Immediate Allergic Reactions to Gadolinium-based Contrast Agents: A Systematic Review and Meta-Analysis[1]

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Purpose: To perform a systematic review and meta-analysis to determine if there are differences in rates of immediate allergic events between classes of gadolinium-based contrast agents (GBCAs).

Materials and Methods: PubMed and Google Scholar databases were searched for studies in which rates of immediate adverse events to GBCAs were reported. The American College of Radiology classification system was used to characterize allergic-like events as mild, moderate, or severe, and the total number of administrations of each GBCA was recorded. Where necessary, authors of studies were contacted to clarify data and eliminate physiologic reactions. Relative risks of GBCA types were estimated by using the Mantel-Haenszel type method.

Results: Nine studies in which immediate reactions to GBCA were recorded from a total of 716978 administrations of GBCA met the criteria for inclusion and exclusion. The overall and severe rates of GBCA allergic-like adverse events were 9.2 and 0.52 per 10000 administrations, respectively: 81% (539 of 662) were mild, 13% (86 of 662) were moderate, and 6% (37 of 662) were severe reactions. The nonionic linear chelate gadodiamide had the lowest rate of reactions, at 1.5 (95% confidence interval [CI]: 0.74, 2.4) per 10000 administrations, which was significantly less than that of linear ionic GBCAs at 8.3 (95% CI: 7.5, 9.2) per 10000 administrations (relative risk, 0.19 [95% CI: 0.099, 0.36]; $P < .00001$) and less than that for nonionic macrocyclic GBCAs at 16 (95% CI: 14, 19) per 10000 administrations (relative risk, 0.12 [95% CI: 0.05, 0.31]; $P < .001$). GBCAs known to be associated with protein binding had a higher rate of reactions, at 17 (95% CI: 15, 20) per 10000 administrations compared with the same chelate classification without protein binding, at 5.2 (95% CI: 4.5, 6.0) per 10000 administrations (relative risk, 3.1 [95% CI: 2.4, 3.8]; $P < .0001$).

Conclusion: These data show the lowest rate of immediate allergic adverse events with use of the nonionic linear GBCA gadodiamide in comparison with those of ionic linear or nonionic macrocyclic GBCAs. A higher rate of immediate allergic adverse events was associated with ionicity, protein binding, and macrocyclic structure.

An earlier incorrect version of this article appeared online. This article was corrected on August 31, 2017.

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The extraordinarily low incidence of adverse reactions to gadolinium-based contrast agents (GBCAs) has frustrated efforts to compare their relative safety, because hundreds of thousands of administrations may be necessary to detect differences at these low rates. Ionic and nonionic iodine-based contrast agents are known to have different immediate reaction rates. GBCA adverse reactions occur less frequently but may also have differences related to chemical structure, ionicity, and affinity for serum proteins (1–5).

Data on immediate reactions to GBCAs have been reported in large case series (2–15). We hypothesized that there are differences in rates of immediate allergic reactions to ionic versus nonionic, linear versus macrocyclic, and protein-binding versus non–protein-binding GBCAs that may be detectable when data from multiple large case series are combined. The purpose of this systematic review and meta-analysis was to determine if there are differences in rates of immediate allergic events among types of GBCAs.

Advances in Knowledge

- In a systematic review of nine studies of immediate reactions to gadolinium-based contrast agents (GBCAs), 1.5 immediate allergic-like adverse events per 10000 administrations of nonionic linear GBCA were reported ($P <$ .00001), which was less than the 8.3 and 16 reactions per 10000 administrations reported for ionic linear GBCA and nonionic macrocyclic GBCA, respectively ($P <$ .001).
- Ionic linear GBCAs known to have protein binding were associated with a higher rate of immediate allergic-like reactions, (17 per 10000 administrations) compared with the same ionic linear chelate classification without protein binding (5.2 per 10000 administrations, $P <$ .0001).
- Linear GBCAs without protein binding had a lower rate of immediate allergic-like reactions (4.4 per 10000 administrations) compared with macrocyclic GBCAs without protein binding (14 per 10000 administrations, P = .01).

Materials and Methods

Search Strategy

This meta-analysis was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, or PRISMA (16). A search of the PubMed and Google Scholar databases for all published studies through February 2017 was conducted independently by two radiology research fellows (B.A.H. and Z.F., with 10 and 3 years of experience, respectively). The following key words were used: "GBCA" or "gadolinium" combined with "adverse effect," "adverse event," or "allergic reaction." Reference lists of the retrieved articles were screened, and additional manual citation searching was performed for each article that met inclusion criteria, with removal of duplicate articles. There were no language limitations. Then, titles and abstracts were reviewed, and comments, letters, reviews, and articles in which rates of immediate adverse reactions to specific GBCAs were not reported were excluded. On the basis of full-text review of the remaining articles, six studies were excluded because reactions to GBCAs were reported generically instead of being attributed to a specific GBCA. Two articles were excluded because they overlapped with subsequent, updated articles on the topic from the same institutions. Finally, we excluded articles in which the authors did not use the American College of Radiology (ACR) Manual on Contrast Media Classification system for dividing acute reactions into three categories (mild, moderate, and severe) (17–20). Since the ACR Manual on Contrast Media evolved during the past 10 years, with a separation of allergic-like and physiologic reactions in the more recent versions (19,20), we contacted authors of articles for further information, when necessary, to exclude physiologic reactions (as defined in the ACR Manual on Contrast Media pages 103–104 [20]) from the data on mild, moderate, and severe allergic-like reactions. We assessed risk of bias in the nine final studies by using A Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions, or ACROBAT-NRSI (21).

Data Extraction

Two authors (B.A.H.and Z.F.) independently read each article that met inclusion and exclusion criteria and extracted the number of administrations; the numbers of mild, moderate, and severe reactions; and the number of deaths for each GBCA. For articles in which both immediate and delayed reactions were

Implication for Patient Care

- When patients with glomerular filtration rates greater than 30 mL/min per 1.73 m^2 and for whom there is clinical concern for allergic reactions require contrast material–enhanced MR imaging, it is reasonable to consider the issues of ionicity, protein binding, and macrocyclic versus linear chelate structure when selecting a GBCA.

