OPEN

10 Years of Nephrogenic Systemic Fibrosis

A Comprehensive Analysis of Nephrogenic Systemic Fibrosis Reports Received by a Pharmaceutical Company from 2006 to 2016

Jan Endrikat, MD, PhD,† Susan Dohanish, RA,‡ Nicolas Schleyer, MA,* Susanne Schwenke, PhD,§ Sheela Agarwal, MD,|| and Thomas Balzer, MD, PhD||*

Objectives: The aim of this study was to critically assess the evaluation and categorization process for nephrogenic systemic fibrosis (NSF) based on reports received by Bayer from 2006 to 2016.

Materials and Methods: A total of 779 NSF reports received by Bayer globally from 2006 to 2016 were included in the analysis. Arlington Medical Resources provided gadolinium-based contrast agent (GBCA) market share. Reports were conservatively categorized based on the Cowper/Girardi criteria. A statistical model simulated the impact of market share and market introduction on the number of unconfounded reports.

Results: For all reports, reported onset of disease ranged from 1996 and 2012. Of 779 reports, 325 involved a Bayer product only, 208 involved only products from other companies (or unknown GBCA), and 246 involved both Bayer and non-Bayer products. Most of all reports (86%) originated from the United States.

Through 2006, Magnevist and Omniscan dominated the US market (>80% combined market share). All other GBCAs with fewer NSF reports comprised the remaining combined market share of less than 20% or were introduced after May 2007, after safety recommendations came into effect.

A total of 563 reports (220 single-agent and 343 multiagent reports) involved Magnevist. In at least 150 of the 343 reports, a different GBCA (Omniscan, 118; OptiMARK, 15; MultiHance, 6; and macrocyclic agent, 11) showed the closest temporal relationship to onset of NSF-like symptoms.

The simulation model demonstrated that patients receiving a GBCA with lower market share and late market introduction are less likely to be observed in an unconfounded setting.

Conclusions: Year of market introduction, as well as US market share in 2000 to 2007, greatly influenced the absolute number of NSF reports for each GBCA, their a priori probability to cause NSF, as well as their a priori probability to be associated with unconfounded cases of NSF. Variability in case interpretation and pharmacovigilance approaches also influence the absolute number of unconfounded cases and should therefore not be used for comparative risk assessments. This should be primarily based on objective product parameters such as structure, stability, pharmacokinetics, and dose.

Key Words: NSF, GBCAs, Cowper/Girardi criteria

(*Invest Radiol* 2018;53: 541–550)

Received for publication December 21, 2017; and accepted for publication, after revision, February 7, 2018.

From the *Bayer AG, Radiology, Berlin, Germany; †Department of Gynecology, Obstetrics and Reproductive Medicine, University Medical School of Saarland, Homburg/Saar, Germany; ‡Bayer AG, Pharmacovigilance Benefit-Risk Management, Whippany, NJ; §SCO:SSiS Statistical Consulting, Dr. C. Schwenke, Berlin, Germany; and ||Bayer AG, Radiology, Whippany, NJ.

Conflicts of interest and source of funding: All authors are employees of Bayer AG, except for Susanne Schwenke. The study was funded by Bayer AG.

Correspondence to: Jan Endrikat, MD, PhD, Bayer AG, Müllerstr. 178, 13353 Berlin, Germany. E-mail: jan.endrikat@bayer.com.

ISSN: 0020-9996/18/5309–0541
DOI: 10.1097/RLI.0000000000000462

Nephrogenic systemic fibrosis (NSF) was first described by Cowper et al in 2000,[1] when they reported on 15 renal dialysis patients dating back to 1997 who had developed a scleromyxedema-like condition characterized by thickening and hardening of the skin of the extremities. Nephrogenic systemic fibrosis is a rare but serious disease that affects primarily the skin and joints and less commonly can involve the internal organs (eg. heart, lungs, liver and muscles).

The first link between NSF and gadolinium-based contrast agents (GBCAs) was suggested in 2006, when Grobner noted the development of skin symptoms in 5 patients with end-stage renal disease 2 to 4 weeks after they underwent contrast-enhanced magnetic resonance angiography with Omniscan.[2,3] Subsequent case analyses have demonstrated that most patients who develop NSF do so within 3 to 6 months of GBCA exposure.[4]

Nearly all NSF patients experience severe renal impairment (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2), usually requiring dialysis or renal transplantation, or acute kidney injury. Interestingly, the converse is not true: most patients with severe renal impairment who receive even multiple doses of GBCAs do not develop NSF, implying the presence of additional risk factor(s) necessitating development of the disease. Multiple cofactors for the development of NSF have been proposed including metabolic acidosis,[2] vascular surgery,[2] or treatment with erythropoietin,[5] although no definitive or comprehensive list of such underlying etiologies is yet understood.

The European Medicines Agency (EMA)[6] and the European Society of Urogenital Radiology[7] defined risk categories for GBCAs with regard to NSF, classifying the macrocyclic GBCAs Gadovist (brand name in United States: Gadavist), Dotarem, and ProHance as having the lowest risk for NSF development. In May 2007, the Food and Drug Administration (FDA) issued a boxed warning in the product labeling of all GBCAs, highlighting the risk of NSF in patients with acute/chronic severe kidney disease (GFR <30 mL/min/1.73 m^2) or acute kidney injury.[8]

One key criterion in the risk classification of the different GBCAs by the authorities was the number of single-agent ("unconfounded") reports.[6,8] Moreover, the *ACR Manual for Contrast Media*, which is widely used by radiologists as a basis for practice guidelines, lists single-agent reporting as their underlying rationale for eGFR testing requirements.[9] Therefore, this analysis aims to provide further insights into these report numbers, which are frequently also cited for regulatory as well as promotional purposes, and to discuss methodological aspects that are of potential relevance for the appropriate interpretation of these numbers. In particular, the following aspects were considered:

1. Year of market introduction and market share of specific GBCAs in the country from where the reports originated;
2. Additional evaluation of multiagent reports with respect to temporal relationship to NSF onset and a critical discussion of the current practice to solely consider single-agent reports;
3. Discussion of potential sources for variability in reporting standards of different companies using the Cowper/Girardi criteria as the basis for assessment of individual reports of NSF.

