (gadobutrol) dosed at 0.1 mmol/kg or vice versa. MRI examinations were read by 3 blinded readers who were experts for each respective body region imaged. The study's primary objective was to demonstrate noninferiority of contrast-enhanced MRI with Vueway (gadopiclenol) vs Gadavist (gadobutrol) for lesion visualization. Secondary objectives included overall preference for either Vueway (gadopiclenol) or Gadavist (gadobutrol); quantitative assessment of lesion enhancement; subgroup analyses (as per protocol) of lesion visualization by off-site readers according to the different body regions, different categories of demographic parameters (age, sex, ethnicity, geographic region), and different MRI system magnetic field strengths; and lesion visualization assessed by radiologists on site.



A total of 260 subjects without protocol deviations were analyzed for this noninferiority study. The PROMISE Trial demonstrated that Vueway (gadopiclenol) at 0.05 mmol/kg was noninferior to Gadavist (gadobutrol) at 0.1 mmol/kg for all qualitative visualization parameters and for all readers (lower limit 95% CI of the difference of at least  $-0.10$ , which was above the noninferiority margin  $[-0.35]$ ;  $P < 0.001$ ). For most subjects (75%–83% [206–228 of 276]), the readers reported no preference between Vueway (gadopiclenol) and Gadavist (gadobutrol) enhanced images. The trial's safety analysis did not find any difference in frequency, intensity, or type of AEs for either agent; most AEs were mild.<sup>39</sup>

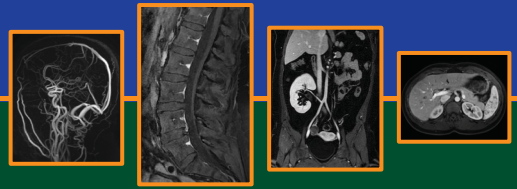
The PROMISE Trial demonstrated that Vueway (gadopiclenol) dosed at 0.05 mmol/kg was comparable to Gadavist (gadobutrol) dosed at 0.1 mmol/kg for head and neck; breast, thorax, abdomen, or pelvis; and musculoskeletal system imaging. The investigators concluded that a high-relaxivity macrocyclic GBCA such as Vueway (gadopiclenol) should preferably be used for contrast-enhanced MRI in individuals who require serial contrast-enhanced MRI examinations, pediatric patients, and patients with impaired renal function.<sup>39</sup>

A phase I trial studied the pharmacokinetics and safety of Vueway (gadopiclenol) in patients with impaired renal function.<sup>40</sup> In this 2-center open-label study, 5 successive cohorts of 8 adult subjects each were enrolled. Cohort 1 included healthy subjects, cohort 2 included subjects with mild renal disease, cohort 3 included subjects with moderate renal disease, cohort 4 included subjects with severe renal disease, and cohort 5 included subjects with end-stage renal disease (ESRD). All subjects received an IV injection of Vueway (gadopiclenol) dosed at 0.1 mmol/kg, i.e., twice the indicated dose. Blood and urine samples were collected at different time points in cohorts 1 to 4, and blood and dialysate samples were collected at each hemodialysis session (4-hour session on day 1, day 3, and day 5) in cohort 5. Vueway (gadopiclenol) elimination and safety were assessed for up to 6 months.

No significant differences in the mean maximum concentration values and the distribution volume were observed among cohorts 1 to 4 subjects. Urinary excretion of Vueway (gadopiclenol) was delayed proportionally with the degree of renal impairment, with a mean fraction of the dose excreted in urine at the end of the collection period ranging between 96% up to 48 hours (healthy subjects and subjects with mild renal impairment) and 85% up to 168 hours (subjects with severe renal impairment). Compared with that of healthy subjects, the mean area under the plasma concentration curve was 54%, 148%, and 769% higher in subjects with mild, moderate, or severe renal impairment, respectively. The mean terminal half-life was prolonged by the degree of renal impairment (1.9, 3.3, 3.8, and 11.7 hours for cohorts 1–4). In subjects with ESRD, Vueway (gadopiclenol) was effectively removed from the plasma (95% to 98%) after the first hemodialysis session. Vueway (gadopiclenol) concentration in plasma was below the limit of quantification for all subjects after the second hemodialysis session, and Vueway (gadopiclenol) concentration was below the limit of quantification in all plasma and urine samples collected at 1, 3, and 6 months.<sup>40</sup>

This study demonstrated, as expected, that there was decreased renal clearance of Vueway (gadopiclenol) that resulted in an increased elimination half-life of this agent in patients with mild to severe renal impairment, but elimination was complete or nearly complete within 7 days.<sup>40</sup> In patients with ESRD, Vueway (gadopiclenol) was effectively removed from the plasma after the first hemodialysis session, and no more than 3 hemodialysis sessions were required to completely clear Vueway (gadopiclenol). The investigators concluded that they had no safety concerns about administering Vueway (gadopiclenol) to patients who have mild to severe renal disease including ESRD. They deemed that no dose adjustments would be necessary for patients with compromised renal function.

It should be noted that while clinical experience with Vueway (gadopiclenol) has been limited to date, the ACR decided to classify this agent as a group II agent (associated with few, if any, unconfounded cases of NSF) because it demonstrates kinetic stability and a long dissociation half-life comparable to other group II agents.<sup>41</sup>



### **iii. Patient-Centric Care**

Patient-centric care—also referred to as “personalized” or “individualized” care—is of growing importance in medicine. Not only are no two patients alike, but when medicine can be tailored to meet the specific needs of an individual patient, outcomes can be improved while containing healthcare expenditures and maximizing safety.

Recently, patient-centric dosing of ionizing radiation and iodinated contrast media has gained increasing attention within the radiology community. Customizing CT and CTA protocols to minimize exposure to ionizing radiation and/or lower contrast dose in susceptible patients has allowed radiologists to acquire diagnostically acceptable exams while maximizing patient safety. The use of patient-centric dosing has been facilitated by technologic and software advances in CT.

Likewise in MRI/MRA, advanced technology and software coupled with higher relaxivity and specialized GBCAs have paved the way for patient-centric dosing of contrast in MR imaging. Today we possess the ability to minimize patients’ exposure to gadolinium while providing examinations that can be life-saving. In many situations we can customize contrast dosing by selecting a specific agent and/or lowering the contrast dose, thereby minimizing gadolinium exposure. This approach is particularly important in patients with renal impairment, patients undergoing serial contrast-enhanced examinations, and in light of reports of gadolinium retention in brain and body tissues.

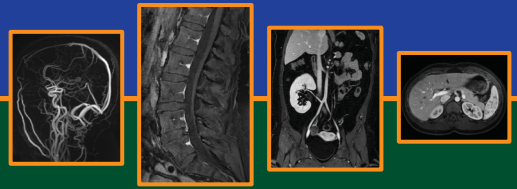
## **B. General Considerations**

Understanding and determining how to make the best use of new hardware and contrast agent options can be challenging. This series of MR protocols for CNS, body MRI, and MRA has been assembled by consensus of an expert panel to aid in this process, with the goal of providing practical tips and specific protocols for each anatomic region for 3 MR scanner vendors: General Electric (GE), Philips, and Siemens. In these protocols, attention has been given to specific recommended imaging parameters at 1.5T and 3T, but also to methods for preparing the patient, streamlining the exam, and making the best use of contrast material to maximize efficacy while ensuring patient safety.

General considerations in preparing patients for CE exams that are addressed in the MR protocols, where relevant, are as follows:

### **i. Body Weight and Contrast Dosing**

Dosing of contrast should be based on patient body weight as described in the prescribing information for each contrast agent. With the exception of Vueway/Elucirem (gadopiclenol) and Eovist (gadoxetate disodium), standard dosing for all products is 0.1 mmol/kg body weight, although for MultiHance (gadobenate dimeglumine) in children <2 years of age, the recommended dose range is 0.05 to 0.1 mmol/kg (0.1-0.2 mL/kg). Vueway/Elucirem (gadopiclenol) is the most recently approved high-relaxivity GBCA<sup>7,8</sup>; it is dosed at 0.05 mmol/kg, thereby allowing gadolinium exposure to be significantly lowered. Among the approved agents, only ProHance (gadoteridol) is approved at doses >0.1 mmol/kg (up to 0.3 mmol/kg cumulative dose),<sup>2</sup> and Eovist (gadoxetate disodium) is dosed at 0.025 mmol/kg. When selecting a contrast agent for liver imaging, there are dosing considerations: despite the higher relaxivity of Eovist (gadoxetate disodium), the approved dose is 4 times lower than MultiHance (gadobenate dimeglumine), resulting in a shorter peak arterial perfusion window; as a result, selection of an appropriate scan delay can be challenging.<sup>42,43</sup> In order to overcome this, when using Eovist (gadoxetate disodium), clinicians may consider using a fixed delay, diluting the dose of bolus, or injecting at a slower rate. Additionally, in cases of cirrhotic liver, the use of a higher off-label dose of Eovist (gadoxetate disodium) may be required.<sup>42,43</sup>



Note that for Gadavist (gadobutrol), because it is the only agent available at a 1.0M concentration, care must be taken to halve the volume in order to deliver the same molar dose as agents formulated at 0.5M in order to prevent overdose.

The very high relaxivity of Vueway (gadopiclenol) and the higher relaxivity of MultiHance (gadobenate dimeglumine) allows the option of using a standard dose for increased sensitivity in procedures where double or triple doses of other ECF agents may have been required to achieve satisfactory diagnostic results:

## • CNS

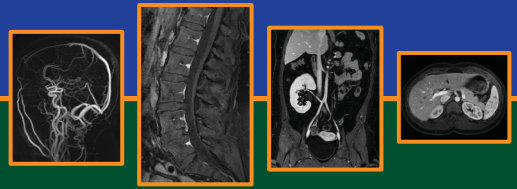
- The standard approved dose for CNS imaging using conventional 0.5M contrast agents and 1M Gadavist (gadobutrol) is 0.1 mmol/kg. However, higher doses of 0.2 or 0.3 mmol/kg are sometimes used for perfusion imaging, MRA, or certain brain protocols.<sup>2,44,45</sup> For high-relaxivity agents such as Vueway (gadopiclenol), a 0.05 mmol/kg dose is suggested, and for MultiHance (gadobenate dimeglumine), a 0.1 mmol/kg dose is suggested. However, in patients with chronic kidney disease (CKD) at risk for nephrogenic systemic fibrosis (NSF), use of a lower dose of a high-relaxivity agent may be beneficial (see section on NSF below). The other high-relaxivity agent, Eovist (gadoxetate disodium), lacks a CNS indication.<sup>3</sup>

## • Body MRI

- For body MRI in general, the dose of GBCA administered depends on the type of agent and patient weight. Conventional contrast agents, as well as Gadavist (gadobutrol), should employ 0.1 mmol/kg body weight. The approved dose for Eovist (gadoxetate disodium) for liver imaging is 0.025 mmol/kg

