Risk of Nephrogenic Systemic Fibrosis after Exposure to Newer Gadolinium Agents

October 2019

Prepared for:
Department of Veterans Affairs
Veterans Health Administration
Health Services Research & Development Service
Washington, DC 20420

Prepared by:
Evidence Synthesis Program (ESP) Center
Durham VA Healthcare System
Durham, NC
Karen M. Goldstein, MD, MSPH, Co-Director
Jennifer M. Gierisch, PhD, MPH, Co-Director

Authors:

Principal Investigators:
Karen M. Goldstein, MD, MSPH
Joseph Lunyera, MBChB, MSc

Co-Investigators:
Dinushika Mohottige, MD, MPH
Anastasia-Stefania Alexopoulos, MBBS
Hilary Campbell, PharmD, JD
C. Blake Cameron, MD, MBI
Nicole Sagalla, MD
Timothy J. Amrhein, MD
Matthew J. Crowley, MD, MHS
Jessee R. Dietch, PhD, MS
Adelaide M. Gordon, MPH
Andrzej S. Kosinski, PhD
Sarah Cantrell, MLIS
John W. Williams Jr, MD MHSc
Jennifer M. Gierisch, PhD, MPH

Research Associates:
Belinda Ear, MPH
Robyn E. Fortman, BA
Avishek Nagi, MS
Christiana O. Oshotse, BA
Liz Wing, MA

U.S. Department of Veterans Affairs
Veterans Health Administration
Health Services Research & Development Service

PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The program is comprised of four ESP Centers across the US and a Coordinating Center located in Portland, Oregon. Center Directors are VA clinicians and recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Center Program and Cochrane Collaboration. The Coordinating Center was created to manage program operations, ensure methodological consistency and quality of products, and interface with stakeholders. To ensure responsiveness to the needs of decision-makers, the program is governed by a Steering Committee comprised of health system leadership and researchers. The program solicits nominations for review topics several times a year via the program website.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, Deputy Director, ESP Coordinating Center at Nicole.Floyd@va.gov.

Recommended citation: Goldstein KM, Lunyera J, Mohottige D, Amrhein TJ, Alexopoulos AS, Campbell H, Cameron CB, Sagalla N, Crowley MJ, Dietch JR, Gordon AM, Kosinski AS, Cantrell S, Williams JW Jr, Gierisch JM. Risk of Nephrogenic Systemic Fibrosis After Exposure to Newer Gadolinium Agents. Washington, DC: Evidence Synthesis Program, Health Services Research and Development Service, Office of Research and Development, Department of Veterans Affairs. VA ESP Project #09-010; 2019. Posted final reports are located on the ESP search page.

This report is based on research conducted by the Evidence-based Synthesis Program (ESP) Center located at the **Durham VA Healthcare System, Durham, NC**, funded by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Quality Enhancement Research Initiative. This work was supported by the Durham Center of Innovation to Accelerate Discovery and Practice Transformation (ADAPT), (CIN 13-410) at the Durham VA Health Care System. The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. No investigators have any affiliations or financial involvement (*eg*, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

ACKNOWLEDGMENTS

This topic was developed in response to a nomination by Patrick Pun, Medical Director, Dialysis Unit, Durham VA Medical Center, for the purpose of guiding the Nephrology Field Advisory Committee's recommendations for development of national and local policies. The scope was further developed with input from the topic nominators (*ie*, Operational Partners), the ESP Coordinating Center, the review team, and the technical expert panel (TEP).

In designing the study questions and methodology at the outset of this report, the ESP consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Operational Partners

Operational partners are system-level stakeholders who have requested the report to inform decision-making. They recommend Technical Expert Panel (TEP) participants; assure VA relevance; help develop and approve final project scope and timeframe for completion; provide feedback on draft report; and provide consultation on strategies for dissemination of the report to field and relevant groups.