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Abbreviations:
ACR = American College of Radiology
CI = confidence interval
GBCA = gadolinium-based contrast agent

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Guarantors of integrity of entire study, A.H.B., Y.Z., M.R.P.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content,D all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, all authors; clinical studies, Y.Z.; experimental studies, Y.Z.; statistical analysis, Y.Z., M.R.P.; and manuscript editing, all authors

Conflicts of interest are listed at the end of this article.

See also the editorial by Davenport in this issue.

Table 1

Characteristics of GBCAs

Characteristic	Gadodiamide (Omniscan)	Gadopentetate (Magnevist)	Gadobutrol (Gadovist)	Gadoxetate (Eovist)	Gadoterate (Dotarem)	Gadobenate (MultiHance)	Gadoteridol (ProHance)	Gadofosveset (Ablavar)
Chemical structure	Linear, nonionic	Linear, ionic	Macrocyclic, nonionic	Linear, ionic	Macrocyclic, ionic	Linear, ionic	Macrocyclic, nonionic	Linear, ionic
Distribution	Extracellular	Extracellular	Extracellular	Extracellular and hepatobiliary*	Extracellular	Extracellular and hepatobiliary*	Extracellular	Blood pool*
T1 relaxivity at 1.5 T ($sec^{-1} \cdot mol/L^{-1}$)								
Plasma (23)	4.3	4.1	5.2	6.9	3.6	6.3	4.1	19
Blood (24)	4.5	4.3	4.6	7.2	3.9	6.2	4.4	19
Osmolality (25) (mOsm/Kg)	650	1960	1603	688	1350	1970	630	1110
Viscosity (26,27) (mPas)	1.4	2.9	5.0	1.2	2.0	5.4	1.3	3.0
No. of articles	4	9	4	7	4	7	5	3
No. of injections	77802	342428	75995	14282	49196	114381	42097	797
No. of reactions per 10^4 injections								
Total	1.5 (0.7, 2.4)	5.2 (4.5, 6.0)	16 (13, 19)	20 (14, 28)	9 (6.5, 12)	17 (14, 19)	16 (13, 20)	91 (37, 168)
Mild	1.2 (0.55, 2.1)	3.9 (3.3, 4.6)	15 (12, 18)	17 (11, 25)	7.2 (5.0, 9.8)	13 (11, 16)	13 (9.4, 16)	77 (28, 149)
Moderate	0.25 (0.02, 0.73)	1.1 (0.81, 1.5)	0.75 (0.26, 1.5)	2.6 (0.63, 5.9)	1.0 (0.32, 2.1)	2.2 (1.4, 3.2)	2.77 (1.4, 4.6)	23 (16, 67)
Severe	0.16 (0.002, 0.57)	0.21 (0.09, 0.4)	0.57 (0.16, 1.2)	1.9 (0.33, 4.9)	1.2 (0.45, 2.4)	1.2 (0.65, 1.9)	1.8 (0.74, 3.3)	0 (0, 34)

Note.—Data in parentheses are 95% confidence intervals (CIs). Numbers in parentheses in row headings are reference numbers.

* Blood pool distribution and hepatobiliary excretion were derived from transiently binding serum albumin or other proteins (protein-binding agents) (28).

reported, data on the delayed reactions were excluded. All discrepancies in the data extractions between the two observers were resolved in consensus with a third reviewer (M.R.P., with 30 years of radiology research experience).

Classification of Adverse Events

All selected articles included use of the ACR Manual on Contrast Media system for classification of acute reactions as mild, moderate, or severe (17–20). Mild allergic-like reactions were self-limited, without evidence of progression and included limited urticaria, pruritus, limited cutaneous edema, limited itching or "scratchy" throat, nasal congestion, sneezing, conjunctivitis, and rhinorrhea. Moderate reactions were more pronounced, commonly required medical treatment, and included diffuse urticaria and/or puritis, diffuse erythema with stable vital signs, facial edema without dyspnea, throat tightness or hoarseness without dyspnea, wheezing, and mild bronchospasm without hypoxia. Severe reactions were potentially life-threatening, with risk of permanent morbidity or death if not treated appropriately, and included diffuse edema or facial edema with dyspnea, diffuse erythema with hypotension, laryngeal edema with stridor and/or hypoxia, wheezing and/or bronchospasm, substantial hypoxia, and anaphylactic shock (17–20).

Classification of GBCA Type

GBCAs were grouped according to their chemical structure and properties (Table 1) (22–28). Each GBCA was either macrocyclic (gadoterate, gadobutrol, and gadoteridol) or linear (all of the rest). GBCAs also were grouped according to ionicity. There were data on a single nonionic linear GBCA (gadodiamide), which was compared with four ionic linear GBCAs to assess the effect of ionicity. Three of the ionic linear GBCAs had moieties that transiently bound serum proteins (eg, albumin) that conferred high relaxivity and blood pool distribution (gadofosveset), high relaxivity and 50% hepatobiliary excretion (gadoxetate), and high relaxivity and 4% hepatobiliary excretion (gadobenate