MATERIAL AND METHODS

Database

The dataset comprised all reports received by Bayer between 2006 and 2016 globally. Duplicate reports and reports with no NSF diagnosis were not included.

Case Reporting

Bayer's Pharmacovigilance Department receives reports of potential adverse drug reactions for all of the company's products globally. In general, adverse drug reaction reports are received from health care professionals, regulatory authorities, patients/consumers, as well as from searches of the scientific literature.

For NSF in particular, the company received most of its reports related to litigation procedures in the United States. Lawsuits would frequently name the manufacturers whose products were more likely to be possibly used, given the historically poor documentation of the specific brand of GBCA administered.

Data Gathering

The pharmacovigilance department comprehensively evaluated all incoming reports for documentation pertaining to GBCA use (including brand, dose, indication, and date of administration), clinical symptoms, laboratory values, and histopathology reports. Repeated queries on all incomplete or missing information were sent to the reporting source using a targeted questionnaire, or in the case of litigation-related reports, the information was sought via subpoena of the patients' medical records.

Case Classification

Once all available information was gathered, each report was categorized as a "single-agent" or "unconfounded" report[7] if it could be confirmed that no additional brand of GBCA was administered to the patient or as "multiagent" or "confounded" report[7] if more than 1 brand of GBCA was documented.

NSF Diagnosis

Finally, Bayer pharmacovigilance personnel used the information obtained from biopsy reports, detailed history of GBCA administration, medical history, and detailed history of the emergence of clinical signs and symptoms, to determine whether the case met the established Cowper/Girardi clinico-histopathological criteria for a diagnosis of NSF (Cowper/Girardi positive reports).[10] Although Broome et al[4] suggested that most NSF occurs within 3 months of the last GBCA administration, Bayer conservatively considered an 18-month onset latency as positive for a temporal association.

In the case of unclear or incomplete information, the most conservative assumption was applied to give the original reporter the benefit of the doubt and to not underestimate the number of cases. It is important to note that this methodology developed and implemented by Bayer is not necessarily the industry standard; there might be legitimate but slightly different processes or criteria applied by other institutions or companies.

Because of privacy regulations and internal Bayer policies, the company is not allowed to disclose individualized pharmacovigilance data to noncompany personnel. Therefore, an independent internal audit of all cases referenced in this manuscript was conducted for data verification.

Market Research

To estimate global use, annual market shares of GBCAs were obtained from Arlington Medical Resources, USA,[11] and complemented with additional sales data from Bayer and IMS.

Simulation Model

A simulation was performed according to Michel and Blenk[12] based on the market shares of the 5 available GBCAs for the years 1997 to 2006. Data for 100,000 patients was simulated such that the number of exposures per patient followed a Poisson distribution with a mean of 4 exposures. Time points of exposures reflected the increase in total numbers of exposures across the 10 years by means of a multinomial distribution. Days in the respective years were drawn randomly

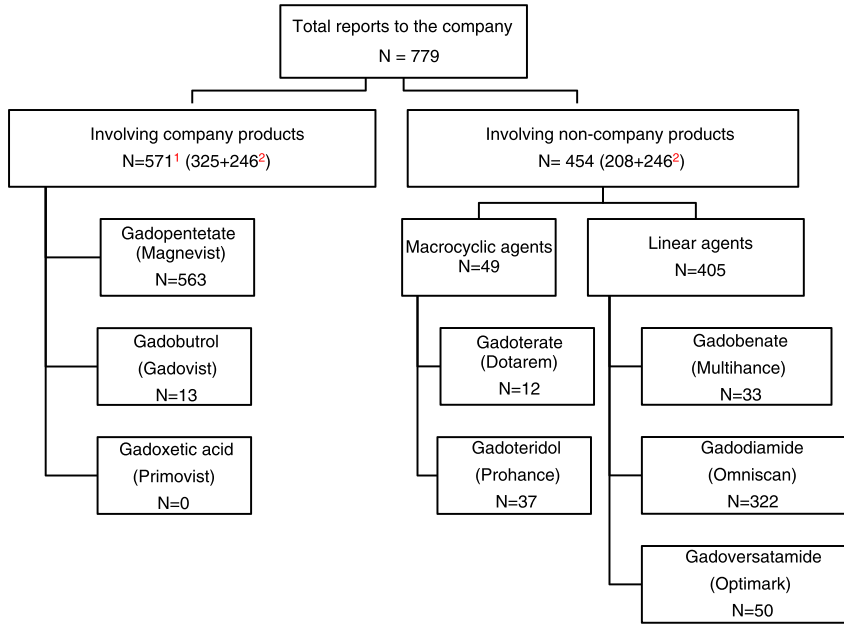

FIGURE 1. Total NSF reports to Bayer (by December 31, 2016).[1] In 5 of the 571 reports involving Bayer products, patients received both Magnevist and Gadovist, and these reports are counted for both products (ie, 5/563 patients who received Magnevist also received Gadovist, and 5/13 patients who received Gadovist also received Magnevist).[2] In 246 of the reports involving non-Bayer products, patients were also reported to have received a Bayer product. Duplicate reports and reports that were confirmed to have no Bayer products administered and no "unknown" GBCAs that could potentially be a Bayer product were subsequently deleted from the database.

from a uniform distribution. The treatments were determined using a multinomial distribution reflecting the market shares of the products for the respective year. In cases of a second exposure within 365 days, the previous treatment had an increased chance of 80% to be drawn again, following the approach by Michel and Blenk.[12]

RESULTS

The dataset analyzed consisted of 779 reports of potential NSF cases received from 2006 to 2016. The earliest disease onset dated back to 1996, based on undocumented patient recollection. A total of 325 reports involved 1 Bayer product only, 208 reports involved only noncompany or unknown products, and 246 reports involved both Bayer products as well as GBCAs manufactured by other companies. Most of Bayer's reports involved the linear ionic GBCA Magnevist (n = 563), followed by the non-Bayer linear nonionic GBCA Omniscan (n = 322) (Fig. 1).