Patrick Pun, MD, MHS
VHA Renal Field Advisory Committee
Medical Director, Dialysis Unit
Durham VA Medical Center

Susan Crowley, MD, FASN
VHA National Program Director for Kidney Disease
Chief, Renal Section
VA Connecticut Healthcare System

Technical Expert Panel (TEP)

To ensure robust, scientifically relevant work, the TEP guides topic refinement; provides input on key questions and eligibility criteria, advising on substantive issues or possibly overlooked areas of research; assures VA relevance; and provides feedback on work in progress. TEP members are listed below:

Brent Wagner, MD, MS, FACP, FASN
Acting Associate Chief of Staff, Research
New Mexico VA Health Care System
Associate Professor of Medicine
University of New Mexico

Clare Haystead, MD
Radiologist, Radiology Service
Durham, VA Medical Center
Assistant Professor of Radiology
Duke University

Roger Chou, MD
Director of the Pacific Northwest Evidence-based Practice Center
Professor of Medicine
Oregon Health & Science University

Ira Krefting, MD
Deputy Director for Safety
Division Medical Imaging Products
Office of Drug Evaluation
US Food and Drug Administration

Peer Reviewers

The Coordinating Center sought input from external peer reviewers to review the draft report and provide feedback on the objectives, scope, methods used, perception of bias, and omitted evidence. Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The Coordinating Center and the ESP Center work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

TABLE OF CONTENTS

TABLES

FIGURES

EVIDENCE REPORT

INTRODUCTION

Nephrogenic systemic fibrosis (NSF) is a debilitating, and in most cases fatal, condition that currently has no definitive treatment. This disease is associated with exposure to certain gadolinium-based contrast agents (GBCA) administered during magnetic resonance imaging (MRI) or angiography (MRA) scans.[1] The first reports of NSF occurred in the early 2000s, when it was originally termed nephrogenic fibrosing dermopathy (NFD) based on the impression that its lesions were limited to the skin.[2,3] Eventually, the term NSF replaced NFD when it became evident that the disease affects multiple organ systems; occurs conspicuously in persons with end-stage renal disease (ESRD); and manifests histologically as increased collagen deposition in superficial soft tissues and internal organs such as the heart, liver, and lungs.[3] Subsequently, starting in 2007, the FDA released a series of warnings about the use of certain GBCAs recognized to be connected to the development of NSF (see Appendix A).[4]

As a diagnostic tool, depending on clinical indication, MRI is much more effective when administered with a contrast agent. Gadolinium is a heavy metal with paramagnetic properties that make it an optimal candidate for use as an MRI contrast agent.[5] However, it is toxic in its free form,[6] and must be stabilized by chelation, or bonding, to a ligand for human use.[3,6] GBCAs can be characterized by the structure of their individual chelate (macrocyclic/linear) and charge (ionic/nonionic),[6] which in turn contribute to the stability of a given GBCA and how easily the gadolinium is disconnected from its ligand.[3,6] These differences in stability of the linkage of gadolinium to the chelate ligand are thought to be a key factor in the risk of NSF, as dissociation of the gadolinium complex releases the unbound gadolinium ion, which triggers a cascade of events in a subset of patients culminating in the histological manifestations of NSF.[7] Newer GBCAs impart greater stability of the gadolinium-ligand bond[5] and thus are thought to be associated with lower, or potentially minimal, NSF risk. Table 1 contains information about the FDA-approved gadolinium agents. An additional critical risk factor for the development of NSF is renal impairment.[7] All GBCAs are cleared, at least in part, from the body by the kidneys, and almost all cases of NSF have occurred in individuals with advanced kidney disease (eGFR <30 mL/min/1.73m^2). However, other patient-level risk factors have been proposed as well, including the severity and chronicity of kidney dysfunction and inflammation.[1,8]

As newer GBCAs with greater chemical stability have become available, guidelines recommending safe and effective administration of these agents have evolved, and, in places, diverged. While some advisory boards recommend liberalized use of the newer classes of GBCAs, others warn against risk for NSF with all classes of GBCAs (see Appendix B for GBCA guidelines). These divergent positions reflect uncertainties regarding the relative safety of newer compared with older classes of GBCAs and the degree of kidney dysfunction that portends risk for NSF. Despite these uncertainties, few studies have assessed risk for NSF with GBCA exposure specifically in relation to newer agents; across the range of kidney function; and according to patients' underlying profile on comorbid factors that might amplify NSF risk, including diabetes and hypertension. Thus, synthesizing the existing evidence about the safety profile of newer, and presumably more stable, GBCAs across the spectrum of kidney function will inform clinical policies. Evidence-based benefits and risks of contrasted MRIs across different patient populations can be weighed in order to limit excess risks for NSF relative to the

general population, while not inadvertently restricting the use of GBCAs in patients who would otherwise benefit from them.