Table 2

Nine Articles in which Immediate Reactions to GBCAs Were Reported

Article, Date of Publication, Study Period, and GBCA	No. of Injections	No. of Immediate Allergic-like Reactions			
		Total	Mild	Moderate	Severe
Prince et al, 2011 (2000–2009) [2]	158 796				
Gadodiamide	55 703	7	6	1	0
Gadopentetate dimeglumine	66 157	25	20	5	0
Gadobenate	33 114	34	24	7	3
Gadoteridol	3371	7	4	2	1
Gadoxetate	451	1	1	0	0
Morgan et al, 2011 (2007–2009), Gadoteridol [9]	28 078	40	30	6	4
Jung et al, 2012 (2004–2010) [7]	141 623				
Gadodiamide	15 959	2	1	0	1
Gadopentetate dimeglumine	42 323	26	22	2	2
Gadobenate	6361	14	12	1	1
Gadoterate	38 580	31	24	3	4
Gadobutrol	33 242	33	30	1	2
Gadoxetate	5158	6	4	1	1
Davenport et al, 2013 (2007–2012) [10]	105 607				
Gadodiamide	24	0	0	0	0
Gadopentetate dimeglumine	31 540	24	18	6	0
Gadobenate	66 152	123	107	11	5
Gadoteriol	5907	12	10	1	1
Gadoxetate	1948	2	1	1	0
Gadofosveset	36	1	1	0	0
Okigawa et al, 2014 (2006–2011) [11]	10 595				
Gadopentetate dimeglumine	3039	4	2	2	0
Gadotriol	3696	6	5	1	0
Gadoxetate	980	3	3	0	0
Gadoterate	2880	2	2	0	0
Bruder et al, 2015 (2007–2009) [12]	34 290				
Gadodiamide	6116	1	1	0	0
Gadopentetate dimeglumine	12 810	9	7	0	2
Gadobenate	706	2	2	0	0
Gadoterate	4235	4	4	0	0
Gadobutrol	9378	3	3	0	0
Gadoteridol	1045	2	2	0	0
Aran et al, 2015 (2007–2014) [13]	194 400				
Gadopentetate dimeglumine	184 218	90	64	23	3
Gadobenate	6236	14	8	4	2
Gadoxetate	3200	10	10	0	0
Gadofosveset	746	5	4	1	0
Power et al, 2016 (2010–2016) [14]	32 981				
Gadopentetate dimeglumine,	1535	0	0	0	0
Gadobutrol	30 373	96	92	3	1
Gadoxetate	1058	5	5	0	0
Gadofosveset	15	1	1	0	0
Granata et al, 2016 (2010–2014) [15]	10 608				
Gadopentetate dimeglumine	806	1	0	1	0
Gadobenate	1812	6	2	1	3
Gadoterate	3501	6	4	1	1
Gadobutrol	3002	3	2	1	0
Gadoxetate	1487	1	1	0	0

Note.—Dates in parentheses indicate the time period during which the study was performed. Numbers in brackets are the reference numbers for each study.

dimeglumine) (28). These three GBCAs were grouped together as ionic linear GBCAs with protein binding. To assess the effect of ionicity in a linear GBCA without the confounding effect of protein binding, we compared the linear nonionic GBCA (gadodiamide) with a linear ionic GBCA without protein binding (gadopentetate dimeglumine). To assess the effect of protein binding in linear GBCAs without the confounding effect of ionicity, we compared the linear ionic protein-binding GBCAs to the linear ionic non–protein-binding GBCA. To compare linear agents to macrocyclic agents without confounding from the property of protein binding, a group of linear GBCAs without protein binding (gadodiamide and gadopentetate dimeglumine) was compared with the macrocyclic group, none of which had protein binding. For further comparison of linear and macrocyclic GBCAs, with elimination of confounding effects of both protein binding and ionicity, a comparison of a nonionic linear (gadodiamide) GBCA with nonionic macrocyclic (gadobutrol and gadoteridol) GBCAs was performed.

Figure 1

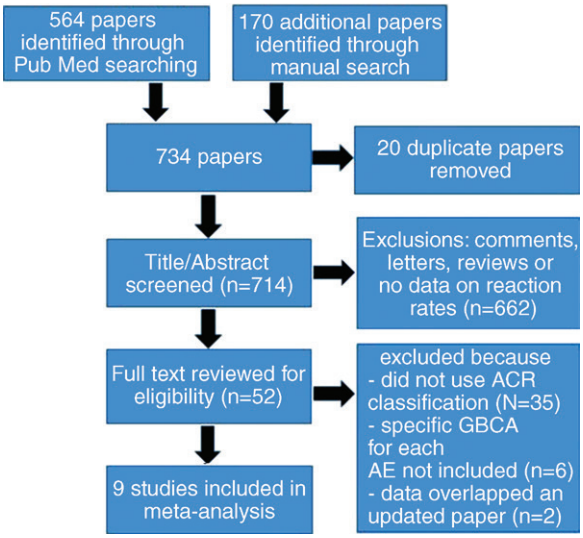


Figure 1: Flowchart shows the article search process. *AE* = adverse event

Statistical Methods

The mild, moderate, severe or fatal, and overall reaction rates; severe or fatal reaction rates; and moderate or severe or fatal reaction rates were compared among different GBCA groups as we have described. For each comparison, we only used data from the articles in which both types of GBCAs were investigated. Relative risk was estimated by using the Mantel-Haenszel type method

Table 3

Comparison of Immediate, Allergic-like Reactions to GBCAs Categorized according to Chelate Molecular Structure

Comparison	No. of Injections	Reaction Risk per 10^4 Injections*	Articles Included	Relative Risk*	Heterogeneity			
					Cochran *Q*	*P* Value	I^2 Value (%)	*P* Value
Linear nonionic vs linear ionic			(2,7,10,12)	0.19 (0.10, 0.36)	0.19	.98	0	<.00001
Linear nonionic	77 802	1.5 (0.74, 2.4)						
Linear ionic	471 888	8.3 (7.5, 9.2)						
Linear nonionic vs non–protein binding linear ionic			(2,7,10,12)	0.28 (0.14, 0.55)	0.39	.94	0	.0002
Linear nonionic	77 802	1.5 (0.74, 2.4)						
Linear ionic (non–protein binding)	342 428	5.2 (4.5, 6.0)						
Non–protein binding linear ionic vs protein binding linear ionic			(2,7,10–15)	0.33 (0.26, 0.41)	12.34	.09	43.3	< .0001
Linear ionic (non–protein binding)	342 428	5.2 (4.5, 6.0)						
Linear ionic (protein binding)	129 460	17 (15, 20)						
Non–protein binding linear vs macrocyclic			(2,7,10–12,14,15)	0.46 (0.26, 0.83)	15	<.02	61	.01
Linear (non–protein binding)	420 230	4.4 (3.8, 5.1)						
Macrocyclic	167 288	14 (12, 16)						
Linear nonionic vs macrocyclic nonionic			(2,7,10,11)	0.12 (0.05, 0.31)	2.7	.44	0	<.0001
Linear nonionic	77 802	1.5 (0.74, 2.4)						
Macrocyclic nonionic	118 092	16 (14, 19)						

* Data in parentheses are 95% CIs.