## • MRA

- In early experience with Vueway (gadopiclenol) for pulmonary angiography, the University of Wisconsin has substituted Vueway (gadopiclenol) at a 0.075 mmol/kg dose with excellent results, replacing 0.15 mmol/kg MultiHance (gadobenate dimeglumine). This early experience will need to be validated for other MRA studies
- In the future, Vueway (gadopiclenol) could replace other GBCAs for MRA using 0.05 mmol/kg Vueway (gadopiclenol) for single-station applications and 0.1 mmol/kg Vueway (gadopiclenol) for peripheral MRA
- In clinical practice, MRA is often performed with a double dose of gadolinium contrast (0.2 mmol/kg). However, a single dose of MultiHance (gadobenate dimeglumine) has been shown to be equivalent to a double dose of Magnevist (gadopentetate dimeglumine) for renal MRA<sup>27</sup> and carotid MRA<sup>46</sup> at 1.5T. Additionally, at 3T, MultiHance (gadobenate dimeglumine) has been shown to significantly improve image quality and contrast enhancement compared to an equivalent 0.1 mmol/kg dose of Magnevist (gadopentetate dimeglumine)<sup>22</sup>
- In a multicenter crossover comparison of 0.1 mmol/kg doses of MultiHance (gadobenate dimeglumine) and Magnevist (gadopentetate dimeglumine) for peripheral MRA, technical adequacy and diagnostic accuracy of CE-MRA were found to be significantly better with MultiHance (gadobenate dimeglumine) as compared with Magnevist (gadopentetate dimeglumine) ( $P < 0.0001$  and  $P \leq 0.0017$ , respectively).<sup>23</sup> A recent crossover comparison study of peripheral artery disease demonstrated that the image quality and diagnostic performance achieved with 0.1 mmol/kg single-dose MultiHance (gadobenate dimeglumine) is at least equivalent to that achieved with 0.2 mmol/kg double-dose Magnevist (gadopentetate dimeglumine)<sup>32</sup>



- In patients with known or suspected steno-occlusive disease of the supra-aortic vessel, a recent crossover comparison demonstrated that the image quality and diagnostic performance achieved with single-dose 0.1 mmol/kg MultiHance (gadobenate dimeglumine) is at least equivalent to that achieved with double-dose 0.2 mmol/kg Magnevist (gadopentetate dimeglumine)<sup>31</sup>
- A comparison of the 1.0M agent Gadavist (gadobutrol) with MultiHance (gadobenate dimeglumine) for MRA of the lower extremities demonstrated that 0.1 mL/kg of both (ie, equivalent volumes) provided similar diagnostic results, despite the fact that using this dosing regimen, MultiHance (gadobenate dimeglumine) was given at half of the approved gadolinium dose.<sup>28</sup> Similarly, for renal MRA, 15 mL of MultiHance (gadobenate dimeglumine) (0.1 mmol/kg) at 3T was found to be equivalent to 15 mL of Gadavist (gadobutrol) (0.2 mmol/kg) at 1.5T<sup>47</sup>
- The 1.0M formulation of Gadavist (gadobutrol) allows for a 50% reduced injection volume and it has been proposed that using this lower volume, one might expect a sharper peak in the contrast bolus. Comparative studies have produced conflicting results. Overall it seems that 1.0M Gadavist (gadobutrol) may be advantageous for MRA compared with conventional Gd contrast agents, depending on the vascular territory being investigated, but this benefit is not greater than the benefit of a higher-relaxivity agent for CE-MRA<sup>10</sup>

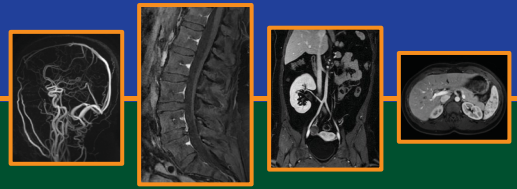
Specific protocol recommendations are available for review in the GE, Philips, and Siemens protocols chapters.

## ***ii. Contrast Variables (eg, Relaxivity, Timing, Injection Flow Rate, Scan Delay, Saline Flush)***

Different MR applications may require different techniques for administering contrast. With the exception of applications such as cerebral or cardiac perfusion, where injection rates may be as high as 4 to 5 mL/sec, a 22-gauge intravenous (IV) line in the antecubital fossa or distal forearm is sufficient. Other than MRA, most contrast-enhanced neurologic MR applications do not require precise contrast timing or flow rate, and many institutions administer the GBCA through a small “butterfly” needle by hand in place of an IV line. In such cases, administration of a saline flush is prudent but may not be absolutely necessary.

Body and MRA applications require more precise contrast timing. For visceral parenchymal imaging (ie, liver, kidney, pancreas), multiple dynamic three-dimensional (3D) datasets are acquired, and exact timing (particularly for the arterial phase) is essential. To capture the arterial phase accurately, many body MR protocols use a timing bolus, a bolus detection method (eg, bolus tracking), or a time-resolved technique (eg, multiple fast arterial phases without the need for any timing). Proper scan timing is then determined by beginning the scan so that data acquisition in the center of k-space coincides with the arterial contrast arrival. Such timing techniques are discussed in the protocols.

Many institutions find an automated contrast injector beneficial so that the patient can be connected to the injector at the beginning of the scan, and then the contrast and the saline flush can be administered easily and automatically from the magnet control room. In addition, power injectors allow more precise and reproducible injection rates, which are critical for avoiding variations between patients in the capture of the arterial phase. Furthermore, using power injectors facilitates the flow of the examination and saves time by eliminating the need for personnel to enter the MRI examination room to inject the contrast agent by hand. However, there are some exceptional situations for which hand injections can be used (eg, when venous access is unreliable and a direct visual control is needed during injection to ensure that extravasation is not occurring). Commercially available long tubing sets are preferred in those cases so that the patient does not need to be moved in and out of the magnet. The contrast is generally injected at approximately 2 mL/sec and followed by 20 to 30 mL normal saline (NS) injected at the same rate. If the test bolus technique is used to capture the arterial phase, we recommend the following:



- Conventional GBCAs: 2 mL at 2 mL/sec
- 1.0M Gadavist (gadobutrol): 1 mL at 2 mL/sec
- High-relaxivity MultiHance (gadobenate dimeglumine): 1 mL at 2 mL/sec
- Extremely high-relaxivity Vueway (gadopiclenol): 1 mL at 2 mL/sec; dilute 0.05 mmol/kg Vueway (gadopiclenol) into 30 mL saline and inject 2 mL of this solution for timing bolus, then inject the remaining 28 mL of Vueway (gadopiclenol) for the MRA
- Eovist (gadoxetate disodium): No test bolus; typically need to use multiphase MRI or a fluoroscopic trigger
- NS flush of 20 to 30 mL at 2 mL/sec

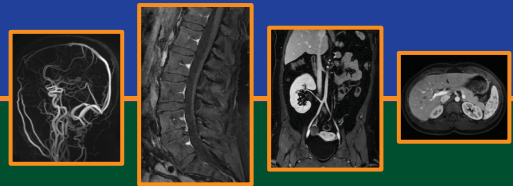
Contrast administration rate and timing are probably most critical for MRA. The general goal is to begin data acquisition (usually centric) precisely when intravascular contrast approaches peak concentration, and then acquire data during the “plateau” and “downslope” phases of contrast passage, ending before it is completely passed. In some applications, such as carotid and peripheral MRA, data acquisition may be much longer than the contrast bolus passage, depending on recirculation for continued enhancement.<sup>10</sup> In general, higher relaxivity contrast media can be administered at lower doses and slower flow rates than other ECF agents. Specific recommendations are provided in the protocols. To provide consistent enhancement of vessels over a range of patients and vessel territories, we have found it helpful to dilute the contrast media into a fixed volume of 30 mL and inject at 2 mL/sec.

For MRA, the expert panel unanimously advocated use of a contrast injector to administer contrast and fluoroscopic triggering for bolus detection (the exception being some time-resolved protocols where multiple time frames are provided by the protocol). It is important to administer 20 to 30 mL NS flush at the same rate as the contrast administration in order to “push” the contrast completely through the veins and into the right side of the heart so that the contrast bolus stays intact. Due to the higher concentration and potentially more compact bolus of Gadavist (gadobutrol), care must be taken to ensure the contrast peak is not missed when using this product. Alternatively, a dilution of Gadavist (gadobutrol) in saline to a concentration of 0.5M or lower can be used.

Certain applications may benefit by dilution of any contrast agent into a volume of saline. For example, investigators have shown that the diluted contrast approach may be beneficial in circumstances where there is less mixing of the contrast agent with blood, including in the pulmonary arteries. Likewise, dilution may be beneficial when the R2 relaxivity associated with high arterial concentrations of GBCA may create signal loss at peak arterial concentrations. These situations may be encountered with high rates of injection, at high field strengths (3T), and in situations where there is little mixing or dispersion of the GBCA in blood.<sup>48,49</sup>

### ***iii. Effect of Static Magnetic Field Strength***

The higher signal and quality gradient coils at 3T have great potential. In general, a smaller number of excitations, or averages, are needed for higher-resolution images. The increased  $r_1$  and  $r_2$  relaxivities of MultiHance (gadobenate dimeglumine) compared with other GBCAs persist at all clinically relevant field strengths tested (0.2T, 0.47T, 1.5T, and 3T).<sup>9,10,13,15</sup> Higher relaxivity correlates with shorter tissue T1 and T2 relaxation times when comparing conventional agents and MultiHance (gadobenate dimeglumine).<sup>9</sup> In practice, these data translate into more robust T1 enhancement (or greater T2 signal loss for susceptibility-weighted imaging) for Vueway (gadopiclenol) and MultiHance (gadobenate dimeglumine) compared with other GBCAs on a per-molar basis at any field strength.<sup>18–32</sup> The improved contrast efficiency of Vueway (gadopiclenol) and MultiHance (gadobenate dimeglumine) means that equal contrast enhancement can be achieved at a lesser dose or that greater contrast enhancement is achieved at the same dose.<sup>18–32</sup>



## iv. Patient Preparation

The MR protocols attempt to describe details of the complete exam, including but not limited to patient positioning and preparation, coil type selection, and IV and electrocardiogram (ECG) requirements, where appropriate. Step by-step pulse sequences and guidance on their implementation are also provided, along with details of GBCA dosing and administration.