Table 1. FDA-Approved Gadolinium Agents[a,b]

Agent Name (Generic)	Brand Name	ACR Category[c]	Structure	Charge/ Ionicity	Elimination Route	Year of FDA Approval
Gadopentetate dimeglumine	Magnevist	Group I	Linear	Ionic	Renal	1988
Gadodiamide	Omniscan	Group I	Linear	Nonionic	Renal	1993
Gadoversetamide	OptiMARK	Group I	Linear	Nonionic	Renal	1999
Gadoteridol	ProHance	Group II	Macrocyclic	Nonionic	Renal	1992
Gadobenate dimeglumine	MultiHance	Group II	Linear	Ionic	Renal + hepatobiliary	2004
Gadobutrol	Gadavist/ Gadovost	Group II	Macrocyclic	Nonionic	Renal	2011
Gadoterate meglumine; gadoteric acid	Dotarem	Group II	Macrocyclic	Ionic	Renal	2013
Gadoexetic acid; Gadoxetate disodium	Eovist	Group III	Linear	Ionic	Renal + hepatobiliary	2008
Gadofosveset trisodium	Ablavar	Not applicable	Linear	Ionic	Renal + hepatobiliary	2008[d]

[a] FDA. Drugs@FDA: FDA Approved Drug Products. Available at https://www.accessdata.fda.gov/scripts/cder/daf/.
[b] Adapted with permission from Leyba and Wagner.[3]
[c] Per ACR Manual on Contrast Media, Version 10.3. 2018.[9]
[d] Removed from market in 2017.

The current review was completed at the request of the Veterans Affairs (VA) Nephrology Field Advisory Committee, which provides independent advice on clinical policy and programming to the VA Office of Specialty Care Services and the National VA Renal program. Due to uncertainty about the safety of certain GBCAs, the current use of gadolinium is restricted in Veterans with advanced kidney disease. These restrictions limit access to high-quality MRI for the diagnosis and management of numerous and potentially life-threatening diseases. The goal of this report is to provide a systematic review of the existing evidence on the risk of NSF with use of newer GBCAs, specifically American College of Radiology (ACR) group II and III agents,[9] to inform the their use within the VA.

METHODS

We followed a standard protocol for this review developed in collaboration with operational partners and a technical expert panel. The PROSPERO registration number is CRD42019135783. The protocol was developed prior to the conduct of the review, and there were no significant deviations after registration. Each step was pilot-tested to train and calibrate study investigators. We adhered to the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines.[10]

TOPIC DEVELOPMENT

This topic was proposed by Patrick Pun, MD, MHS, and the Nephrology Field Advisory Committee.

Key Questions

The Key Questions (KQs) for this report were:

KQ 1: When exposed to newer gadolinium-based contrast agents (defined as American College of Radiology group II and III agents), what is the occurrence of nephrogenic systemic fibrosis per index GBCA exposure among:

- **A.** All patients without restriction by kidney function
- **B.** Patients with key risk factors for chronic kidney disease (*eg*, diabetes and hypertension)
- **C.** Patients with any degree of kidney disease (*ie*, acute kidney injury or chronic kidney disease)

KQ 2: When compared with older gadolinium-based contrast agents (American College of Radiology group I agents), what is the occurrence of nephrogenic systemic fibrosis per index GBCA exposure for newer GBCAs among:

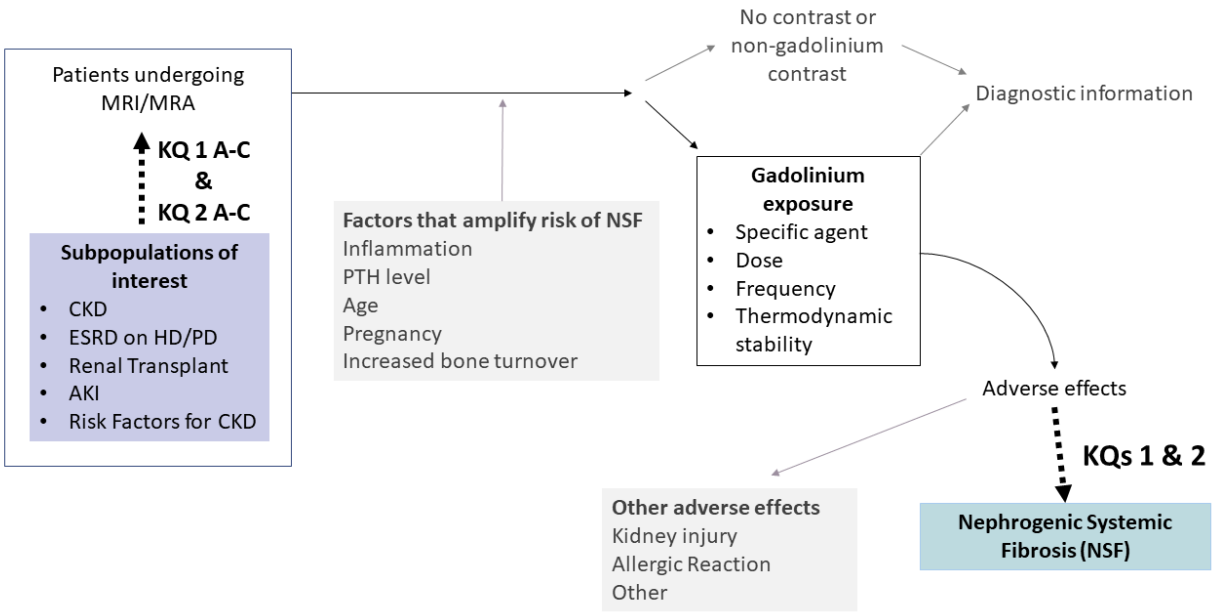
- **A.** All patients without restriction by kidney function
- **B.** Patients with key risk factors for chronic kidney disease (*eg*, diabetes and hypertension)
- **C.** Patients with any degree of kidney disease (*ie*, acute kidney injury or chronic kidney disease)

Conceptual Model

We developed a conceptual model to clarify the relationship of the KQs to the overall pathway of patients who undergo MRI studies with GBCAs. As depicted in Figure 1, patients who undergo an MRI or MRA imaging study may or may not receive gadolinium exposure to obtain the clinically required diagnostic information. KQ 1 addresses the rate of nephrogenic systemic fibrosis (first box) in all patients who receive GBCA exposure during the course of an MRI/MRA study. Of particular interest are certain subpopulations (KQ 1A-C) identified in the purple box (*eg*, patients with different types of kidney-related disease). Similarly, KQ 2 addresses the relative risk of NSF among patients who receive newer versus older GBCAs during

the course of an MRI/MRA study and examines the risk in the same key subpopulations (KQ 2 A-C). We have also identified other important concepts such as individual patient factors that may increase or modify the risk of NSF and other types of adverse effects among patients who are exposed to GBCAs.

Figure 1. Conceptual Model



Abbreviations: AKI=acute kidney injury; CKD=chronic kidney disease; ESRD=end-stage renal disease; HD=hemodialysis; KQ=key question; MRA=magnetic resonance angiography; MRI=magnetic resonance imaging; PD=peritoneal dialysis; PTH=parathyroid hormone

SEARCH STRATEGY

In collaboration with an expert medical librarian, we conducted a primary literature search from inception to January 7, 2019 of MEDLINE® (via PubMed®), Embase, Cochrane Register of Controlled Trials, and Web of Science. We used a combination of database-specific subject headings and keywords (*eg,* gadolinium, contrast media, nephrogenic fibrosis) and searched in the titles and abstracts (Appendix C). We also conducted hand searches of key references[7,9,11-27] for relevant citations that may not have been captured in the database search.