Table 4

Moderate Plus Severe (Including Fatal) Immediate Allergic-like Reactions to GBCAs

Comparison	No. of Injections	Reactions Risk per 10^4 injections*	Articles Included in Comparison	Relative Risk*	Heterogeneity			
					Cochran *Q*	*P* Value	I^2 Value (%)	*P* Value
Ionicity			(2,7,10,12)	0.20 (0.05, 0.76)	0.757	.860	0	.017
Linear nonionic	77 802	0.38 (0.07, 0.9)						
Linear ionic	471 888	1.9 (1.5, 2.3)						
Protein binding			(2,7,10–15)	0.42 (0.26, 0.68)	7.5	.27	20.5	.0004
Linear ionic (non–protein binding)	342 428	1.4 (1.0, 1.8)						
Linear ionic (protein binding)	129 460	3.3 (2.4, 4.4)						
Linear vs macrocyclic			(2,7,10,11)	0.19 (0.05, 0.66)	5.1	.08	60.5	.009
Linear nonionic	77 802	0.38 (0.07, 0.93)						
Macrocyclic nonionic	118 092	2.0 (1.3, 2.9)						

* Data in parentheses are 95% CIs.

Figure 2

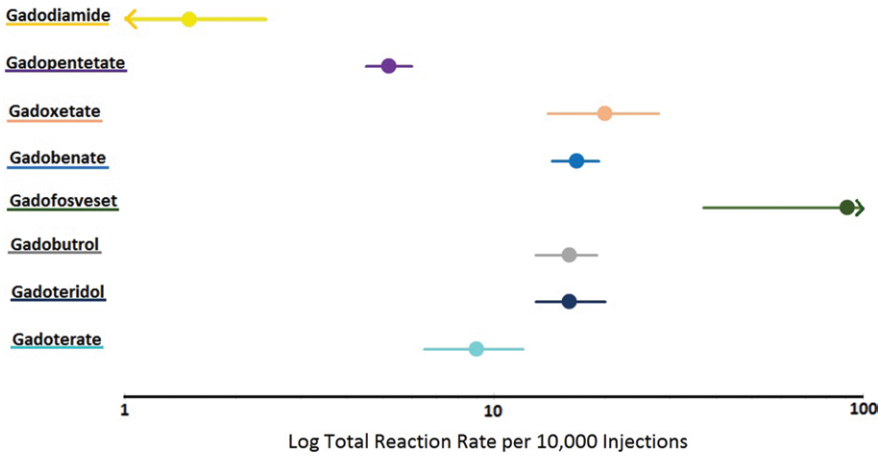


Figure 2: Graph shows rates of immediate mild, moderate, and severe allergic-like reactions to GBCA, combining data from all nine articles. Horizontal lines indicate 95% CIs.

of Rothman and Boice (29), and an χ^2 test was performed with the hypothesis that relative risk would equal 1. We considered a type I error of .05 as indicative of a significant difference ($P < .05$). We also conducted additional meta-analyses by comparing overall reaction rates between the GBCA with the lowest reaction rate and each of the other agents. For all meta-analyses, we performed heterogeneity assessment by using both the Cochran *Q* and I^2 statistics. A moderate heterogeneity among studies was determined as a *P* value of the Cochran *Q* less than 0.1 and an I^2 greater than 50%, and severe heterogeneity was considered with a *P* value of the Cochran *Q* less than .05 or an I^2 greater than 75%. Random effects were added when severe heterogeneity was detected (30,31). For all statistical calculations, we used software (StatsDirect statistical software version 3.0.198; StatsDirect, Altrincham, England).

Results

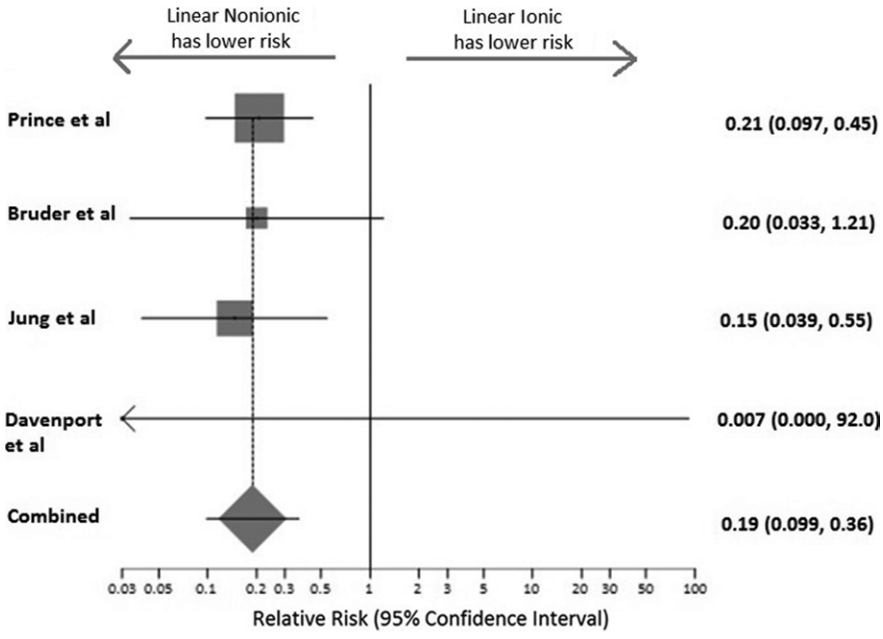
Nine articles met the criteria and included a total of 716978 GBCA administrations (Table 2, Fig 1), with 983 administrations reported to have resulted in immediate adverse reactions. Three articles reported only allergic-like reactions (7,10,14). The other six articles reported both allergic and physiologic reactions. In one of these (9), all physiologic reactions could be excluded without contacting the authors. In the remaining five articles (2,11–13,15) in which both allergic-like and physiologic reactions were reported, authors were contacted for clarification. In this way, 321 physiologic reactions were eliminated, leaving 662 allergic-like reactions (Table 2).