After more than 145 million administrations of Magnevist (December 31, 2017, >150.9 million), 563 reports were received in which Magnevist administration was reported. Of these, 343 were multiagent reports and 220 were single-agent reports. Seventy-four of the single-agent reports met the Cowper/Girardi criteria as being "consistent with" or "diagnostic of" NSF (Fig. 2).

After more than 32 million administrations of Gadovist (December 31, 2017, >47.3 million), 13 reports were received with reported administration of Gadovist. Eight of these were multiagent reports and 5 were single-agent reports. Three of the single-agent reports were diagnostic of/consistent with NSF based on the Cowper/Girardi criteria (Fig. 3).

After more than 3.6 million administrations of Primovist (Eovist in the United States) (December 31, 2017, >4.6 million), no report of NSF or NSF-like symptoms has been received from any source.

Most of Magnevist NSF reports came from 3 countries: United States, Germany, and Denmark. Most of all reports (485/563 [86%]), of single-agent reports (191/220 [87%]), and of Cowper/Girardi positive reports (68/74 [92%]) were from the United States. More than half of all US reports were litigation related.

In comparison with the United States, other countries with large market shares of Magnevist during this same time period had very few reports. Notably, only 6 single-agent Cowper/Girardi positive reports arose from Europe and no reports originated from Canada, Japan, or other regions with large market shares of Magnevist (Table 1).

The number of Magnevist NSF reports increased steadily from 1996 to 2006 and declined sharply after the FDA box warning in 2007. In each year, most of all reports, single-agent reports, and Cowper/Girardi positive reports came from the United States. The last global disease onset was in 2012, the last in the United States, in 2010 (Fig. 4).

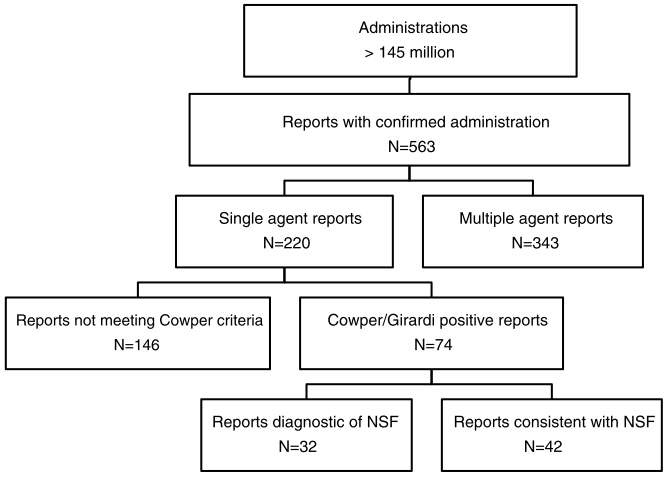

FIGURE 2. NSF reports involving Magnevist (by December 31, 2016). Bayer received its first MV NSF report in 2006 – however, the reported onset dates go back to 1996.

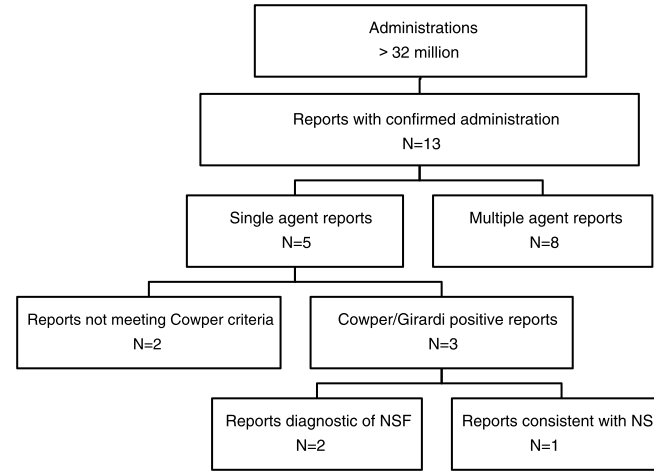

FIGURE 3. NSF reports involving Gadovist (Gadavist) (by December 31, 2016).

From 1996 to the end of 2006, Magnevist and Omniscan dominated the US market, with a combined market share of greater than 80%. In 2006, Magnevist had a market share of greater than 50%, and Omniscan, greater than 30%. The other US-approved GBCAs each had US market shares of 10% or lower, that is, ProHance, less than 6%; OptiMARK, less than 2%; and MultiHance, less than 1%. Neither Primovist, Gadovist, or Dotarem was marketed in the United States at that time (approved in 2008, 2011, and 2013, respectively). When looking at NSF disease onset, symptom onset peaked in 2006, 1 year before the introduction of the boxed warning, with 17 single-agent Cowper/Girardi positive reports recorded. Case reports with new onset fell drastically after awareness based on the Grobner publication[2] and implementation of the FDA warning[8] (Fig. 5).