STUDY SELECTION

We used the artificial intelligence (AI) technology developed as part of the DistillerSR software (Evidence Partners Inc., Manotick, ON, Canada), called DistillerAI, to assist with screening abstracts.[28] Using prespecified inclusion/exclusion criteria (Table 2), the titles and abstracts of a subset of articles (approximately n=100) identified through our primary search were classified independently by 2 senior investigators (KMG, JL) for relevance to the KQs. After resolving disagreements between the 2 investigators, this set of included and excluded articles was used to train the Distiller AI program.

The Distiller AI program screened the remaining titles and abstracts and assigned a prediction score of relevance to the study questions. All citations classified with a prediction score ≤0.5 underwent screening by a single investigator. Potentially relevant studies included by the investigator or with an AI prediction score >0.5 underwent full-text screening. At the full-text screening stage, 2 independent investigators agreed on a final inclusion/exclusion decision (see Appendix D for justification of excluded studies). All articles meeting eligibility criteria were included for data abstraction. All results were tracked in an electronic database (for referencing, EndNote®, Clarivate Analytics, Philadelphia, PA; for data abstraction, DistillerSR; Evidence Partners Inc., Manotick, ON, Canada).

Table 2 describes the study eligibility criteria organized by PICOTS elements (population, intervention, comparator, outcome, timing, setting) and other criteria such as study design, language, and publication type. We included a broad range of study designs ranging from randomized trials to case reports in order to capture any study type quantitatively reporting NSF in association with GBCA exposure. Studies were excluded if they did not report the number of patients exposed by specific GBCA. Similarly, studies were excluded if they only identified the specific GBCA exposure for those patients ultimately diagnosed with NSF but not the rest of the study population. We also included case reports and case series for patients with NSF that clearly described exposure to an ACR group II and/or III GBCA.

In order to align our KQs with existing guidelines pertaining to the use of GBCAs and their associated risk of NSF, we adopted the groupings for GBCAs given by the American College of Radiology (ACR) in their 2018 guidelines.[9] Thus, "newer gadolinium-based contrast agents" are referred to throughout the report as ACR group II/III agents and "older gadolinium-based contrast agents" are referred to as ACR group I agents.

Table 2. Study Eligibility Criteria

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Population	• Adults and children • Deceased patients via autopsy	None
Intervention	ACR group II agents[a]: • Gadoteridol (Prohance®) • Gadobenate dimeglumine, Gadobenic acid (MultiHance®) • Gadobutrol (Gadavist®, Gadovist®, Gadograf®) • Gadoterate meglumine, Gadoteric acid (Dotarem®, Clariscan®, Artirem® ACR group III agents: • Gadoxetate disodium (Eovist®, Primovist®) • Gadofosveset (Ablavar®, Vasovist®, AngioMARK®)	ACR group I agents excluded unless compared with group II and III gadolinium-based contrast agents: • Gadopentetate dimeglumine (Magnevist®) • Gadodiamide (Omniscan®) • Gadoversetamide (Optimark®) • Non–FDA-approved gadolinium-based contrast agents
Comparator	Any, including no comparator	None

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Outcomes	Nephrogenic systemic fibrosis (NSF), including nephrogenic fibrosing dermopathy (either confirmed or suspected cases; cases associated with multiple types of gadolinium or multiple doses acceptable)	None
Timing	For longitudinal study designs only: at least 2 weeks' follow-up	For longitudinal study designs only: fewer than 2 weeks' follow-up
Setting	Administered for any reason; outpatient or inpatient	None
Study design	• Randomized controlled trial • Prospective or retrospective cohort • Case series, case control, case report	Systematic review, narrative review, or studies that do not report patient-level data for both gadolinium-based contrast agent exposures and NSF cases
Language	English	Non-English
Countries	Any	None
Years	Any	None
Publication Type	• Full publications • Letters that report case(s)	• Meeting abstracts • Editorials • Dissertations and letters not reporting cases or case series

[a] American College of Radiology Guidelines.[9]

DATA ABSTRACTION

Data from published reports were abstracted into a customized DistillerSR database by 1 reviewer and over-read by a second reviewer. Disagreements were resolved by consensus or by obtaining a third reviewer's opinion when consensus was not reached. Data elements included descriptors to assess applicability, quality elements, intervention/exposure details, and outcomes.