## C. Special Considerations

### i. Prior Contrast/GBCA Reactions

According to the American College of Radiology (ACR) *Manual on Contrast Media*, patients with a prior reaction to a GBCA are up to 5 times more likely to experience a GBCA-related acute AE.<sup>41</sup> The ACR guidelines suggest that in these cases, a different contrast agent be used the second time and those patients be premedicated with corticosteroids and antihistamines (**Table 4**).<sup>41</sup> However, it is important to note that allergic reactions to GBCAs have been found to occur even in patients premedicated with corticosteroids or antihistamines.<sup>50</sup>

The approved labeling for all GBCAs lists hypersensitivity as a contraindication or a warning/precaution; however, true allergic reactions occur infrequently, ranging from 0.004% to 0.7%.<sup>41</sup> Moreover, hypersensitivity reactions are associated with patient immune system functionality and overall condition rather than the administered GBCA.<sup>51</sup> With all GBCAs, the prescribing information suggests closely monitoring patients for hypersensitivity reactions during administration.<sup>1-8</sup>

**Table 4. Commonly Used Premedication Regimens for MRI<sup>41</sup>**

Medication	Dose	Frequency
<b>Option 1</b> Prednisone <sup>a</sup> plus diphenhydramine (Benadryl <sup>®</sup> )	50 mg PO  50 mg IV, IM, or PO	13 h, 7 h, and 1 h before injection of contrast medium  1 h before injection of contrast medium
<b>Option 2</b> Methylprednisolone <sup>b</sup> (Medrol <sup>®</sup> )	32 mg PO	12 h and 2 h before injection of contrast medium

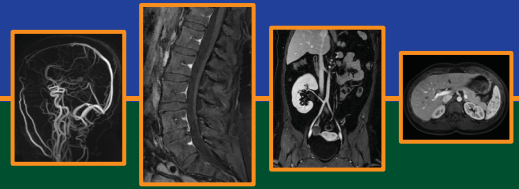
IM = intramuscularly; IV = intravenously; MRI = magnetic resonance imaging; PO = per os (orally).

<sup>a</sup>Hydrocortisone 200 mg IV may be substituted for oral prednisone.

<sup>b</sup>An antihistamine may be added to this regimen, as in option 1.

### ii. Patients with Asthma, Allergic Respiratory Disorders, and Prior Reactions to Iodinated Contrast Agents

Patients with asthma and allergies, as well as those with a previous reaction to an iodinated agent, should be monitored carefully because of their increased risk for experiencing adverse reactions. In general, patients with unrelated allergies are at a 2- to 3-fold increased risk of an allergic-like contrast reaction, but due to the modest increased risk, restricting contrast medium use or premedicating solely on the basis of unrelated allergies is not recommended.<sup>41</sup>



### iii. Nephrogenic Systemic Fibrosis

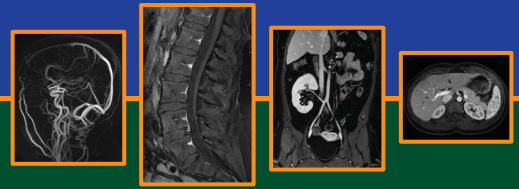
Nephrogenic systemic fibrosis is a rare but potentially disabling and life-threatening scleroderma-like disorder affecting patients with reduced renal function. Almost all cases of NSF occurred in patients with CKD Stages 4 and 5 (glomerular filtration rate [GFR] <30 mL/min/1.73 m<sup>2</sup>). However, several cases have been observed in patients with Stage 3 CKD (GFR 30–59 mL/min/1.73 m<sup>2</sup>) and in patients with acute renal failure.<sup>41,52</sup> The association of NSF with exposure to GBCAs was made in 2006.<sup>53</sup> Additional risk factors identified include repeated GBCA administration and/or use of high doses of contrast.<sup>41</sup>

The exact pathophysiology of NSF is not fully understood; however, several lines of evidence support a mechanism of transmetallation.<sup>41</sup> Transmetallation involves the dissociation of gadolinium from its chelate and replacement with another ion. Free gadolinium ions, known to be toxic, would then be available to accumulate in the tissue, particularly in patients with poor renal function and, thus, longer elimination times.<sup>54</sup> Among the different GBCAs, there are significant differences in measured stability (ie, conditional stability constants [thermodynamic stability constants measured at physiologic pH] and kinetic stabilities) (**Table 5**): the macrocyclic agents (Vueway/Elucirem [gadopiclenol], ProHance [gadoteridol], Gadavist [gadobutrol], and Dotarem/Clariscan [gadoterate meglumine]) have the highest kinetic stabilities, followed by the linear ionic agents (MultiHance [gadobenate dimeglumine] and Eovist [gadoxetate disodium]). The linear nonionic agents, Omniscan (gadodiamide) and OptiMARK (gadoversetamide), have the lowest kinetic stabilities<sup>55</sup> and have been withdrawn from the market. Based on the conditional stability constants, Gadavist (gadobutrol) is the least stable. Regardless of the parameter used, it is believed that the less stable an agent, the more likely it is to be involved in the process of transmetallation. Consistent with this theory, the vast majority of NSF cases have occurred after administration of Omniscan (gadodiamide), followed by Magnevist (gadopentetate dimeglumine) and OptiMARK (gadoversetamide), with most cases occurring following administration of 1 of these 3 agents.<sup>41,56-58</sup> Accordingly, in 2010, the FDA contraindicated all 3 of these agents in patients with severe CKD (ie, estimated GFR [eGFR] <30 mL/min/1.73 m<sup>2</sup>) and/or acute renal injury.<sup>41,56-58</sup> These agents have since been withdrawn from the market.

**Table 5. Stabilities of GBCAs**<sup>11,12,55</sup>

Brand Name	Contrast Agent	Conditional Stability Constant at pH 7.4	Kinetic Stability
MultiHance	Gadobenate dimeglumine	18.4	Medium
Eovist	Gadoxetate disodium	18.7	Medium
Dotarem/Clariscan	Gadoterate meglumine	19.3	High
ProHance	Gadoteridol	17.1	High
Gadavist	Gadobutrol	14.7	High
Vueway/Elucirem	Gadopiclenol	15.5	Extremely high

GBCAs = gadolinium-based contrast agents.



The ACR also recently modified its recommendations, stratifying the available GBCAs into categories according to NSF risk: Group I agents, or agents associated with the greatest number of NSF cases, include Omniscan (gadodiamide), OptiMARK (gadoversetamide), and Magnevist (gadopentetate dimeglumine), which have now been withdrawn from the market by their manufacturers. Group II agents, or agents associated with few, if any, NSF cases, include MultiHance (gadobenate dimeglumine), ProHance (gadoteridol), Dotarem/Clariscan (gadoterate meglumine), Gadavist (gadobutrol), and Vueway/Elucirem (gadopiclenol). The group III agent, Eovist (gadoxetate disodium), is of unknown risk as data remain limited, because Eovist (gadoxetate disodium) has not been available in the United States long enough for evaluation (**Table 6**). While clinical experience with Vueway/Elucirem (gadopiclenol) has been limited to date, the ACR decided to classify this agent as a group II agent because it demonstrates kinetic stability and a long dissociation half-life comparable to other group II agents.<sup>41</sup>

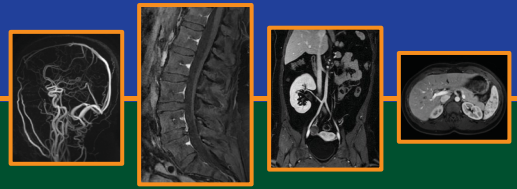
**Table 6. NSF Risk Stratification for Available GBCAs<sup>41</sup>**

Brand Name	Contrast Agent	ACR Group
ProHance	Gadoteridol (Gd-HP-DO3A)	II
Gdavist	Gadobutrol (Gd-BT-DO3A)	II
MultiHance	Gadobenate dimeglumine (Gd-BOPTA)	II
Dotarem/Clariscan	Gadoterate meglumine (Gd-DOTA)	II
Vueway/Elucirem	Gadopiclenol	II
Eovist	Gadoxetate disodium (Gd-EOB-DTPA)	III

ACR = American College of Radiology; GBCAs = gadolinium-based contrast agents; NSF = nephrogenic systemic fibrosis.

The following precautions to minimize the risk of NSF are recommended:

- High-risk patients should be identified (as mentioned above, eGFR <30 mL/min/1.73 m<sup>2</sup>), preferably by screening of renal function (especially in patients >60 years of age, with hypertension, diabetes, or severe hepatic disease)<sup>59</sup>
- Several guidelines, including those of the ACR<sup>59</sup> have, until now, also accepted patients' medical histories as valid screening tools. However, it is important to note that a significant number of patients with severe kidney disease may be unaware of their disease<sup>60</sup>
- Patients at risk should be given the lowest possible dose of a group II or group III agent, and every effort should be made to minimize the accumulated dose over time.<sup>41,59,61</sup> In addition, these patients should obtain a radiologist-signed order of consent, as well as give informed consent stating that they understand the risks and benefits of the procedure



- Patients on hemodialysis should be scheduled for their contrast-enhanced imaging examination immediately prior to a scheduled hemodialysis session<sup>41</sup>
- An updated FDA Alert, originally published September 9, 2010, requires the following Boxed Warning on all GBCA product labeling<sup>62</sup>:

## **WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)**

See full prescribing information for complete boxed warning

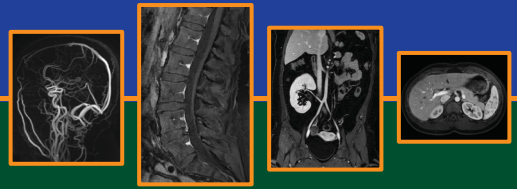
Gadolinium-based contrast agents (GBCAs) increase the risk of NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrast MRI or other modalities.

- The risk for NSF appears highest among patients with:
  - Chronic, severe kidney disease (GFR <30 mL/min/1.73m<sup>2</sup>), or
  - Acute kidney injury.
- Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (e.g. age >60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing

It is important to note that prohibiting all GBCA use in patients with severe CKD is not always warranted since in these patients, the risk of developing NSF following exposure to a GBCA is estimated between 1% and 7%.<sup>41</sup> Instead, a careful evaluation of the risks versus the benefits of a CE-MRI examination should be made and, if a decision to proceed with a CE exam is made, the use of an agent with a low associated NSF risk should be considered.