TABLE 1. Magnevist NSF Reports by Country, 1996–2016

Country	Reports With Reported Administration	Single Agent Reports	Cowper/Girardi Positive Reports
Austria	4	–	–
Belgium	2	1	–
Bermuda	1	–	–
Canada	5	2	–
Denmark	11	4	–
France	3	1	–
Germany	30	12	4
United Kingdom	2	1	–
Ireland	3	3	1
Italy	1	1	1
Japan	9	1	–
The Netherlands	2	–	–
Norway	3	2	–
Spain	1	1	–
Switzerland	1	–	–
United States	485 (350)*	191 (104)*	68 (49)*
Σ	563	220	74

*Litigation-related cases in the United States in brackets.

NSF indicates nephrogenic systemic fibrosis.

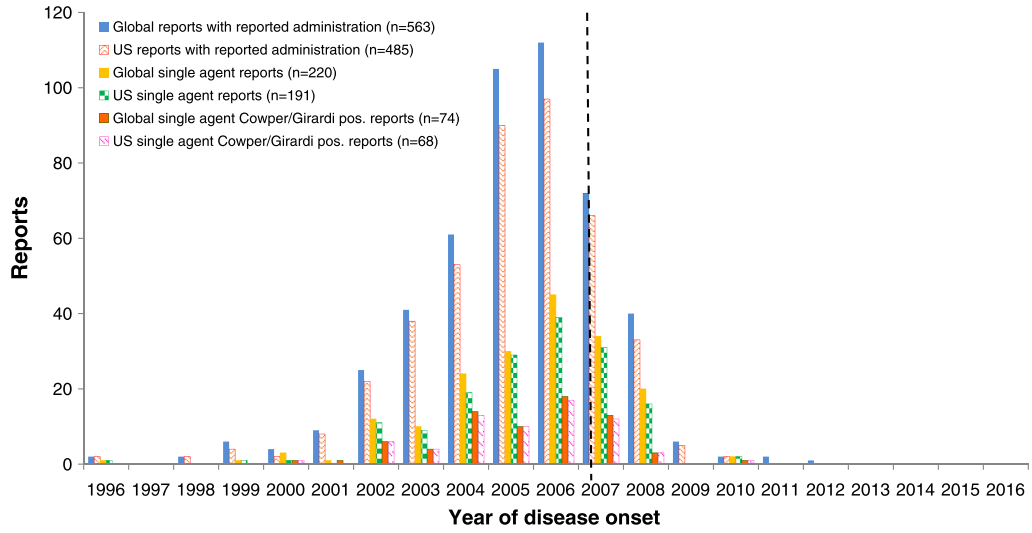

FIGURE 4. Number of global and US Magnevist NSF reports by year of disease onset. Vertical dotted line indicates the introduction of the Box Warning by the FDA, May 2007.

Of the 563 reports with Magnevist administration, 343 were multiple-agent reports. In this group of multiagent reports, at least 150 reports were identified in which a noncompany product showed the closest temporal association to NSF onset. These reports were forwarded as a courtesy to the other manufacturers. In 93% of these reports, the product used in closest temporal relationship to the development of NSF was a different linear agent: Omniscan (n = 118), OptiMARK (n = 15), or MultiHance (n = 6). In 11 reports, a macrocyclic GBCA was administered in closest temporal association to the onset of NSF-like symptoms (ProHance, n = 6; Gadovist, n = 2; Dotarem, n = 3). Most reports were from the United States (Table 2). In some reports, the product administered in closest temporal association to NSF onset remained unknown.

Tables 3 to 5 show Magnevist cases where another GBCA was administered in closest temporal association to onset of symptoms in detail. Most patients developed NSF within 6 months or less after administration of this other GBCA: For Omniscan, these were 94 of 118 (79.7%); for OptiMARK, 9 of 15 (60%) (Table 3); and for MultiHance, 3 of 6 (50%) (Tables 3 and 4). For the 11 cases where a macrocyclic agent was administered in closest temporal association, in 5 (45%) cases, the NSF onset occurred within 6 months of macrocyclic administration (Tables 3 and 5). In comparison, 41 of 74, or 55%, of Magnevist single-agent Cowper/Girardi positive patients experienced NSF within 3 months of the last Magnevist administration.

Of 100,000 simulated patients, 73,426 (73.4%) patients were observed in a confounded setting, whereas 26,574 (26.6%) were observed in an unconfounded setting. Of 84,752 simulated patients who were treated with Magnevist, 80.2% were in a confounded setting. Products with single digit market shares showed more than 94% of their NSF reports in a confounded setting (Table 6).

DISCUSSION

After the accumulation of 10 years of knowledge on NSF, Bayer performed an in-depth analysis of all reported NSF cases and established a contextual framework through which these cases could be discussed.

The goal of this analysis was to incorporate less widely discussed aspects for NSF risk assessment, such as (1) the year of market introduction and the market share of the GBCAs, (2) the interpretation of multiagent reports with special focus on the sequence of previous