Key characteristics abstracted included patient descriptors, specifics of gadolinium agent exposure (*eg,* specific agent, dose, number of doses received), comparator (if any), outcomes (confirmed or suspected diagnosis of NSF), and source of study funding. Note that if a study included a non-contrast comparator arm, we did not abstract data from the non-contrast arm as the comparison between GBCA exposure and non-GBCA exposure was not the focus of this review. Multiple reports from a single study were treated as a single data point, prioritizing results based on the most complete and appropriately analyzed data. Key features relevant to applicability included the match between the sample and target populations (*eg*, age, Veteran status).

We defined cases of NSF as "confounded" when there was clear evidence that the patient had been exposed to multiple GBCAs prior to the development of NSF; conversely, "unconfounded" refers to cases in which a patient was noted specifically to have been exposed only to a single GBCA (even if multiple doses of the same GBCA) prior to disease development. When it was not clearly stated whether or not a patient had received exposures to multiple GBCAs, we considered them conservatively as confounded.

QUALITY ASSESSMENT

Quality assessment was done by the investigator abstracting or evaluating the included article and was over-read by a second, highly experienced investigator. Disagreements were resolved by consensus between the 2 investigators or, when needed, by arbitration by a third investigator.

For randomized, nonrandomized, and controlled before-after studies, we used criteria from the Cochrane EPOC risk of bias (ROB) tool.[29] These criteria are adequacy of randomization and allocation concealment; comparability of groups at baseline; blinding; completeness of follow-up and differential loss to follow-up; whether incomplete data were addressed appropriately; validity of outcome measures; protection against contamination; selective outcomes reporting; and conflict of interest. We assigned a summary ROB score (low, unclear, high) to individual studies, defined as follows:

- Low ROB: Bias, if present, is unlikely to alter the results seriously.
- Unclear ROB: Information required to determine risk of bias was not clearly specified in the peer-reviewed paper or unable to be obtained to make a judgment.
- High ROB: Bias may alter the results seriously.

For observational cohort and case-control studies, we adapted the Newcastle-Ottawa scale (from the version modified by Guyatt et al).[30] This scale includes quality assessment criteria for selection of cases and controls, comparability of cases and controls, and ascertainment of exposure (or outcome as relevant). For questions relevant to cohort studies with an exposed and unexposed group, we consider "exposed" to mean patients who received any ACR Group II or III agent of interest and "nonexposed" to mean patients who received an agent not of primary interest (*eg*, ACR Group I agents). For cohorts that only report an exposed group, we included a "not applicable" response option for questions specific to exposed and nonexposed groups. Similarly, we modified a question about matching for confounding variables to include adequate statistical adjustment or stratification for confounders if matching was not applicable. See Appendix E for our modified ROB form. Given the number of eligible cohort and case-control studies, we did not evaluate the ROB for case reports or case series studies.

DATA SYNTHESIS

We summarized the primary literature using data abstracted from the eligible studies. Summary tables describe the key characteristics of the primary studies overall and by specific gadolinium agent. Next, we determined the feasibility of completing a quantitative synthesis (*ie*, meta-analysis) to estimate summary effects. The feasibility of conducting a meta-analyses depended on the volume of relevant literature, conceptual homogeneity of the included studies, and completeness of results reported in those included studies. Due to heterogeneity of study methodology, patient population, and follow-up time points across studies, we elected not to conduct meta-analysis.

While we did not calculate summary estimates across studies, we do present forest plots of the point estimates from individual studies grouped by category of kidney function (all patients, patients with risk factors for CKD, and patients with CKD of any stage) within each KQ. To create these categories, we identified the stages of CKD that were included by a given study. For studies that only reported eGFR ranges, we converted them to standard CKD stages (note: some

studies did not report eGFR but only CKD stages). We did not include studies in the forest plots that were not designed to identify cases of NSF as a primary outcome, although the findings of these studies are reported narratively in each result section. Also, there was inconsistency in the reporting of whether or not cases of NSF were confounded across included studies. Thus, in order to facilitate comparisons in the forest plots, the number of cases of NSF reported for each study is the total found in a given study and may include confounded cases.