### ***iv. Gadolinium Retention***

During the past several years, multiple published studies have reported residual brightness in tissues within the deep nuclei of the brain in patients who have undergone repeat contrast-enhanced MRIs. These hyperintense areas are noted principally in the globus pallidus and the dentate nucleus. The persisting changes in signal brightness have been associated with the retention of gadolinium from GBCAs, and most of the patients cited in these reports have normal renal function.<sup>63-68</sup> These findings have led to concerns about the long-term safety of GBCAs and raise the question as to whether gadolinium retention from GBCAs could be harmful. To date, no studies or substantiated case reports have demonstrated any adverse clinical effects in humans or mammals caused by gadolinium retention in the brain.<sup>68</sup>

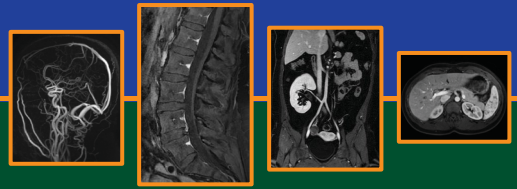


The question has been posed: Are linear GBCAs more prone to gadolinium retention than macrocyclic agents? The findings to date have been mixed; some studies demonstrate significantly higher odds for gadolinium retention to be caused by linear agents than macrocyclic agents, while other studies have not come to this conclusion.<sup>63</sup> The International Society for Magnetic Resonance in Medicine (ISMRM) issued a position paper in 2017. The ISMRM supports the clinical importance of GBCAs for detecting disease and saving lives. In most instances, they consider the benefits of GBCA use to outweigh any potential risks of gadolinium retention. The ISMRM supports further research on determining the mechanism(s) of gadolinium retention. They note that some macrocyclic agents might deposit less gadolinium than some linear agents, but evidence demonstrates that gadolinium retention in the brain occurs after the administration of macrocyclic agents.<sup>63</sup> Based on the available evidence, it must be noted that the extent of gadolinium retention varies not only among the individual GBCAs, but also among agents within the same structural class (ie, linear vs macrocyclic).

The regulatory environment is also mixed. At the end of 2017, the European Medicines Agency suspended marketing authorization for all linear GBCAs with the exception of Eovist (gadoxetate disodium) and MultiHance (gadobenate dimeglumine), which can still be used for liver scans because these agents are taken up in the liver and meet an important diagnostic need.<sup>69</sup> In addition, Magnevist (gadopentetate dimeglumine) can be used intra-articularly for joint scans because the dose of gadolinium used is very low and the route of administration is different.<sup>69</sup> Conversely in the United States, the ACR, the American Society of Neuroradiology, and the FDA have reviewed and upheld the value of both linear and macrocyclic agents for detecting disease and monitoring response to treatment.<sup>70,71</sup>

*“GBCAs provide crucial, life-saving medical information. Each time a gadolinium-enhanced MRI study is considered, it would be prudent to consider the clinical benefit of the diagnostic information or treatment result that MRI or MRA may provide against the unknown potential risk of gadolinium deposition in the brain for each individual patient. Particular attention should be paid to pediatric and other patients who may receive many GBCA-enhanced MRI studies over the course of their lifetimes. If the decision for an individual patient is made to use a GBCA for an MRI study, multiple factors need to be considered when selecting a GBCA, including diagnostic efficacy, relaxivity, rate of adverse reactions, dosing/concentration, and propensity to deposit in more sensitive organs such as the brain. As this gadolinium deposition phenomenon remains a relatively undefined clinical phenomenon, and accurate and complete data may be useful as investigations proceed, the identity and dose of GBCA used should be recorded after each intravenous administration.”<sup>71</sup>*

In 2018, the FDA added additional information about the potential for gadolinium retention to all GBCA package inserts as well as a patient medication guide. Because many patients do not have convenient access to package inserts, or are not interested, some healthcare centers have developed their own GBCA information sheets. The one below was developed by the radiology department of the University of Wisconsin School of Medicine and Public Health.



**Figure 3. University of Wisconsin School of Medicine and Public Health GBCA Patient Information Sheet**



## Department of Radiology

UNIVERSITY OF WISCONSIN  
SCHOOL OF MEDICINE AND PUBLIC HEALTH

### Gadolinium Contrast Agents for Magnetic Resonance Imaging

#### What is a gadolinium contrast agent?

A gadolinium contrast agent is a clear liquid we inject into a vein during some MRI scans to improve the detection of certain diseases. Since 1988, gadolinium contrast agents have been used in hundreds of millions of patients worldwide. They provide an enormous benefit to patients by improving the diagnosis of a large number of diseases. In many circumstances, the use of gadolinium during an MRI scan may be the only way to diagnose a disease, and helps doctors to treat, monitor, and cure the disease.

#### Are gadolinium contrast agents safe?

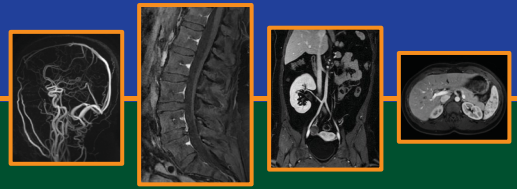
Gadolinium contrast agents are extremely safe. However, some patients with an allergy to such agents should consult with their doctor before a gadolinium contrast agent is used. More recently, it has been shown that MRI can detect tiny amounts of the gadolinium in the brains of patients who have received many previous doses of gadolinium. The Food and Drug Administration has been investigating this effect since 2015. To date, no symptoms or diseases are linked to gadolinium deposition in the brain, despite hundreds of millions of doses administered since 1988. There continues to be research in this area to better understand this phenomenon and its possible consequences. However, to date, there are no known side effects related to this observation.

#### Is it in my best interest to receive an MRI with gadolinium contrast if recommended by my doctor?

Physicians and patients should always weigh the benefit of MRI examinations with gadolinium contrast agents against the uncertain consequences of a small amount of gadolinium depositing in the brain. Any patients with concern of receiving gadolinium contrast agent should freely discuss their concerns with their radiology doctor prior to their MRI exam.

For additional detailed information on this topic, please see the following statements from international experts:

1. [Position paper from the International Society for Magnetic Resonance in Medicine \(ISMRM\).](#)
2. [Joint statement from the American College of Radiology \(ACR\) and the American Society of Neuroradiology \(ASNR\); ACR Contrast Manual, v10.3, 2017, Chapter 13, p.78-79\).](#)



## v. High-risk Populations

### a. Renal Impairment and Proinflammatory Conditions

Prior to receiving GBCAs, patients with a history of renal disease, hypertension, or diabetes should have their eGFR checked and compared with previous values to determine whether renal impairment is acute or chronic.

### b. Cardiovascular Disease

There are no specific recommendations regarding the use of GBCAs in patients with cardiovascular disease. However, good judgment is recommended. Dose volume and history of gadolinium allergies are important to note.

### c. Implants

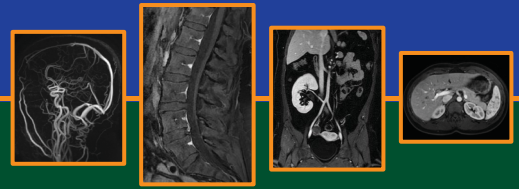
Special precautions should be undertaken for implantable medical devices. All implantable medical device hardware should be included in the assessment of the patient's suitability for MR examinations. Coordination with the healthcare provider managing the device (ie, cardiologist/electrophysiologist) and consultation with a representative from the device manufacturer is of paramount importance to determine whether the system (pulse generator and leads) is "MR Conditional."<sup>72</sup>

Radiologists and their staff should note that the entire system (pulse generator and leads) must be labeled "MR Conditional" for a system to in fact be considered MR conditionally safe. Furthermore, an "MR Conditional" system is considered safe only if all of the MR conditions for safe use are followed. The presence of abandoned leads from previous non-labeled systems or "mix-and-match" systems (combined "MR Conditional" labeled and non-labeled hardware) renders the system as a whole "MR Unsafe" or at best "MR Unknown." Importantly, because of the potential for heating, an abandoned (unattached to a pulse generator) "MR Conditional" lead should be considered, from a risk assessment point of view, as "MR Unsafe." The patient's attestations as to their device MR compatibility is not sufficient to establish MR safety.<sup>72</sup>

For cardiac pacemakers: if an MRI procedure is deemed absolutely necessary, it must be performed as follows: use a 1.5T MRI system only, the MRI system should be set to "Normal Operating Mode" for dB/dt, and SAR should be limited to <2.0 W/kg body coil and <3.2 W/kg head. In general, fast scans are performed with fast spoiled gradient echo technique, and steady-state free precession techniques are to be avoided.

### d. Pregnancy

GBCAs should not be administered during the first and second trimesters of pregnancy; caution should be exercised during the third. A GBCA may enter the amniotic fluid and recirculate rather than being excreted, which increases the exposure duration and, at least in theory, increases the chance of the chelate bond breaking and releasing free gadolinium. Therefore, the ACR recommends avoiding GBCAs during pregnancy unless the exam cannot be performed without contrast, no other options are available, and it is deemed medically necessary.<sup>41</sup> If MRI is still indicated in a pregnant patient, noncontrast time-of-flight sequences such as steady-state free precession and single-shot techniques (eg, T2 FSE) can be suggested.



## D. Immediate Adverse Events

GBCAs have been used in the vast majority of CE-MRI procedures, have long been considered safe for routine clinical use, and lack the nephrotoxicity associated with a large volume of iodinated contrast media. Although the reported incidence of AEs varies with MR procedure, study population, study design, and site of study,<sup>1-8</sup> few differences have been noted between different agents in terms of incidence or type of AE (Table 7).

**Table 7. Reported Incidence of Common Adverse Events of FDA-Approved GBCAs<sup>1-8</sup>**

Adverse Event	ProHance (gadoteridol) (N=3174)	Gadavist (gadobutrol) (N=7713)	MultiHance (gadobenate dimeglumine) (N=4967)	Dotarem/Clariscan (gadoterate meglumine) (N=2867)	Vueway/Elucirem (gadopiclenol) (N=708)	Eovist (gadoxetate disodium) (N=1989)
Back pain, %	NA	NA	NA	NA	NA	0.6
Blood pressure increased/hypertension, %	NA	NA	NA	<0.2	NA	0.4
Dizziness, %	0.4	0.5	0.5	<0.2	0.3	0.6
Feeling cold, %	<0.4	<0.1	<0.5	<0.2	NA	0.1
Feeling hot, %	<0.4	0.4	1.0	<0.2	≤0.2	0.8
Headache, %	0.7	1.7	1.2	0.4	0.7	1.1
Injection site reaction, %	- <sup>a</sup>	0.4	1.1	- <sup>b</sup>	- <sup>d</sup>	0.4
Nausea, %	1.4	1.2	1.3	0.6	0.4	1.1
Paresthesia, %	<0.4	0.2	0.5	<0.2 <sup>c</sup>	≤0.2 <sup>e</sup>	0.3
Pruritus, %	<0.4	0.2	<0.5	<0.2	≤0.2	0.3
Rash, %	<0.4	0.3	<0.5	0.2	≤0.2 <sup>f</sup>	0.3
Taste perversion/dysgeusia, %	0.9	0.4	0.7	<0.2	≤0.2	0.4
Urticaria, %	0.4	0.1	<0.5	NA	NA	NA
Vasodilatation, %	<0.4	NA	NA	NA	NA	NA
Vomiting, %	<0.4	0.4	<0.5	<0.2	≤0.2	0.4
Localized swelling	NA	NA	<0.5	NA	0.3	NA

FDA = US Food and Drug Administration; GBCAs = gadolinium-based contrast agents; NA = not available.