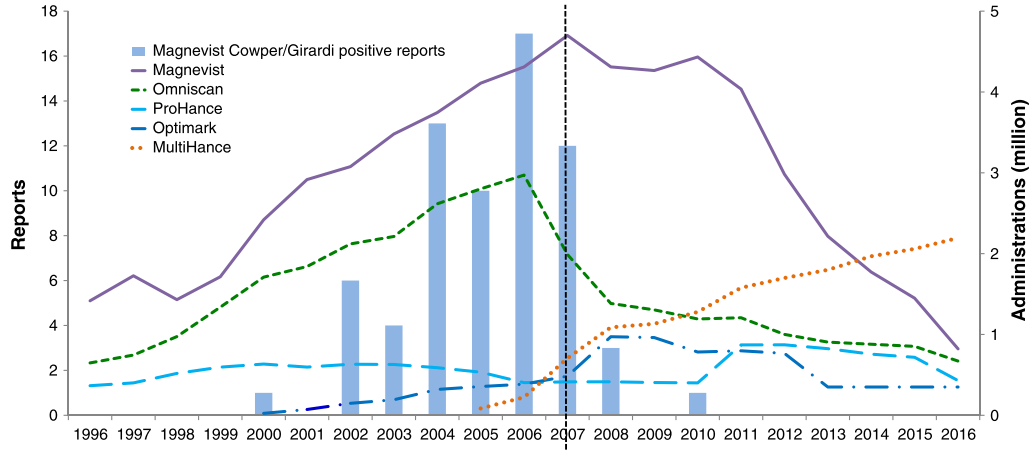

FIGURE 5. US annual GBCA administrations (lines, right ordinate) and US Magnevist single agent Cowper/Girardi positive reports (by NSF onset date) (n = 68) (columns, left ordinate). Vertical dotted line indicates the introduction of the Box Warning by the FDA, May 2007. Not included as introduced into the market after May 2007: Primovist (2008), Gadavist (2011), Dotarem (2013).

TABLE 2. Magnevist Multiple Agent Reports (n = 343), 1988–2016

GBCA	Number of GBCA Administrations*	Closest Temporal Association of GBCA to NSF Onset Globally (n = 343) (n = 150 for Non-Magnevist and Non-unknown GBCA)	Closest Temporal Association of GBCA to NSF Onset, United States Only (n = 304)
Gadopentetate dimeglumine (Magnevist)	2264	112 (32.7%)	99 (32.6%)
Gadodiamide (Omniscan)	749	118† (34.4%)	104 (34.2%)
Gadoversetamide (OptiMARK)	73	15† (4.4%)	15 (4.9%)
Gadobenate dimeglumine (MultiHance)	44	6† (1.7%)	6 (2.0%)
Gadoteridol (ProHance)	49	6† (1.7%)	4 (1.3%)
Gadobutrol (Gadovist)	7	2† (0.6%)	0 (0%)
Gadoterate meglumine (Dotarem)	21	3† (0.9%)	0 (0%)
Unknown GBCAs or NSF onset predated all known GBCAs	791	81 (23.6%)	76 (25.0%)

*Most reports include numerous GBCA administrations; therefore, multiple agents per report (n = 343) were possible. See examples on Tables 5 and 6.

†Sum up to n = 150.

GBCA indicates gadolinium-based contrast agent; NSF, nephrogenic systemic fibrosis.

administration of other GBCAs, and (3) potential differences in evaluation and reporting standards by different companies.

First and most basically, NSF report numbers need to be seen in the context of utilization rate and dosing: Magnevist was the first and for a time the only GBCA available worldwide. Magnevist had the highest market share (>50%) in the United States until May 2007 and also some years beyond. In the 74 Cowper/Girardi positive reports (Fig. 2), the severely renally impaired patients received multiple (up to 19) and/or high doses (with individual doses as high as 0.62 mmol/kg) of the contrast medium, sometimes for unapproved indications.

Until 2007, other GBCAs than Magnevist and Omniscan had a comparably low US market shares (ProHance, Optimark, and MultiHance—all below 10%) or were not approved in the United States at that time (Primovist, Gadovist, and Dotarem) (Fig. 5).

As is confirmed by a simulation model, the different numbers of NSF cases for the different GBCAs are not unexpected, given the very low prevalence of NSF. Because of the consistently high market share of higher than 50% over the simulated 10 years, Magnevist was the agent that was observed most often in an unconfounded setting (63.1% of all unconfounded cases). Especially agents with a late introduction into the market (MultiHance, Primovist, Gadovist, and Dotarem) and/or a low market share (Optimark and ProHance, both <10%) had a markedly lower chance to be observed in an unconfounded setting of 2 or more exposures.

Therefore, any comparison of report numbers of GBCAs or "ratios of reports/administrations" over time since market introduction is significantly biased and hence misleading, as this would not take into account the market presence in different countries before and after May 2007. Therefore, those numbers need to be used with appropriate and utmost caution and are not suited for reliable differential risk assessments between GBCAs.

The reports that Bayer has received involving noncompany GBCAs are presumed to encompass a small sample of reports for those products. But in general, data published by the health authorities are supportive of the trends seen in the Bayer internal data. An EMA report published in 2010[6] and by the FDA in 2011[8] list single-agent reports of various GBCAs in relation to total administrations. According to the FDA's table (January 21, 2011) with US data through December 2009, more than 105 million administrations of Magnevist triggered 179 single-agent reports, whereas for Omniscan, more than 49 million administrations triggered 505 single-agent reports. Two single-agent reports were each listed for MultiHance and ProHance. Gadavist and Dotarem were not on the US market at that time.[8] The EMA's table shows a similar pattern.[6]

TABLE 3. Magnevist Multiple Agent Reports With Other GBCAs Showing Closest Temporal Relationship to NSF Onset: Time Elapsed Between Last GBCA (Non-Magnevist) Administration Versus Last Magnevist Administration and Symptom Onset

		Time Elapsed After Last GBCA Administration			Time Elapsed After Last Magnevist Administration		
GBCA	Total No. of Reports	≤6 mo	>6 mo	Unknown	≤6 mo	>6 mo	Unknown/Other
Omniscan	118	94	20	4	20	35	63*
OptiMARK	15	9	6	0	1	8	6†
MultiHance	6	3	3	0	1	3	2‡
Gadovist	2	2	0	0	0	2	0
Dotarem	3	1	2	0	0	2	1§
ProHance	6	2	4	0	0	6	0

*In 26 of these Omniscan cases, symptoms predated Magnevist administration; in 25 cases, no Magnevist was documented.