Because of the variability in methods across included studies and the low numbers of NSF cases found, we report the occurrence of NSF cases per index GBCA exposure as opposed to a relative risk, prevalence, or incidence. This allows for accurate reporting of the phenomena of interest and for comparisons across studies that use both the term incidence and prevalence. We refer to "index GBCA exposure" as the contrast agent identified in each study as the primary exposure in questions related to NSF occurrence, acknowledging that some patients were exposed to multiple agents potentially both before and after the index exposure. Finally, we calculated an exact upper 95% confidence interval (CI) for each individual study, which is also displayed in the forest plots. Analyses were performed with the R statistical package version 3.5.3 (R Foundation; https://www.R-project.org/). Exact 95% confidence intervals[31] were obtained with the binom.test function.

Because quantitative synthesis was not indicated, we narratively analyzed outcomes for both KQs. For narrative analyses, we gave more weight to evidence from higher quality studies (*ie*, low ROB) when possible. Our narrative synthesis focused on documenting and identifying patterns of NSF development across categories of kidney function and types of GBCA exposure. For KQ 2, we did not calculate risk ratios or odd ratios for the following reasons: the included studies were not designed for this type of comparison originally, it was unclear if the populations receiving different GBCAs were directly comparable, and there is reason to suspect confounding by indication (*eg*, certain GBCAs are preferred for MRIs of different organs). We also analyzed potential reasons for inconsistency in treatment effects across studies by evaluating differences in the study population, intervention, comparator, and outcome definitions.

RATING THE BODY OF EVIDENCE

The certainty of evidence (COE) for each key question was assessed using the approach described by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) working group.[32] We limited GRADE ratings to those outcomes identified by the stakeholders and technical expert panel as critical to decision-making (*ie*, development of NSF). Additionally, we limited COE assessment to the highest order study designs (*ie,* EPOC criteria studies, prospective and retrospective cohorts). In brief, this approach requires assessment of four domains: risk of bias, consistency, directness, and precision. Additional domains to be used when appropriate are coherence, dose-response association, impact of plausible residual confounders, strength of association (magnitude of effect), and publication bias. These domains were considered qualitatively, and a summary rating was assigned after discussion by 2 investigators (KMG, AMG) as high, moderate, low, or very low COE. COE was not assessed for studies that only enrolled patients with chronic liver disease.

PEER REVIEW

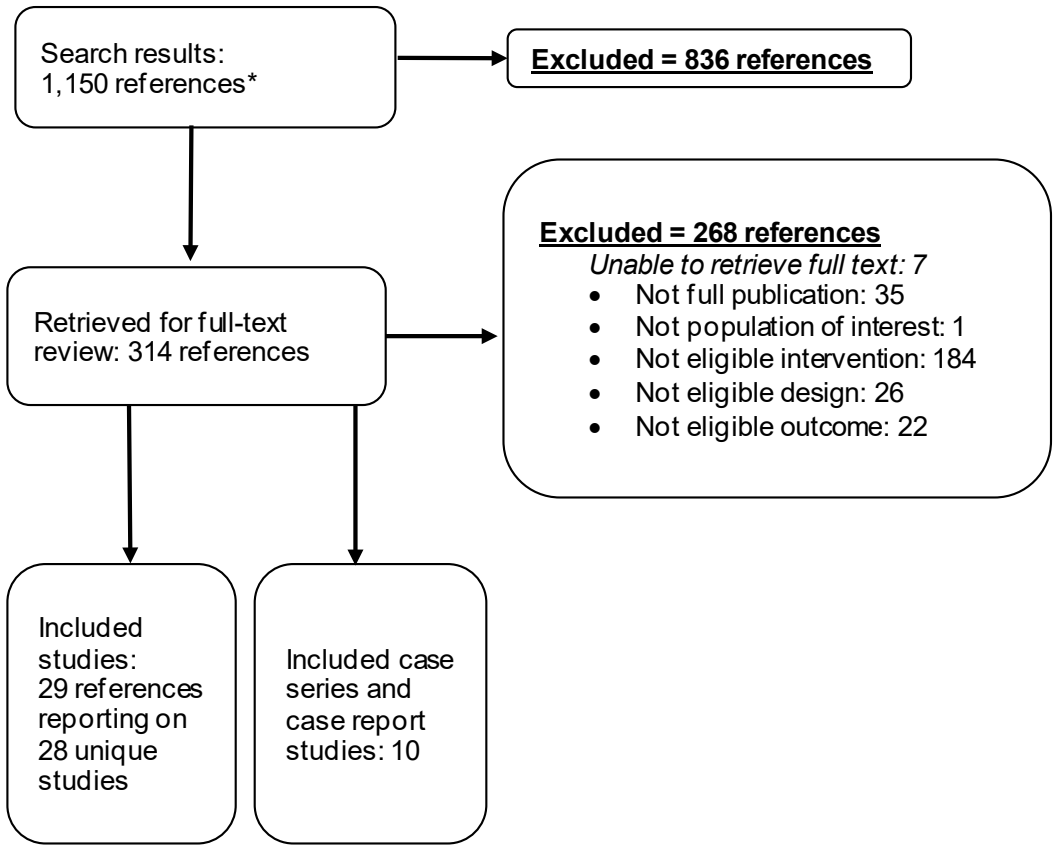
A draft version of this report was reviewed by technical experts and clinical leadership. A transcript of their comments and our responses is in Appendix F.