The overall rate of patients who had immediate allergic-like reactions was 9.2 per 10000 administrations and the overall rate of severe immediate allergic-like reactions was 0.52 per 10000 administrations. Breakdowns according to individual GBCA appear in Table 1 and Figure 2, and according to chemical structure in Tables 3 and 4. In this cohort, 81% (539 of 662) of reactions were mild, 13% (86 of 662) were moderate, and 6% (37 of 662) were severe.

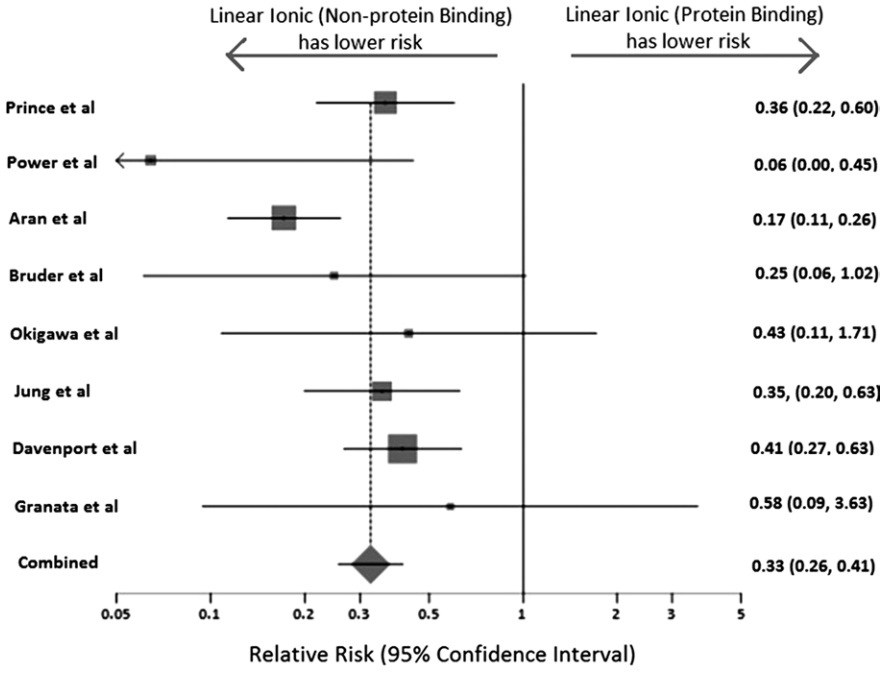
The nonionic linear GBCA, gadodiamide, had the lowest overall rate of immediate adverse reactions, at 1.5 per 10000 administrations, which was significantly less than that for linear ionic GBCAs, at 8.3 per 10000 administrations (relative risk, 0.19; $P < .00001$) (Fig 3a) and less than that for nonionic macrocyclic agents, at 16 per 10000 administrations (relative risk, 0.12; $P < .001$) (Fig 3d). These data and CIs are included in Table 3.

The nonionic linear GBCA also had the lowest rate of moderate and severe

Figure 3



a.

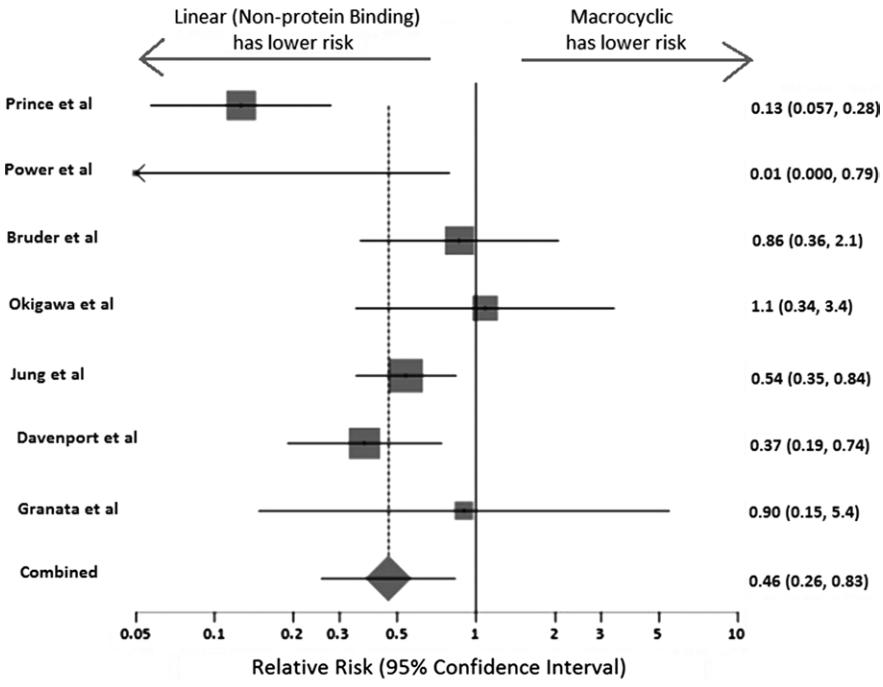


b.

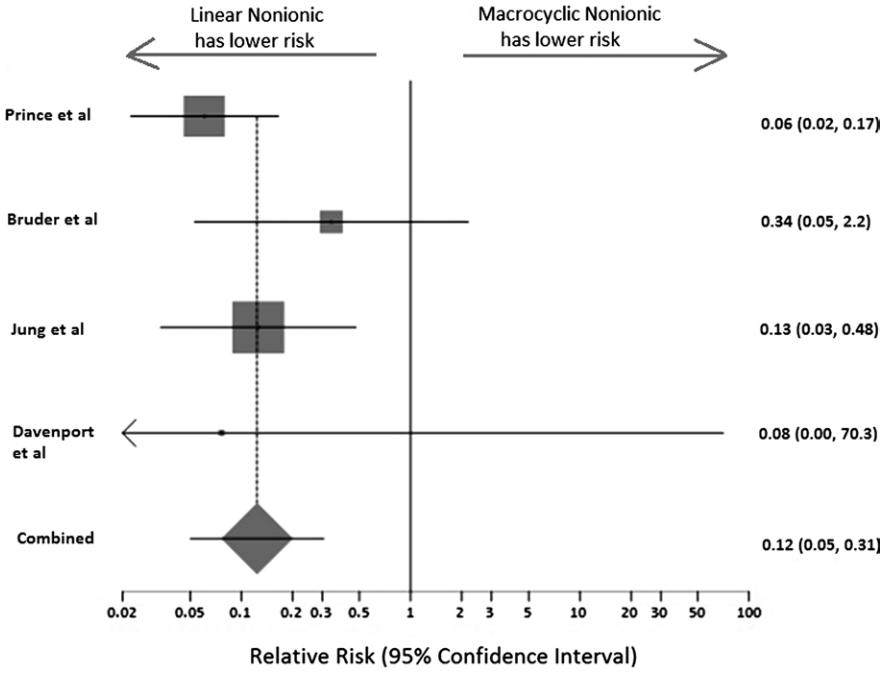
Figure 3: Forest plots show relative risk for immediate, allergic-like reactions to GBCAs. **(a)** Plot shows data for four articles in which total allergic-like reactions to linear ionic and linear nonionic GBCAs were were compared. **(b)** Plot shows data from eight articles in which linear ionic with protein binding and linear ionic without protein binding GBCAs were compared. *(Fig 3 continues).*