<sup>a</sup>Injection site reactions reported separately, all <0.4%: injection site coldness, injection site erythema, injection site pain, and injection site warmth.

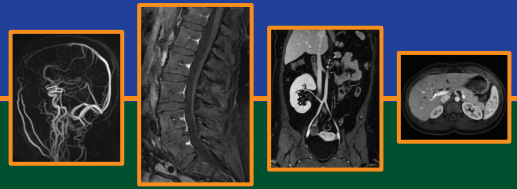
<sup>b</sup>Injection site reactions reported separately, as follows: injection site pain (0.4%) and injection site coldness (0.2%).

<sup>c</sup>Burning sensation reported separately (<0.2%).

<sup>d</sup>Injection site reactions reported separately, as follows: injection site pain (0.7%), injection site warmth (0.4%), injection site coldness (0.3%), and injection site paresthesia (≤0.2%).

<sup>e</sup>Reported as oral paresthesia. <sup>f</sup>Reported as maculopapular rash.

- **Mild reactions** are generally those considered self-limiting, such as headache, nausea, taste perversion, and urticaria (hives) with mild pruritus.<sup>41,73</sup> The ACR recommends reassuring patients who experience these symptoms and observing them to ensure that the reaction does not evolve into a more severe event<sup>41</sup>
- **Moderate reactions** involve tachycardia or bradycardia, hypertension, bronchospasm, and laryngeal swelling.<sup>41</sup> Any moderate reaction calls for immediate treatment and continued observation to prevent it from developing into a life-threatening event<sup>41</sup>
- **Severe reactions:** Patients have experienced rare anaphylactoid and anaphylactic reactions after every GBCA; therefore, personnel trained in contrast reaction recognition and management should be readily available when gadolinium is administered<sup>41</sup>



## ***i. Treating Reactions to Contrast Agents***

Certain medications and equipment must be available to treat reactions, including partial nonrebreather oxygen masks, valve and mouth masks, oxygen, flow valve, nasal prongs, tubing, suction (wall mounted or portable with tubing and catheters), oral airways, stethoscopes, sphygmomanometer, tourniquet, tongue depressor, tracheostomy set, and endotracheal tubes and laryngoscopes. In addition, epinephrine, antihistamine, atropine,  $\beta$ -agonist inhaler, nitroglycerin, aspirin, and fluids should be on hand.<sup>41,74</sup>

The ACR recommends all patients who experience a reaction should be monitored for 20 to 30 minutes after the injection of a GBCA to ensure complete recovery from symptoms.<sup>41</sup> However, as mentioned above, the monitoring times recommended in the prescribing information vary for the different GBCAs. The ACR also recommends premedicating at-risk patients with corticosteroids and antihistamines, when appropriate, and closely monitoring patients with a history of asthma, allergic respiratory disorder, or previous reaction to GBCAs or iodinated contrast agents.<sup>41,59</sup> Hydration is important for all patients, particularly those with renal insufficiency or paraproteinemias, and for neonates, the elderly, and debilitated individuals who may be compromised by dehydration.

### **a. Contrast Extravasation<sup>41</sup>**

- Initial treatment includes
  - Elevation of the affected extremity above the heart
  - Application of cold packs or warm compresses
  - Observation
  - Consultation with the referring physician or surgeon for severe extravasation injury

### **b. Immediate Type Reactions<sup>41</sup>**

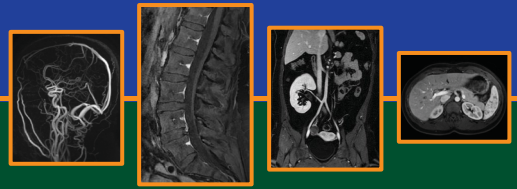
- Oxygen
- Antiemetics for nausea and vomiting
- Antihistamines for symptomatic urticaria, angioedema, or diffuse erythema
- $\beta$ -Agonist for bronchospasm
- Leg elevation
- Fluid therapy

### **c. NSF**

- There is presently no treatment for NSF. Plasmapheresis, a process by which plasma is removed from the blood by a device called a cell separator, has demonstrated some success.<sup>75</sup> Physical and ultraviolet therapies, corticosteroids, and photopheresis have also been associated with anecdotal success<sup>76</sup>

## ***E. Ferumoxytol as a Possible Alternative to GBCAs***

Vascular imaging often requires significant doses of contrast. In patients with CKD, vascular imaging can be challenging due to AEs associated with contrast media, such as contrast-induced nephropathy (CIN) during CT using iodine-based contrast agents and NSF during MRI/MRA using GBCAs. Ferumoxytol (brand name Feraheme) is an iron oxide nanoparticle compound with superparamagnetic properties. It was originally developed as a blood pool contrast agent for MRI, but now is commonly used for the treatment of anemia. To date, the developer has not pursued approval of this agent as contrast media; ferumoxytol is currently approved only for use in the treatment of iron deficiency anemia in patients with CKD.<sup>77</sup> There is growing interest in using ferumoxytol for vascular imaging, particularly in patients who may be intolerant of GBCAs due to severe renal impairment.



The structure of ferumoxytol as a blood pool agent is compelling. Its structural attributes include (1) dextran-derivative coating designed to be nonreactive (less immunogenic, lower labile iron release), theoretically minimizing acute adverse reactions; (2) tiny particle size (30 nm, or 750 kDa) providing for long and stable intravascular residence time because of its low affinity for macrophages; and (3) it contains no gadolinium. Ferumoxytol has a long intravascular half-life of approximately 14 to 15 hours and high relaxivity at both 1.5T and 3T, which makes it an ideal alternative to GBCAs in certain vascular applications.<sup>78</sup>

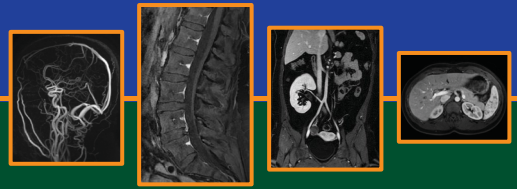
A multicenter ferumoxytol MRI registry (ferumoxytol for off-label imaging use) demonstrated the safety of this agent for use in MRI. The registry was conducted between January 2003 and October 2018 and included 3215 patients (median age, 58 years; 1897 male patients); with a total of 4240 ferumoxytol administrations. The ferumoxytol dose ranged from 1 to 11 mg/kg body weight. There were no severe (life-threatening or fatal) AEs. Eighty-three (1.9%) of 4240 AEs were related or possibly related to ferumoxytol (75 mild [1.8%], 8 moderate [0.2%]). Thirty-one AEs were classified as allergic-like reactions using ACR criteria, but were consistent with minor infusion reactions observed with parenteral iron. The registry investigators concluded that ferumoxytol has a positive safety profile for use in MRI.<sup>78</sup>

Ferumoxytol has been used by radiologists and researchers for an array of predominantly vascular MR applications. A recent study analyzed the use of ferumoxytol for high-resolution 3D cardiovascular magnetic resonance venography (CMRV) for central venous occlusion. The premise of the study focused on the fact that while CMRV is regarded as the technique of choice for imaging the central veins, it is not always ideal. This is because GBCAs are less suited for steady-state venous imaging as compared to first-pass arterial imaging and GBCAs are contraindicated in patients with renal impairment in whom evaluation of venous anatomy is frequently required. Fifty-two consecutive adult patients with renal impairment and suspected venous occlusion underwent ferumoxytol-enhanced CMRV; breath-held, high-resolution, 3D steady-state CMRV was performed through the chest, abdomen, and pelvis. Two blinded reviewers independently scored 21 named venous segments for quality and patency. Correlative catheter venography in 14 patients was used as the reference standard for diagnostic accuracy. Retrospective chart review was conducted to determine clinical impact of ferumoxytol CMRV. The study concluded that ferumoxytol-enhanced MR venography is a practical, accurate, and robust technique for high-resolution mapping of central thoracic, abdominal, and pelvic veins and can be used to inform image-guided therapy.<sup>79</sup>

## 2. MR SAFETY

In general, MR imaging is considered to be a relatively safe diagnostic modality. The risks inherent in clinical MR imaging have long been understood and have not significantly changed, even as increasing numbers of exams are performed at higher magnetic field strength (eg, 3T). The principal hazards associated with any static magnetic field are projectile effects if ferromagnetic materials are inadvertently brought in close proximity to the MR system, and the possibility of metallic implants experiencing substantial magnetic field interactions and moving internally due to forces induced by the external magnetic field. Both of these effects are potentially a greater concern as the static magnetic field strength of the MR system increases.

Other hazards exist as well. Radiofrequency (RF) energy transmitted into patients (excitation pulses) may cause the tissues of the body to heat up. Because certain pulse sequences cause more heating than others, the FDA has provided guidance on the rate of RF energy deposition, termed specific absorption rate (SAR), which is permissible. SAR limitations are generally monitored by the software of the MR system so that maximum allowable SAR cannot be reached. SAR limitations become more of a problem at 3T because SAR increases with the square of the magnetic field.<sup>80</sup>



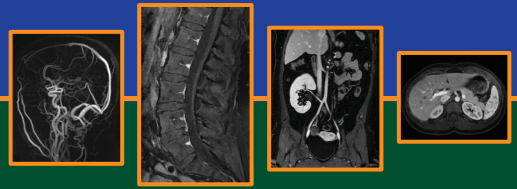
MR systems require the use of RF pulses to create the MR signal. This RF energy is transmitted readily through free space from the transmit RF coil to the patient. However, the use of RF coils, physiologic monitors, electronically activated devices, and external accessories or objects made from conductive materials may cause excessive heating, resulting in burn injuries to patients undergoing MR procedures. The nature of high-frequency electromagnetic fields is such that the energy can be transmitted across open space and through insulators. Therefore, only devices with carefully designed current paths can be made safe for use during MR procedures. Simply insulating conductive material (eg, wire or lead) or separating it from the patient may not be sufficient to prevent excessive heating or burns from occurring. Heating of implants and similar devices may also occur in association with MR procedures, but this tends to be problematic primarily for objects made from conductive materials that have elongated shapes, such as leads, guidewires, and certain types of catheters (eg, catheters with thermistors or other conducting components).<sup>81</sup>

Furthermore, certain geometrical shapes exhibit the phenomenon of “resonance,” which increases their propensity to concentrate RF currents. At the operating frequencies of present-day MR systems, conducting loops of tens of centimeters in size may create problems and, therefore, must be avoided, unless high impedance is used to limit RF current. Importantly, even loops that include small gaps separated by insulation may still conduct current.<sup>81</sup>