†In 4 of these OptiMARK cases, symptoms predated Magnevist administration; in 1 case, no Magnevist was documented.

‡In these 2 MultiHance cases, no Magnevist was documented.

§In this Dotarem case, no Magnevist was documented.

GBCA indicates gadolinium-based contrast agent; NSF, nephrogenic systemic fibrosis.

TABLE 4. Magnevist Multiple Agent Reports in Which the Linear Agent MultiHance was Administered in Closest Temporal Relationship to NSF Onset

Country (Source)	Patient	Medical History	GBCA History and Diagnosis	Elapsed Time Between Last Magnevist Administration and NSF Onset	Elapsed Time Between Last GBCA Administration and NSF Onset
United States	69 y, female	Acute renal failure, eGFR < 30 mL/min/1.73 m^2	2004 Jun: Magnevist 2005 Nov: Magnevist × 2 2006 Apr: Magnevist 2006 May: Magnevist 2006 Nov: Magnevist × 3 2007 Mar: Magnevist 2007 Apr: MultiHance (large dose) 2007 Jun: MultiHance (large dose) **2007 Jun: NSF-like signs and symptoms**	3 mo	≤1 mo
United States*	78 y, female	End-stage renal disease, hemodialysis	2000 Sep-2005 Jun: 11 unknown GBCAs 2005 Sep: Omniscan 2006 Jul: unknown GBCA (not Bayer product) 2007 Feb: MultiHance 2007 May: MultiHance 2007 Sep: MultiHance **2007 Dec: NSF-like signs and symptoms**	No Magnevist documented (≥2 y + 3 mo)	3 mo
United States*	54 y, female	End-stage renal disease, peritoneal dialysis	2006 Mar: unknown GBCA 2007 Feb: Omniscan 2007 Mar: unknown GBCA 2008 Jul: MultiHance 2009 Nov: MultiHance **2010 Apr: NSF diagnosis**	No Magnevist documented (>3 y + 2 mo)	5 mo
United States	56 y, male	Acute renal failure	2003 Nov: Omniscan + unknown GBCA 2004 Apr: Magnevist 2006 May: Magnevist 2007 Aug: MultiHance **2008 May: NSF diagnosis**	2 y	9 mo
United States	85 y, female	ESRD, peritoneal and hemodialysis	2005 Jan: Magnevist 2006 Feb: unknown GBCA 2006 Feb: Magnevist 2006 Mar: MultiHance **2007 Feb: NSF-like signs and symptoms**	1 y	11 mo
United States	59 y, female	End-stage renal disease, hemodialysis	1998 Jul: unknown GBCA 1998 Aug: Magnevist 2002 Aug: "presumably Magnevist" 2005 Jul: MultiHance **2007 Jul: NSF-like symptoms** 2007 Aug: unknown GBCA **2007 Sep: NSF diagnosis**	5 y	2 y

Of note, as with other cases, temporal association alone is not proof of causation.

Bold data indicates onset of NSF/NSF-like symptoms.

*These cases were reported to the company as Magnevist cases but the investigations clearly showed that Magnevist was not administered.

NSF indicates nephrogenic systemic fibrosis; GBCA, gadolinium-based contrast agent; ESRD, endstage renal disease.

TABLE 5. Magnevist Multiple Agent Reports in Which the Macrocyclic Agents Gadovist (n = 2), Dotarem (n = 3), and ProHance (n = 6) Were Administered in Closest Temporal Relationship to NSF Onset

Country (Source)	Patient	Med History	GBCA History and Diagnosis	Elapsed Time Between Last Magnevist Administration and NSF Onset	Elapsed Time Between Last GBCA Administration and NSF Onset
Switzerland	65 y, female	Chronic renal failure, peritoneal dialysis	1999 Feb: Magnevist 2000 Oct: unknown GBCA 2000 Nov: Gadovist 2004 Jan: Dotarem 2004 Aug: Dotarem 2005 Jul: Dotarem 2005 Oct: Gadovist **2005 Nov: NSF-like signs and symptoms**	6 y + 9 mo	1 mo
Denmark	37 y, female	Hemodialysis since Oct 23, 2007	2005 May: Magnevist 2006 Apr: Magnevist 2007 Jan: Magnevist 2007 Aug: Resovist 2008 Jan: Gadovist **2008 Spring: NSF-like signs and symptoms** **2010 May: NSF diagnosis**	Approx 16 mo	Approx 6 mo
Austria	62 y, female	End-stage renal disease	1998 Apr: Omniscan 2002 Sep: Magnevist 2003 June: Dotarem 2003 Sept: Dotarem 2004 Mar: Dotarem **2004 Jun: NSF diagnosis**	2 y	3 mo
Denmark*	45 y, male	Chronic renal insufficiency	1997: unknown GBCA 2006: Dotarem **2006: NSF diagnosis**	No Magnevist documented (>9 y)	≤1 y
Denmark	47 y, female	End-stage renal disease	2002 Jan and/or Feb: Magnevist 2004: unknown GBCA 2004 Aug: Dotarem 2005 NOS: Dotarem **2004–2005: NSF-like signs and symptoms** **2010 Jun: biopsy compatible with NSF** **2010 Aug: Dotarem**	3 y	≤1 y
United States	44 y, female	End-stage renal disease, hemodialysis and peritoneal dialysis	2004 Jul: Magnevist 2004 Dec: Magnevist 2005 Apr: Magnevist 2006 Feb: MultiHance 2006 Jul: ProHance **2007 Apr: NSF-like signs and symptoms** 2007 Sep: ProHance	2 y	9 mo