(including fatal) adverse reactions, at 0.38, compared with linear ionic GBCAs, at 1.9 per 10000 administrations (relative risk, 0.2; $P = .017$) (Table 4, Fig 4a). In the comparison of gadodiamide with each of the other GBCAs individually, on the basis of the relative risk of reaction, use of gadodiamide resulted in fewer total reactions, at 1.5 per 10000 injections, than did use of gadopentetate dimeglumine, at 5.2 per 10000 injections (relative risk, 0.27 [95% CI: 0.14, 0.55]; $P = .0002$) gadobenate at 17 (relative risk, 0.1 [95% CI: 0.05, 0.20]; $P < .0001$); gadoterate at nine (relative risk, 0.16 [95% CI: 0.05, 0.54]; $P = .003$); gadobutrol at 16 (relative risk, 0.16 [95% CI: 0.05, 0.54]; $P = .003$); and gadoteridol at 16 (relative risk, 0.07 [95% CI: 0.02, 0.18]; $P < .0001$) reactions per 10000 injections (Fig 2). A comparison to gadofosveset and gadoxetate with gadodiamide could not be performed because of the lack of articles in which gadodiamide was used with those GBCAs. Although gadofosveset had the highest overall rate of immediate allergic-like reactions at 91 (95% CI: 37, 168) per 10000 injections, it had the lowest number of administrations (only 797) and did not have any severe reactions (Table 1). Linear agents without protein binding had a lower reaction rate, at 4.4 (95% CI: 3.8, 5.1) per 10000 injections, compared with macrocyclics (also without protein binding), at 14 per 10000 injections (relative risk, 0.46; $P = .01$) (Table 3, Fig 3c). This comparison had moderate heterogeneity (Cochran Q, 15; $P < .02$; I^2, 61%) and was the only comparison that required the random effects model to mitigate heterogeneity, although the statistical significance of the difference did not change compared with that of the fixed effects model. Furthermore, a comparison in which we controlled for both ionicity and protein binding showed that nonionic linear GBCA had a lower relative risk compared with nonionic macrocyclic GBCAs for all reactions (0.12 [95% CI: 0.05, 0.31]; $P < .0001$) and for moderate and severe reactions (0.19 [95% CI: 0.05, 0.66], $P = .009$) (Fig 3d). The comparison of ionic linear GBCA without protein binding (gadopentetate dimeglumine) to ionic macrocyclic GBCA (gadoterate) involved a smaller number of injections and did not show a significant difference.

Figure 3 (continued)



c.



d.

Figure 3 *(continued).* **(c)** Plot shows data from seven articles in which linear without protein binding and macrocyclic (also without protein binding) GBCAs were compared. **(d)** Plot shows data from four articles in which linear nonionic and macrocyclic nonionic GBCAs were compared. Size of squares indicates relative weighting of studies. Horizontal lines indicate 95% CIs.

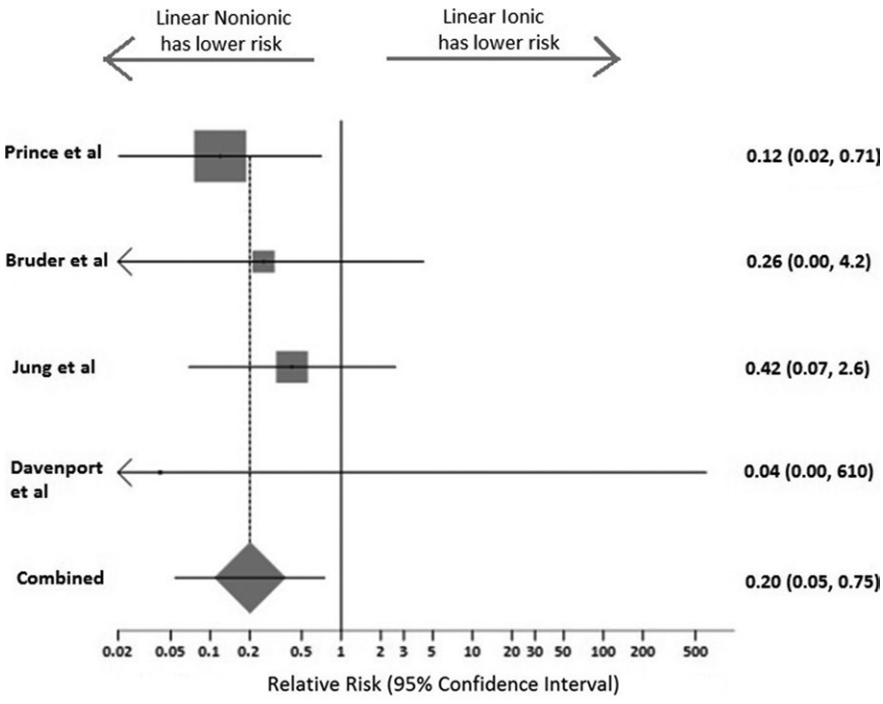
We also did not observe a difference between ionic macrocyclic and nonionic macrocyclic GBCAs.