Notably, many incidents of excessive heating have been reported in patients undergoing MR procedures in the United States that were unrelated to equipment problems or the presence of conductive external or internal implants or materials.<sup>81,82</sup> These incidents included first-, second-, and third-degree burns that were experienced by patients. In many of these cases, the reports indicated that the limbs or other body parts of the patients were in direct contact with body RF coils or other transmit RF coils of the MR systems or there were skin-to-skin contact points suspected of being responsible for these injuries.<sup>82</sup>

To prevent patients from experiencing excessive heating and possible burns in association with MR procedures, the following guidelines are recommended<sup>81</sup>:

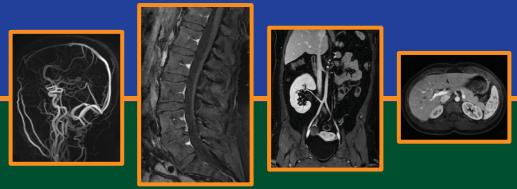
- Prepare the patient for the MR procedure by ensuring that there are no unnecessary metallic objects contacting the patient’s skin (eg, metallic drug delivery patches, jewelry, necklaces, bracelets, key chains)
- Prepare the patient for the MR procedure by using insulation material (ie, appropriate padding) to prevent skin-to-skin contact points and the formation of “closed loops” from touching body parts
- Insulating material (minimum recommended thickness, 1 cm) should be placed between the patient’s skin and the transmit RF coil that is used for the MR procedure (alternatively, the RF coil itself can be padded). For example, position the patient so there is no direct contact between the patient’s skin and the body RF coil of the MR system. This may be accomplished by having the patient place his/her arms over his/her head or by using elbow pads or foam padding between the patient’s tissue and the body RF coil of the MR system. This is especially important for MR examinations that use the body coil or other large RF coils for transmission of RF energy
- Use only electrically conductive devices, equipment, accessories (eg, ECG leads and electrodes), and materials that have been thoroughly tested and determined to be safe and compatible for MR procedures
- Carefully follow specific MR safety criteria and recommendations for implants made from electrically conductive materials (eg, bone fusion stimulators and neurostimulation systems)
- Before using electrical equipment, check the integrity of the insulation and/or housing of all components, including surface RF coils, monitoring leads, cables, and wires. Preventive maintenance should be practiced routinely for such equipment



- Remove all nonessential electrically conductive materials from the MR system (unused surface RF coils, ECG leads, cables, wires, etc)
- Keep electrically conductive materials that must remain in the MR system from directly contacting the patient by placing thermal and/or electrical insulation between the conductive material and the patient
- Keep electrically conductive materials that must remain within the body RF coil or other transmit RF coil of the MR system from forming conductive loops. **Note:** The patient's tissue is conductive and, therefore, may be involved in the formation of a conductive loop, which can be circular, U-shaped, or S-shaped
- Position electrically conductive materials to prevent "cross points." For example, a cross point is the point where a cable crosses another cable, where a cable loops across itself, or where a cable touches either the patient or the sides of the transmit RF coil more than once. Notably, even the close proximity of conductive materials with each other should be avoided because some cables and RF coils can capacitively couple (without any contact or crossover) when placed close together
- Position electrically conductive materials to exit down the center of the MR system (ie, not along the side of the MR system or close to the body RF coil or other transmit RF coil)
- Do not position electrically conductive materials across an external metallic prosthesis (eg, external fixation device or cervical fixation device) or similar device that is in direct contact with the patient
- Allow only properly trained individuals to operate devices (eg, monitoring equipment) in the MR environment
- Follow all manufacturer instructions for the proper operation and maintenance of physiologic monitoring or other similar electronic equipment intended for use during MR procedures
- Electrical devices that do not appear to be operating properly during the MR procedure should be removed from the patient immediately
- Closely monitor the patient during the MR procedure. If the patient reports sensations of heating or other unusual sensations, discontinue the MR procedure immediately and perform a thorough assessment of the situation
- RF surface coil decoupling failures can cause localized RF power deposition levels to reach excessive levels. The MR system operator will recognize such a failure as a set of concentric semicircles in the tissue on the associated MR image or as an unusual amount of image nonuniformity related to the position of the RF coil
- Administering contrast material as part of the MR exam increases risk, including the possibility of contrast extravasation during the administration process and adverse drug reactions. It is therefore of the utmost importance to identify patients at particular risk and use the lowest possible dose necessary to achieve the needed diagnostic accuracy

### 3. PATIENT SCREENING

To minimize MRI-associated incidents and accidents, it is important that personnel are provided up-to-date, accurate safety information on a regular basis.<sup>83</sup> Information is evolving, and new areas of interest include the safe use of GBCAs in patients with renal dysfunction in light of NSF and evaluation of items such as implants and devices as MRI-compatible, including at 3T.



Certain aspects of patient screening for MR procedures are best carried out during the scheduling process. These activities should be conducted by a healthcare worker specifically trained in MR safety (ie, an individual who is trained to understand the potential hazards and issues associated with the MR environment and procedures and who is sufficiently familiar with the institution's screening procedures). In scheduling the patient, it should be determined whether the patient has an implant that may be contraindicated or requires special attention during the MR procedure (eg, a ferromagnetic aneurysm clip, pacemaker, or neurostimulation system), and whether there is a physical condition that needs careful consideration (eg, the patient is pregnant, has a disability, or has a metallic foreign body).<sup>84</sup> One condition that should be carefully considered before a patient undergoes an MR procedure is renal failure. Patients should be asked if they have a history of renal dysfunction or if they are taking nephrotoxic medications. Patients with suspected renal dysfunction should have their blood urea nitrogen and serum creatinine levels tested or their eGFR calculated. In addition, in this subset of patients, the ACR recommends obtaining an eGFR within 6 weeks of GBCA administration.<sup>41</sup>

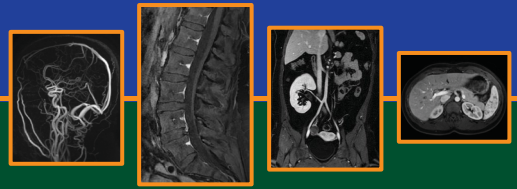
Preliminary screening helps to prevent scheduling patients who are inappropriate candidates for MR examinations. Following preliminary screening, the patient should undergo comprehensive screening in the MR department. This should involve the use of a printed screening form to document the screening procedure, a review of the information on the screening form, and a verbal conversation verifying the information and giving the patient an opportunity to address his or her concerns. An MR-safety trained healthcare professional must conduct this aspect of patient screening. An example of such a form can be found at [www.MRIsafety.com](http://www.MRIsafety.com).<sup>83,84</sup>

## 4. CONCLUSIONS AND FUTURE DIRECTIONS

The application of GBCAs in MR imaging has improved the ability of radiologists to detect and characterize pathological processes within the human body. While these agents and MR imaging overall are considered extremely safe, proper patient screening is paramount, particularly screening for renal dysfunction to minimize the possibility of a patient developing NSF.

In the near future, new technologies will greatly improve the accuracy, potentially reduce the contrast agent dose needed, and expand the applications of MRI/MRA. Improved coils, postprocessing software, and deep-learning image reconstruction will have a significant impact on how we utilize this important imaging modality.

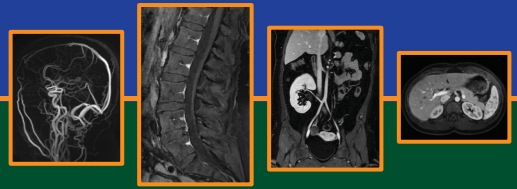
Point-of-care MRI (POC-MRI) is now becoming a reality in the United States. In 2020, the FDA approved the first ultra-low field strength POC-MRI. The Swoop<sup>®</sup> Portable MR Imaging System<sup>™</sup> was developed by Hyperfine.<sup>85,86</sup> It is a portable 0.064T unit indicated for CNS imaging of the head. The units are designed to be used at bedside in settings such as emergency departments, ICUs, and other situations in which rapid access to brain imaging is required. The Swoop system weighs approximately 1400 lb, is motorized and transport-controlled by a joystick, plugs into conventional electric outlets—using only 900 watts—and is small enough to be transported through doorways and on elevators. Available imaging sequences currently include T1, T2, FLAIR, and DWI (with ADC map). The combination of the Swoop system in conjunction with a high-relaxivity GBCA such as Vueway (gadopiclenol) may allow extremely rapid access to MR imaging of the brain in acute situations such as suspected stroke, assessment of cranial trauma, pediatric hydrocephalus, and brain lesion detection.



In an abstract presented at the annual meeting of the Radiological Society of North America in November 2023, the investigators sought to study the relative relaxivities of 2 GBCAs in ultra-low field MRI.<sup>87</sup> Using the Swoop system, the relative relaxivities of Gadavist (gadobutrol) and Vueway (gadopiclenol) were assessed. At 0.064T, the average  $r_1$  for Gadavist (gadobutrol) was 8.7 and for Vueway (gadopiclenol) was an astounding 32.6. These early data suggest that in critical situations, neuroimaging with ultra-low field strength POC-MRI could be significantly enhanced with an agent such as Vueway (gadopiclenol).

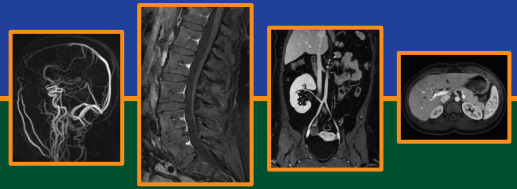
MR imaging procedures should, in general, be avoided in pregnant patients and patients with pacemakers and implantable cardioverter defibrillators, unless determined by an MR-safety specialist (ie, a radiologist or cardiologist) to be absolutely necessary and performed in accordance with highly specific safety precautions. The GBCAs approved for use in MR imaging in the United States – ProHance (gadoteridol), MultiHance (gadobenate dimeglumine), Eovist (gadoxetate disodium), Gadavist (gadobutrol), Dotarem/Clariscan (gadoterate meglumine), and Vueway/Elucirem (gadopiclenol) – have similar immediate AE profiles and are safe for use in most individuals. However, they should be used with extreme caution in patients with a prior adverse reaction to contrast media (including GBCAs and iodinated contrast agents), patients with respiratory disorders such as asthma, and patients with impaired renal function.

GBCAs have been associated with the development of NSF in renally impaired patients, and steps should be taken to minimize the risk for this condition in these individuals, including initiating a comprehensive patient screening process, administering as low a dose of a GBCA as possible, selecting an appropriate GBCA, and, when appropriate, performing hemodialysis in patients who have renal insufficiency as soon as possible after the MR exam. Repeated administration of GBCAs has also recently been associated with gadolinium retention in the brain, causing residual brightness in the globus pallidus and the dentate nucleus of some patients. To date, no adverse clinical consequences of gadolinium retention have been demonstrated, and research is ongoing to ensure optimum patient safety.