Continued next page

TABLE 5. *(Continued)*

Country (Source)	Patient	Med History	GBCA History and Diagnosis	Elapsed Time Between Last Magnevist Administration and NSF Onset	Elapsed Time Between Last GBCA Administration and NSF Onset
United States	52 y, female	End-stage renal disease	2003 Sept: Magnevist 2007 May: ProHance **2007 Summer: NSF-like symptoms** 2007 Nov: ProHance 2008 Mar: MultiHance	Almost 4 y	<3 mo
Japan	72 y, male	Moderate renal dysfunction, declining	2002 Mar: Magnevist 2005 Aug: Omniscan 2006 Mar: ProHance 2006 Oct: ProHance 2007 Apr: Magnevist 2007 Dec: ProHance **2008 Jun: NSF-like signs and symptoms**	1 y + 2 mo	6 mo
United States	41 y, female	ESRD, HD	2001 Jul: Magnevist 2002 Mar: Magnevist 2002 Jul: Magnevist 2002 Aug: ProHance 2002 Sep: ProHance **2003 Jun: NSF-like signs and symptoms**	11 mo	9 mo
United States	57 y, female	Renal insufficiency (according to patient, unconfirmed by medical records)	Patient claims to have received 24 CE-MRIs over a 5-y period. The following could be found in medical records: 2001 Apr: unknown GBCA 2002 Mar: unknown GBCA 2002 May: unknown GBCA 2003 Jan: ProHance 2004 Jul: Magnevist 2006 May: unknown GBCA 2006 Oct: ProHance **2007–2008 Aug: NSF-like signs and symptoms**	3–4 y	1–2 y
Germany	23 y, female	End stage renal disease, hemodialysis	2002: Magnevist 2005: ProHance **2011: NSF-like symptoms**	9 y	6 y

Of note, as with other cases, temporal association alone is not proof of causation.

Bold data indicates onset of NSF/NSF-like symptoms.

*These cases were reported to the company as Magnevist cases, but the investigations clearly showed that Magnevist was not administered.

NSF indicates nephrogenic systemic fibrosis; GBCA, gadolinium-based contrast agent; CE-MRI, contrast-enhanced magnetic resonance imaging; ESRD, endstage renal disease; NOS, not otherwise specified.

The second and probably most significant criticism with the current reporting standard is the limitation to single-agent cases. Nephrogenic systemic fibrosis occurs almost exclusively in multimorbid patients who received multiple doses of GBCAs spread over numerous magnetic resonance imaging (MRI) examinations. Statistically speaking, patients receive, on average, 3.5 MRI exams over their lifetime,[13] and therefore, many patients who received an MRI after 2006, with high likelihood, would have had an MRI with Magnevist or Omniscan before that. Consequently, the likelihood of a single-agent NSF case with a new agent would be exceedingly rare. And of course, most of the use of these more recently approved or less used agents occurred after a potential association of GBCAs and NSF was identified, and therefore, safer clinical practices had already gone into effect (including discontinuation of high dosing, repeated use, and off-label procedures in at-risk patients).

TABLE 6. Simulation Model on Impact of Market Share and Market Entry During the Time Period 1997–2006 on Number of Unconfounded and Confounded NSF Reports (N = 100,000)

	Patients Receiving Agent (of 100,000 Patients Simulated, Patients May Receive Multiple Agents)	Patients Receiving Agent in a Confounded Setting (of All Patients Receiving the Agent as per Column 2)	Patients Receiving Agent in an Unconfounded Setting (of All Patients Receiving an Agent in an Unconfounded Setting)
Total	100,000	73,426	26,574
Magnevist	84,752/100,000 (84.8%)	67,988/84,752 (80.2%)	16,764/26,574 (63.1%)
Omniscan	70,537/100,000 (70.5%)	62,570/70,537 (88.7%)	7,967/26,574 (30.0%)
ProHance	29,113/100,000 (29.1%)	27,610/29,113 (94.8%)	1,503/26,574 (5.7%)
OptiMARK	7,831/100,000 (7.8%)	7,542/7,831 (96.3%)	289/26,574 (1.1%)
MultiHance	1,586/100,000 (1.6%)	1,535/1,586 (96.8%)	51/26,574 (0.2%)

NSF indicates nephrogenic systemic fibrosis.

Although the inclusion of multiagent cases certainly adds a level of variability, it is standard pharmacovigilance practice to consider temporal relationship in any causality assessment. The data from Bayer's case reports are supportive of this approach (Tables 4 and 5), given the stark contrast between the time of onset of symptoms from administration of the last GBCA compared with the time since the last Magnevist administration.

Finally, it is worth noting that Bayer has taken a very conservative approach in its reporting and counting of cases of NSF, an approach that might differ among companies. Following the rules for spontaneous reporting, Bayer reported and counted all cases that were presented to the company as NSF whether or not that diagnosis was confirmed clinically or histopathologically. It has been suggested in previous publications that this approach may diverge from that taken by other companies.[14] In addition, NSF is a very difficult diagnosis to make, and Bayer applied the Cowper/Girardi criteria[10] very conservatively, giving "the benefit of the doubt" in many cases despite a lack of evidence that exactly matches these criteria. For example, although 1 of the clinical criteria is "marked induration/peau d'orange,' Bayer assigned a score of 1 for any mention of "induration." For the histopathological finding of "CD34+ cells with tram tracking," Bayer assigns a score of 1 for any mention of either CD34+ cells OR tram tracking. For "thick and thin collagen bundles," any mention of collagen bundles, thick or thin, scores a 1. The result is that even the subset of cases that Bayer considers to be possibly representative of NSF are very likely to be overestimated. In conclusion, lack of standardization results in potential variability and hence concluding on product/safety risk differences between GBCAs based on minimal numerical differences in unconfounded NSF reports is unscientific and should not be used for product differentiation or even misleading promotional purposes.