All GBCAs with protein binding (gadoxetate, gadofosveset, and gadobenate) were linear ionic GBCAs. Protein binding was associated with a greater rate of reactions, at 17 (95% CI: 15, 20) per 10000 injections compared with gadopentetate dimeglumine, the one ionic linear agent without protein binding, at 5.2 (95% CI: 4.5, 6.0) per 10000 injections (relative risk, 3.1 [95% CI: 2.4, 3.8]; $P < .0001$) (Fig 3b). Moreover, the rate of severe or fatal reactions was greater for protein binding (gadoxetate, gadofosveset, and gadobenate) linear ionic GBCAs, at 1.23 (95% CI: 0.7, 1.9) per 10000 injections, compared with a non–protein-binding linear ionic GBCA (gadopentetate dimeglumine), at 0.21 (95% CI: 0.09, 0.04) per 10000 injections (relative risk, 6.3 [95% CI: 2, 20]; $P = .0021$) (Figs 3d, 4b).

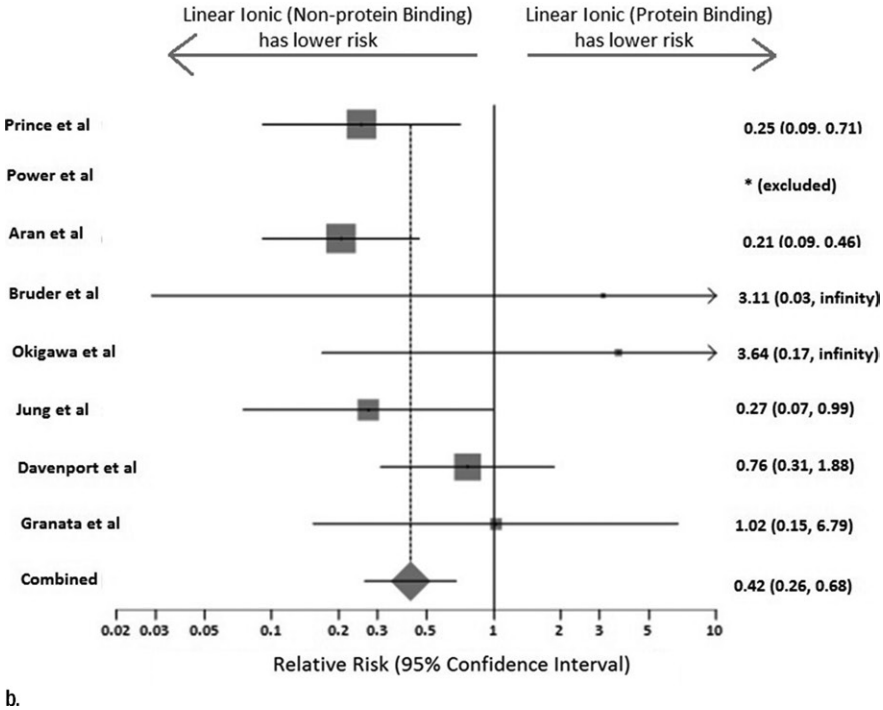
There were two deaths caused by severe reactions to GBCAs, with a rate of 2.7 per 1 million administrations. An ionic GBCA with protein binding, gadobenate dimeglumine caused one death, and the other death was related to a macrocyclic GBCA, gadobutrol.

By using ACROBAT-NRSI (21), we found a moderate risk of bias due to missing data in six articles. In two articles (12,14), data were missing on the type of GBCA that induced reactions. In five articles (2,11–13,15), data on physiologic and allergic reactions were initially pooled. Authors were contacted to resolve these biases. In one article (10), investigators reported data collection partially funded by industry. None of the other studies reported industry agreements related to the study, but eight of 67 authors reported industry agreements unrelated to the study. In seven articles, moderate bias due to confounding was present (eg, use of gadoxetate for liver MR imaging and different GBCAs for other indications). All nine studies had a low risk of bias in selection of cases into the study in the reported results, in measurement of outcomes, and finally a moderate risk of overall bias (Table 5).

Figure 4



a.



b.

Figure 4: Forest plots show relative risk for immediate, allergic-like reactions to GBCA that were moderate or severe (including fatal). **(a)** Plot shows data from four articles in which total allergic-like reactions to linear ionic and linear nonionic GBCAs were compared. **(b)** Plot shows data from eight articles in which linear ionic with protein binding and linear ionic GBCAs without protein binding were compared. *(Fig 4 continues).*

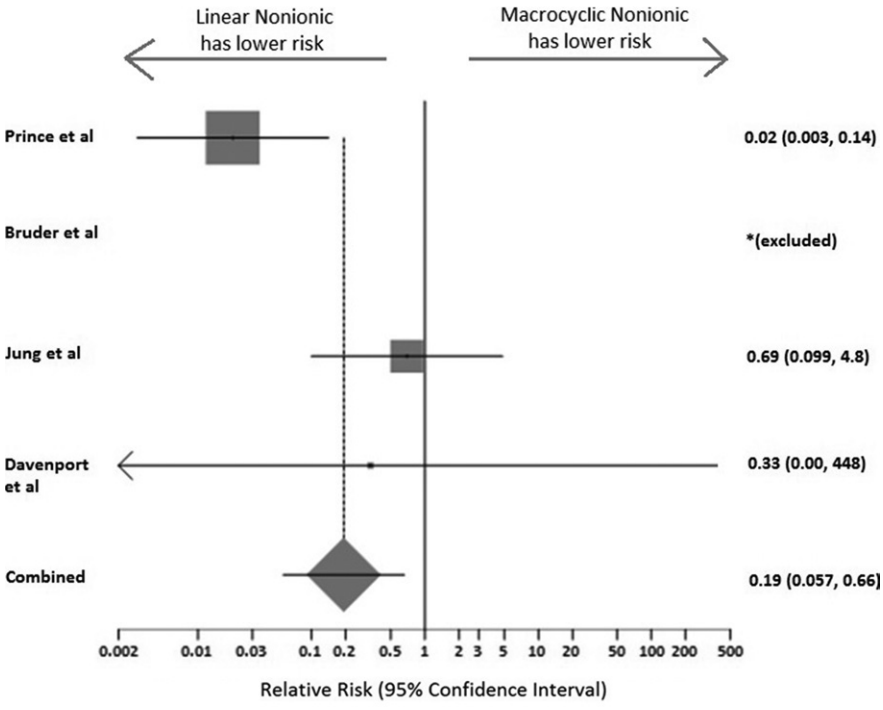
Discussion

The extraordinarily low rate of immediate reactions to GBCAs and the rare incidence of fatal reactions has led to a generalization that all GBCAs are safe, especially compared with iodine-based contrast media (1–5). Differences in reaction rates between GBCAs have been hypothesized but are difficult to prove due to the large number of patients needed to show statistically significant differences for such rare events (2,7,9–15,32). These data combined from nine well-designed studies (2,7,9–15) including 716 978 GBCA administrations show a higher rate of reactions associated with the properties of ionicity, protein binding, and cyclic structure.