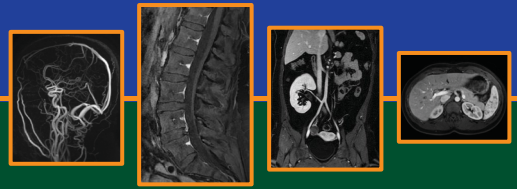


## 5. REFERENCES

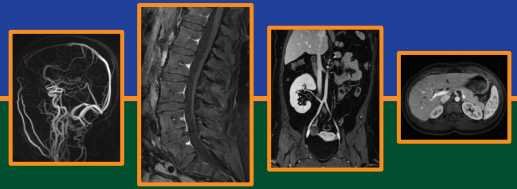
1. ProHance (gadoteridol) injection [prescribing information]. Monroe Township, NJ: Bracco Diagnostics Inc.; June 2022.
2. MultiHance (gadobenate dimeglumine) injection [prescribing information]. Monroe Township, NJ; Bracco Diagnostics Inc.; August 2018.
3. Eovist (gadoxetate disodium) injection [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; December 2021.
4. Gadavist (gadobutrol) injection [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; April 2022.
5. Dotarem (gadoterate meglumine) injection [prescribing information]. Princeton, NJ: Guerbet LLC; April 2022.
6. Clariscan (gadoterate meglumine) injection [prescribing information]. Marlborough, MA: GE Healthcare Inc.; November 2020.
7. Vueway (gadopiclenol) injection [prescribing information]. Monroe Township, NJ; Bracco Diagnostics Inc.; September 2022.
8. Elucirem (gadopiclenol) injection [prescribing information]. Princeton, NJ: Guerbet LLC; October 2022.
9. Rohrer M, Bauer H, Mintorovitch J, Requardt M, Weinmann H-J. Comparison of magnetic properties of MRI contrast media solutions at different magnetic field strengths. *Invest Radiol.* 2005;40:715–724.
10. Giesel FL, Mehndiratta A, Essig M. High-relaxivity contrast-enhanced magnetic resonance neuroimaging: a review. *Eur Radiol.* 2010;20:2461–2474.
11. Kirchin MA, Runge VM. Contrast agents for magnetic resonance imaging: safety update. *Top Magn Reson Imaging.* 2003;14:426–435.
12. Robic C, Port M, Rousseaux O, et al. Physicochemical and pharmacokinetic profiles of gadopiclenol: a new macrocyclic gadolinium chelate with high T1 relaxivity. *Invest Radiol.* 2019;54(8):475–484.
13. de Haën C, Cabrini M, Akhnana L, Ratti D, Calabi L, Gozzini L. Gadobenate dimeglumine 0.5 M solution for injection (MultiHance): pharmaceutical formulation and physicochemical properties of a new magnetic resonance imaging contrast medium. *Appl Radiol.* 2003;32(4 suppl):12–20.
14. Runge VM. Safety of magnetic resonance contrast media. *Top Magn Reson Imaging.* 2001;12:309–314.
15. Pintaske J, Martirosian P, Graf H, et al. Relaxivity of gadopentetate dimeglumine (Magnevist), gadobutrol (Gadovist), and gadobenate dimeglumine (MultiHance) in human blood plasma at 0.2, 1.5, and 3 Tesla. *Invest Radiol.* 2006;41:213–221 [erratum in: *Invest Radiol.* 2006;41:859].
16. Spinazzi A, Lorusso V, Pirovano G, Kirchin M. Safety, tolerance, biodistribution and MR imaging enhancement of the liver with gadobenate dimeglumine. *Acad Radiol.* 1999;6:282–291.
17. Heiland S, Erb G, Ziegler S, Krix M. Where contrast agent concentration really matters – a comparison of CT and MRI. *Invest Radiol.* 2010;45:529–537.
18. Rowley HA, Scialfa G, Gao PY, et al. Contrast-enhanced MR imaging of brain lesions: a large-scale intraindividual crossover comparison of gadobenate dimeglumine versus gadodiamide. *AJNR Am J Neuroradiol.* 2008;29:1684–1691.
19. Rumboldt Z, Rowley HA, Steinberg F, et al. Multicenter, double-blind, randomized, intraindividual crossover comparison of gadobenate dimeglumine and gadopentetate dimeglumine in MRI of brain tumors at 3 Tesla. *J Magn Reson Imaging.* 2009;29:760–767.
20. Maravilla KR, Maldjian JA, Schmalfuss IM, et al. Contrast enhancement of central nervous system lesions: multicenter intraindividual crossover comparative study of two MR contrast agents. *Radiology.* 2006;240:389–400.
21. Essig M, Tartaro A, Tartaglione T, Pirovano G, Kirchin MA, Spinazzi A. Enhancing lesions of the brain: intraindividual crossover comparison of contrast enhancement after gadobenate dimeglumine versus established gadolinium comparators. *Acad Radiol.* 2006;13:744–751.
22. Bueltmann E, Erb G, Kirchin MA, Klose U, Naegele T. Intra-individual crossover comparison of gadobenate dimeglumine and gadopentetate dimeglumine for contrast-enhanced magnetic resonance angiography of the supraaortic vessels at 3 Tesla. *Invest Radiol.* 2008;43:695–702.



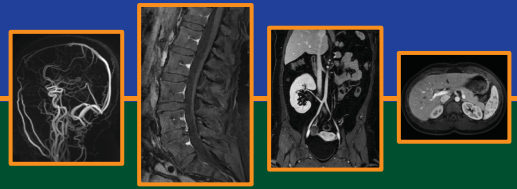
23. Gerretsen SC, le Maire TF, Miller S, et al. Multicenter, double-blind, randomized, intraindividual crossover comparison of gadobenate dimeglumine and gadopentetate dimeglumine for MR angiography of peripheral arteries. *Radiology*. 2010;255:988–1000.
24. Pediconi F, Catalano C, Padula S, et al. Contrast-enhanced MR mammography: improved lesion detection and differentiation with gadobenate dimeglumine. *Am J Roentgenol*. 2008;191:1339–1346.
25. Schneider G, Maas R, Schultze Kool L, et al. Low-dose gadobenate dimeglumine versus standard dose gadopentetate dimeglumine for contrast-enhanced magnetic resonance imaging of the liver: an intra-individual crossover comparison. *Invest Radiol*. 2003;38:85–94.
26. Frydrychowicz A, Nagle SK, D'Souza SL, Vigen KK, Reeder SB. Optimized high-resolution contrast-enhanced hepatobiliary imaging at 3 tesla: a cross-over comparison of gadobenate dimeglumine and gadoxetic acid. *J Magn Reson Imaging*. 2011 Jul 12 [Epub ahead of print.]
27. Prokop M, Schneider G, Vanzulli A, et al. Contrast-enhanced MR angiography of the renal arteries: blinded multicenter crossover comparison of gadobenate dimeglumine and gadopentetate dimeglumine. *Radiology*. 2005;234:399–408.
28. Achenbach M, Figiel JH, Burbelko M, Heverhagen JT. Prospective comparison of image quality and diagnostic accuracy of 0.5 molar gadobenate dimeglumine and 1.0 molar gadobutrol in contrast-enhanced run-off magnetic resonance angiography of the lower extremities. *J Magn Reson Imaging*. 2010;32:1166–1171.
29. Martincich L, Faivre-Pierret M, Zechmann CM, et al. Multicenter, double-blind, randomized, intraindividual crossover comparison of gadobenate dimeglumine and gadopentetate dimeglumine for breast MR imaging (DETECT Trial). *Radiology*. 2011;258:396–408.
30. Gilbert FJ, van den Bosch HC, Petrillo A, et al. Comparison of gadobenate dimeglumine-enhanced breast MRI and gadopentetate dimeglumine-enhanced breast MRI with mammography and ultrasound for the detection of breast cancer. *J Magn Reson Imaging*. 2014;39:1272–1286.
31. Li Y, Li X, Li D, et al. Multicenter, intraindividual comparison of single-dose gadobenate dimeglumine and double-dose gadopentetate dimeglumine for MR angiography of the supra-aortic arteries (the Supra-Aortic VALUE study). *AJNR Am J Neuroradiol*. 2013;34:847–854.
32. Wang J, Yan F, Liu J, et al. Multicenter, intra-individual comparison of single dose gadobenate dimeglumine and double dose gadopentetate dimeglumine for MR angiography of the peripheral arteries (the Peripheral VALUE Study). *J Magn Reson Imaging*. 2013;38:926–937.
33. Essig M, Lodemann KP, LeHuu M, Schonberg SO, Hubener M, Van Kaick G. Comparison of MultiHance and Gadovist for cerebral MR perfusion imaging in healthy volunteers [article in German]. *Radiologe*. 2002;42:909–915.
34. Giesel FL, von Tengg-Kobligh H, Wilkinson ID, et al. Influence of human serum albumin on longitudinal and transverse relaxation rates ( $r_1$  and  $r_2$ ) of magnetic resonance contrast agents. *Invest Radiol*. 2006;41:222–228.
35. Katakami N, Inaba Y, Sugata S, et al. Magnetic resonance evaluation of brain metastases from systemic malignancies with two doses of gadobutrol 1.0 m compared with gadoteridol: a multicenter, phase II/III study in patients with known or suspected brain metastases. *Invest Radiol*. 2011;46:411–418.
36. Seidl Z, Vymazal J, Mechl M, et al. Does higher gadolinium concentration play a role in the morphologic assessment of brain tumors? Results of a multicenter intraindividual crossover comparison of gadobutrol versus gadobenate dimeglumine (the MERIT study). *AJNR Am J Neuroradiol*. 2012 March 1 [Epub ahead of print].
37. Bendszus M, Roberts D, Kolumban B, et al. Dose finding study of gadopicleinol, a new macrocyclic contrast agent, in MRI of central nervous system. *Invest Radiol*. 2020;55(3):129–137.
38. Loevner LA, Kolumban B, Hutóczki G, et al. Efficacy and safety of gadopicleinol for contrast-enhanced MRI of the central nervous system: the PICTURE randomized clinical trial. *Invest Radiol*. 2023;58(5):307–313.
39. Kuhl C, Csósz T, Piskorski W, Miszalski T, Lee JM, Otto PM. Efficacy and safety of half-dose gadopicleinol versus full-dose gadobutrol for contrast-enhanced body MRI. *Radiology*. 2023;308(1):e222612.
40. Bradu A, Penescu M, Pitrou C, Hao J, Bourrinet P. Pharmacokinetics, dialysability, and safety of gadopicleinol, a new gadolinium-based contrast agent, in patients with impaired renal function. *Invest Radiol*. 2021;56(8):486–493.