Several clinical studies performed in renally impaired patients confirmed the low risk of developing NSF after administration of Magnevist (data on file), Gadovist,[15,16] Primovist,[17] MultiHance,[18–20] Dotarem,[21] and ProHance.[18]

In conclusion, this comprehensive analysis highlights numerous aspects that are insufficiently reflected in the existing GBCA risk classification systems. Pure report numbers are probably the weakest criterion to compare the true risk for NSF as long as the above-mentioned aspects are not factored in. The currently published report numbers should be used with caution and are certainly not suited for commercially promoted risk differences.

This analysis demonstrates the limitations of relying on case reports, particularly single-agent reports, when assessing the risk of NSF associated with any GBCA. Given the reliance by both professional society guidelines and health authorities on these numbers, the authors propose bias minimization strategies including correction for market introduction year, market share, temporal association, and reporting standards. Comparative risk assessments should be primarily based on objective product parameters such as stability, pharmacokinetics, and dose.

REFERENCES

1. Cowper SE, Robin HS, Steinberg SM, et al. Scleromyxoedema-like cutaneous diseases in renal-dialysis patients. *Lancet*. 2000;356:1000–1001.
2. Grobner T. Gadolinium—a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplant*. 2006;21:1104–1108.
3. Grobner T. Erratum: Gadolinium—a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplant*. 2006;21:1745.
4. Broome DR, Girguis MS, Baron PW, et al. Gadodiamide-associated nephrogenic systemic fibrosis: why radiologists should be concerned. *AJR Am J Roentgenol*. 2007;188:586–592.
5. Goveia M, Chan BP, Patel PR. Evaluating the role of recombinant erythropoietin in nephrogenic systemic fibrosis. *J Am Acad Dermatol*. 2007;57:725–727.
6. EMA. Assessment report for gadolinium-containing contrast agents. 2010. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/gadolinium_31/WC500099538.pdf. Accessed December 14, 2017.
7. Thomsen HS, Morcos SK, Almen T, et al. Nephrogenic systemic fibrosis and gadolinium-based contrast media: updated ESUR Contrast Medium Safety Committee guidelines. *Eur Radiol*. 2013;23:307–318.
8. FDA. Gadolinium-based contrast agents (GBCAs) and the NSF risk: regulatory. https://www.fda.gov/Drugs/default.htm. Updated 2011. Accessed December 14, 2017.
9. ACR Manual on Contrast Media, Version 10.3, 2017. https://www.acr.org/~/media/ACR/Documents/PDF/QualitySafety/Resources/Contrast-Manual/Contrast_Media.pdf. Accessed December 14, 2017.
10. Girardi M, Kay J, Elston DM, et al. Nephrogenic systemic fibrosis: clinicopathological definition and workup recommendations. *J Am Acad Dermatol*. 2011;65:1095–1106.e7.
11. Decision Resources Group. AMR imaging—the imaging market guide. https://decisionresourcesgroup.com/solutions/medtech-solutions/what-is-amr-imaging. Bayer proprietary database. Accessed December 14, 2017.
12. Michel A, Blenk T. Nephrogenic Systemic Fibrosis (NSF) and Gadolinium-Based Contrast Agents (GBCAs). A Statistical Simulation Study. *Pharmacoepidemiol Drug Saf*. 2010;19:S84.
13. Abujudeh HH, Kaewlai R, Kagan A, et al. Nephrogenic systemic fibrosis after gadopentetate dimeglumine exposure: case series of 36 patients. *Radiology*. 2009;253:81–89.
14. Edwards BJ, Laumann AE, Nardone B, et al. Advancing pharmacovigilance through academic-legal collaboration: the case of gadolinium-based contrast agents and nephrogenic systemic fibrosis—a Research on Adverse Drug Events and Reports (RADAR) report. *Br J Radiol*. 2014;87:20140307.
15. Michaely HJ, Aschauer M, Deutschmann H, et al. Gadobutrol in renally impaired patients: results of the GRIP Study. *Invest Radiol*. 2017;52):55–60.
16. Prince MR, Lee HG, Lee CH, et al. Safety of gadobutrol in over 23,000 patients: the GARDIAN study, a global multicentre, prospective, non-interventional study. *Eur Radiol*. 2017;27:286–295.
17. Lauenstein T, Ramirez-Garrido F, Kim YH, et al. Nephrogenic systemic fibrosis risk after liver magnetic resonance imaging with gadoxetate disodium in patients

with moderate to severe renal impairment: results of a prospective, open-label, multicenter study. *Invest Radiol*. 2015;50:416–422.

18. Soulez G, Bloomgarden DC, Rofsky NM, et al. Prospective cohort study of nephrogenic systemic fibrosis in patients with stage 3-5 chronic kidney disease undergoing MRI with injected gadobenate dimeglumine or gadoteridol. *AJR Am J Roentgenol*. 2015;205:469–478.
19. Martin DR, Kalb B, Mittal A, et al. No incidence of nephrogenic systemic fibrosis after gadobenate dimeglumine administration in patients undergoing dialysis or those with severe chronic kidney disease. *Radiology*. 2018;286: 113–119.
20. Bruce R, Wentland AL, Haemel AK, et al. Incidence of nephrogenic systemic fibrosis using gadobenate dimeglumine in 1423 patients with renal insufficiency compared with gadodiamide. *Invest Radiol*. 2016;51:701–705.
21. Soyer P, Dohan A, Patkar D, et al. Observational study on the safety profile of gadoterate meglumine in 35,499 patients: the SECURE study. *J Magn Reson Imaging*. 2017;45:988–997.