Ionic agents automatically separate into fragments, one positively charged and one negatively charged when they are injected into the blood stream, which doubles the number of particles in solution, doubling the osmolality and raising the viscosity, which may contribute to a higher reaction rate (33–35). Thus, it is not surprising that the GBCA with the lowest rate of immediate allergic-like reactions was nonionic, and this property is well established as conferring a lower rate of reactions for iodine-based contrast agents (1,36–42). No effect of ionicity was observed for macrocyclic agents, although there are fewer data on macrocyclic GBCAs.

The favorable low reaction rate for nonionic linear GBCAs stands in contrast to their worrisome lower kinetic stability, which is thought to increase the risk of nephrogenic systemic fibrosis and gadolinium retention in the brain (22,43–45). Because risk of development of nephrogenic systemic fibrosis can be decreased by screening renal function before administration, nonionic linear agents may be considered for patients with normal renal function who are at increased risk of allergic reactions. This may include patients with asthma, severe allergies, or a history of prior reaction to other GBCAs. It may also be considered at centers that lack an immediately available code team to help treat severe reactions (eg, outpatient imaging centers), which can be

Figure 4 (continued)



c.

Figure 4 *(continued).* **(c)** Plot shows data from four articles in which linear nonionic and macrocyclic nonionic GBCAs were compared. Size of squares indicates relative weighting of studies. Horizontal lines indicate 95% CIs.

beyond the ability of a single radiologist to handle.

Protein binding may confer the favorable qualities of higher GBCA relaxivity, hepatobiliary excretion, or sequestration within the blood pool (28). Our observation of a higher rate of reactions for GBCAs with protein binding is also consistent with those of prior reports (46).

Macrocyclic GBCAs had a greater rate of reactions compared with linear GBCAs, which was confirmed in a comparison of nonionic linear to nonionic macrocyclic GBCAs that was controlled for ionicity and protein-binding effects. This greater rate of allergic-like reactions must be considered with other aspects of safety including the favorable stability of macrocyclic agents that reduces risk of nephrogenic systemic fibrosis and gadolinium retention in the brain (43,47,48). An overall assessment of safety should not focus on a single GBCA property.

The two deaths reported in these nine publications correspond to a rate of 2.8 per 1 million administrations. Both deaths involved GBCAs with factors contributing to higher risk (2,7). Gadobenate is ionic and protein binding. Gadobutrol is macrocyclic. It is also important to consider that death due to an adverse reaction is a multifactorial event. It depends on the skills of the hospital staff in differentiating the symptoms of anaphylaxis from other differential diagnoses such as a vasovagal reaction or panic attack and in responding quickly before the reaction becomes life threatening (6,49–54). The use of power injection may be a risk factor if it delays recognition and treatment of reactions. In at least one of these deaths, the patient received GBCA by means of power injection (2), which contributed to a delay in diagnosis. Data on the method of injection for the other death were not available (7). When a power injector is used, the

Table 5

Risk of Bias in the Included Studies

Type of Bias	Prince et al (2)	Morgan et al (9)	Jung et al (7)	Davenport et al (10)	Okigawa et al (11)	Bruder et al (12)	Aran et al (13)	Power et al (14)	Granata et al (15)
Bias due to confounding	Moderate	Low	Moderate	Moderate	Moderate	Low	Moderate	Moderate	Moderate
Bias in selection of cases into the study	Low	Low	Low	Low	Low	Low	Low	Low	Low
Bias due to missing data	Moderate	Moderate	Low	Low	Moderate	Moderate	Moderate	Moderate	Moderate
Bias in measurement of outcomes	Low	Low	Low	Low	Low	Low	Low	Low	Low
Bias in selection of the reported result	Low	Low	Low	Low	Low	Low	Low	Low	Low
Bias due to conflict of interest	Moderate	Low	Low	Moderate	Low	Low	Low	Moderate	Low
Overall bias	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate

close-proximity patient monitoring that automatically occurs with hand injections should not be allowed to lapse.

Limitations of this meta-analysis included the retrospective analysis of data, which may have created a selection bias, and a dependence on meticulous record keeping for data accuracy. It was not possible to control for temporal biases, such as the Weber effect (10,55), because data on when each GBCA was used at each institution were not available. However, combining data from countries with different GBCA introduction dates (Korea, Japan, European countries, and the United States) with data collections spanning from 2000 to 2016 was expected to minimize temporal biases that might have been present.

Not all of the GBCAs were used by all of the authors, so differences in how each center reported events could have biased the results. We mitigated this risk by requiring that all articles involved the use of the ACR classification system for contrast material reactions, and we contacted authors to eliminate physiologic reactions. Eliminating physiologic reactions reduced heterogeneity. The limitation of study heterogeneity was also mitigated by using a random effects model when Cochran heterogeneity was high. Only one comparison required use of the random effects model due to high heterogeneity, and when we also used a fixed effects model for that comparison, the significance did not change. There was a variation in the number of subjects per study, ranging from 10608 to 194400, which could have overweighted the effect of larger studies. Finally, in spite of the large number of GBCA administrations, the very low incidence of moderate and severe reactions limited the statistical power for their evaluation.

In conclusion, by combining data from nine studies of immediate reactions to GBCA we showed that protein binding, macrocyclic structure, and ionicity are associated with higher rates of allergic-like adverse events.

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