41. American College of Radiology. *ACR Manual on Contrast Media*. Published April 2023. Accessed January 18, 2024. [https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast\\_Media.pdf](https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf)
42. Ringe KI, Husarik DB, Sirlin CB, Merkle EM. Gadoxetate disodium-enhanced MRI of the liver: part I, protocol optimization and lesion appearance in the noncirrhotic liver. *AJR Am J Roentgenol*. 2010;195:13–28.
43. Cruite I, Schroeder M, Merkle EM, Sirlin CB. Gadoxetate disodium-enhanced MRI of the liver: part 2, protocol optimization and lesion appearance in the cirrhotic liver. *AJR Am J Roentgenol*. 2010;195:29–41.
44. Van Dijk P, Sijens PE, Schmitz PI, Oudkerk M. Gd-enhanced MR imaging of brain metastases: contrast as a function of dose and lesion size. *Magn Reson Imaging*. 1997;15:535–541.
45. Sze G, Johnson C, Kawamura Y, et al. Comparison of single- and triple-dose contrast material in the MR screening of brain metastases. *AJNR Am J Neuroradiol*. 1998;19:821–828.
46. Pediconi F, Fraioli F, Catalano C, et al. Gadobenate dimeglumine (Gd-DTPA) vs gadopentetate dimeglumine (Gd-BOPTA) for contrast-enhanced magnetic resonance angiography (MRA): improvement in intravascular signal density and contrast to noise ratio [article in English, Italian]. *Radiol Med (Torino)*. 2003;106:87–93.
47. Attenberger UI, Michaely HJ, Wintersperger BJ, et al. Three-dimensional contrast-enhanced magnetic-resonance angiography of the renal arteries: interindividual comparison of 0.2 mmol/kg gadobutrol at 1.5 T and 0.1 mmol/kg gadobenate dimeglumine at 3.0 T. *Eur Radiol*. 2008;18:1260–1268.
48. Tomasian A, Salamon N, Krishnam MS, Finn JP, Villablanca JP. 3D high-spatial-resolution cerebral MR venography at 3T: a contrast-dose-reduction study. *AJNR Am J Neuroradiol*. 2009;30:349–355.
49. Schiebler ML, Nagle SK, François CJ, et al. Effectiveness of MR angiography for the primary diagnosis of acute pulmonary embolism: clinical outcomes at 3 months and 1 year. *J Magn Reson Imaging*. 2013;38:914–925.
50. Dillman JR, Ellis JH, Cohan RH, Strouse PJ, Jan SC. Allergic-like breakthrough reactions to gadolinium contrast agents after corticosteroid and antihistamine premedication. *AJR Am J Roentgenol*. 2008;190:187–190.
51. Abujudeh HH, Kosaraju VK, Kaewlai R. Acute adverse reactions to gadopentetate dimeglumine and gadobenate dimeglumine: experience with 32,659 injections. *AJR Am J Roentgenol*. 2010;194:430–434.
52. Perez-Rodriguez J, Lai S, Ehst BD, Fine DM, Bluemke DA. Nephrogenic systemic fibrosis: incidence, associations, and effect of risk factor assessment—report of 33 cases. *Radiology*. 2009;250:371–377.
53. Grobner T. Gadolinium—a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplant*. 2006;21:1104–1108.
54. Thomsen HS. Nephrogenic systemic fibrosis: a serious late adverse reaction to gadodiamide. *Eur Radiol*. 2006;16:2619–2621.
55. Idée JM, Port M, Robic C, Medina C, Sabatou M, Corot C. Role of thermodynamic and kinetic parameters in gadolinium chelate stability. *J Magn Reson Imaging*. 2009;30:1249–1258.
56. Magnevist (gadopentetate dimeglumine) injection [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; July 2018.
57. Omniscan (gadodiamide) injection [prescribing information]. Marlborough, MA: GE Healthcare Inc.; October 2018.
58. OptiMARK (gadoversetamide) injection [prescribing information]. Princeton, NJ: Guerbet LLC; August 2018.
59. Kanal E, Barkovich AJ, Bell C, et al; ACR Blue Ribbon Panel on MR Safety. ACR guidance document for safe MR practices: 2007. *AJR Am J Roentgenol*. 2007;188:1447–1474.
60. Plantinga LC, Crews DC, Coresh J, et al; for the CDC CKD Surveillance Team. Prevalence of chronic kidney disease in US adults with undiagnosed diabetes or prediabetes. *Clin J Am Soc Nephrol*. 2010;5:673–682.
61. Marckmann P, Skov L, Rossen K, Heaf JG, Thomsen HS. Case-control study of gadodiamide-related nephrogenic systemic fibrosis. *Nephrol Dial Transplant*. 2007;22:3174–3178.
62. US Food and Drug Administration. FDA drug safety communication: new warnings for using gadolinium-based contrast agents in patients with kidney dysfunction. Published September 9, 2010. Current as of February 6, 2018. Accessed December 18, 2023. <http://www.fda.gov/drugs/drugsafety/ucm223966.htm>
63. Gulani V, Calamante F, Shellock FG, Kanal E, Reeder SB; International Society for Magnetic Resonance in Medicine. Gadolinium deposition in the brain: summary of evidence. *Lancet Neurol*. 2017;16:564–570.



64. Kanda T, Ishii K, Kawaguchi H, Kitajima K, Takenaka D. High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images: relationship with increasing cumulative dose of a gadolinium-based contrast material. *Radiology*. 2014;270:834–841.
65. Errante Y, Cirimele V, Mallio CA, Di Lazzaro V, Zobel BB, Quattrocchi CC. Progressive increase of T1 signal intensity of the dentate nucleus on unenhanced magnetic resonance images is associated with cumulative doses of intravenously administered gadodiamide in patients with normal renal function, suggesting dechelation. *Invest Radiol*. 2014;49:685–690.
66. Radbruch A, Weberling LD, Kieslich PJ, et al. Gadolinium retention in the dentate nucleus and globus pallidus is dependent on the class of contrast agent. *Radiology*. 2015;275:783–791.
67. McDonald RJ, McDonald JS, Kallmes DF, et al. Intracranial gadolinium deposition after contrast-enhanced MR imaging. *Radiology*. 2015;275:772–782.
68. Ramalho J, Castillo M, AIObaidy M, et al. High signal intensity in globus pallidus and dentate nucleus on unenhanced T1-weighted MR images: evaluation of two linear gadolinium-based contrast agents. *Radiology*. 2015;276:836–844.
69. European Medicines Agency (EMA). EMA's final opinion confirms restrictions on use of linear gadolinium agents in body scans [press release]. London, England: EMA; July 21, 2017. Accessed January 17, 2024. <https://www.ema.europa.eu/en/news/emas-final-opinion-confirms-restrictions-use-linear-gadolinium-agents-body-scans>
70. US Food and Drug Administration. FDA Drug Safety Communication: FDA warns that gadolinium-based contrast agents (GBCAs) are retained in the body; requires new class warnings [safety announcement]. Silver Spring, MD: FDA; December 19, 2017. Updated May 16, 2018. Accessed January 17, 2024. <https://www.fda.gov/Drugs/DrugSafety/ucm589213.htm>
71. American College of Radiology/American Society of Neuroradiology. ACR–ASNR position statement on the use of gadolinium contrast agents. Created May 2016. In: *ACR Manual on Contrast Media*. 2023:82. Accessed January 18, 2024. [https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast\\_Media.pdf](https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf)
72. Kanal E, Barkovich AJ, Bell C, et al; on behalf of Expert Panel on MR Safety. ACR guidance document on MR safe practices: 2013. *J Magn Reson Imaging*. 2013;37(3):501–530.
73. Shellock FG, Parker JR, Venetianer C, Pirovano G, Spinazzi A. Safety of gadobenate dimeglumine (MultiHance): summary of findings from clinical studies and postmarketing surveillance. *Invest Radiol*. 2006;41:500–509.
74. European Society of Urogenital Radiology (ESUR). ESUR Guidelines on Contrast Agents. Version 10.0. 2018. Accessed January 17, 2024. <https://www.esur.org/esur-guidelines-on-contrast-agents/>
75. Aires NB, Sotto MN, Nico MM. Nephrogenic fibrosing dermopathy: report of two cases. *Acta Derm Venereol*. 2007;87:521–524.
76. Broome DR, Girguis MS, Baron PW, Cottrell AC, Kjellin I, Kirk GA. Gadodiamide-associated nephrogenic systemic fibrosis: why radiologists should be concerned. *AJR Am J Roentgenol*. 2007;188:586–592.
77. Stoumpos S, Hennessy M, Vesey AT, et al. Ferumoxytol magnetic resonance angiography: a dose-finding study in patients with chronic kidney disease. *Eur Radiol*. 2019;29(7):3543–3552.
78. Nguyen KL, Yoshida T, Kathuria-Prakash N, et al. Multicenter safety and practice for off-label diagnostic use of ferumoxytol in MRI. *Radiology*. 2019;293(3):554–564.
79. Shahrouki P, Moriarty JM, Khan SN, et al. High resolution, 3-dimensional Ferumoxytol-enhanced cardiovascular magnetic resonance venography in central venous occlusion. *J Cardiovasc Magn Reson*. 2019;21(1):17.
80. Shellock F. Bioeffects of Radiofrequency Fields. 2011.
81. Shellock FG. Guidelines to prevent excessive heating and burns associated with MRI procedures. Accessed January 6, 2024. [https://www.appliedradiology.org/courses/3277/PayInteractive/PDF\\_Downloads/07\\_Burn\\_Prevention\\_Guidelines.pdf](https://www.appliedradiology.org/courses/3277/PayInteractive/PDF_Downloads/07_Burn_Prevention_Guidelines.pdf)



82. Shellock FG, Crues JV. MR procedures: biologic effects, safety, and patient care. *Radiology*. 2004;232:635–652.
83. Shellock FG, Spinazzi A. MRI safety update 2008: part 2, screening patients for MRI. *AJR Am J Roentgenol*. 2008;191:1140–1149.
84. Shellock F. Screening Form. Accessed January 18, 2024. <http://www.mrisafety.com/ScreeningForm.html>
85. Meet Swoop Portable MR Imaging System. Hyperfine. Accessed January 6, 2024. <https://hyperfine.io/assets/pdfs/Swoop%20System%20Brochure%20-%20LBL-001459%20v1.pdf>
86. US Food and Drug Administration. 510(k) premarket notification: Lucy Point-of-Care Magnetic Resonance Imaging Device. Approved February 6, 2020. Accessed January 6, 2024. <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K192002>
87. Ragunathan S. Longitudinal relaxivity estimation of gadolinium-based contrast agents at 64 mT. Abstract presented at: Annual Meeting of the Radiological Society of North America; November 28, 2023; Chicago, IL. Abstract T5B-SPPH-13. Accessed January 6, 2024. <https://reg.meeting.rsna.org/flow/rsna/rsna23/rsna2023/page/sessioncatalog/session/1695063018597027wwnD>

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