RESULTS

LITERATURE FLOW

We identified 2,862 studies through searches of MEDLINE® (via PubMed®), Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, and Web of Science (Figure 2). An additional 156 articles were identified through reviewing bibliographies of relevant review articles for a total of 3,018 articles. After removing duplicates, there were 1,150 articles. After applying inclusion and exclusion criteria to titles and abstracts, 314 articles remained for full-text review. Of these, 28 unique studies and 10 case reports and case series were retained for data abstraction. The 28 unique studies consisted of 26 cohort studies (10 prospective and 16 retrospective), 1 case control study, and 1 nonrandomized trial. Included studies were conducted across 6 continents, with most taking place in North America, Europe, and Asia. Because of the large number of higher-order evidence studies identified of relevance to the key questions, we have focused the majority of the report on the included cohort, case control, and nonrandomized studies (*ie*, evidence profile, results, and certainty of evidence) (n=28). We do, however, include a brief summary of the included case series and case studies at the end of the results section.

Figure 2. Literature Flow Chart



* Search results from MEDLINE (637), Embase (307), Web of Science (33), Cochrane (3), and identified from relevant articles (170) were combined.

EVIDENCE PROFILE

Table 3 shows the evidence profile of studies included in this systematic review. Appendix G contains detailed study characteristics for the included studies. For a glossary of terms, refer to Appendix H.

Table 3. Evidence Profile for Studies of Gadolinium Agents and NSF

	KQ 1 (n=16)	KQ 2 (n=12)
Study design	1 Nonrandomized 15 Cohort studies	1 Case-control 11 Cohort studies
Number of patients	80,932	118,849
Region	7 USA 3 Europe 4 Multi-country 1 Japan	7 Europe 4 USA 1 China
Median age (range)	63.3 (49.5 to 72.6) 1 study NR	59.9 (51.9 to 77) 3 studies NR
Sex %	52% Women	12% Women 2 studies NR
Race %	11% White <1% Black 8 studies NR	<1% White <1% Black 11 studies NR
Renal status, n study	3 All Patients 3 Any CKD 6 CKD stage 3-5 3 Dialysis 1 Chronic liver disease	2 All Patients 3 Any CKD 2 CKD stage 3-5 4 Dialysis 1 Chronic liver disease
Risk factors for CKD	9 studies NR 1% hypertension (8 studies reported) 2% diabetes (5 studies reported) 1% prior dialysis (4 studies reported)	9 studies NR <1% hypertension (1 study reported) <1% diabetes (2 studies reported) <1% prior dialysis (2 studies reported)
Index gadolinium exposures	Group II: 80,715 Group III: 217	Group I: 110,345 Group II: 8,499 Other: 5
Risk of bias	Overall cohorts 9 High 6 Unclear 0 Low Nonrandomized trial objective[a] 1 High Nonrandomized trial patient-reported[a] 1 NA	Overall cohorts 7 High 3 Unclear 1 Low Overall case-control 1 Unclear

[a] The nonrandomized trial was rated for risk of bias for objective outcomes (*ie*, non–patient-reported outcomes) and patient-reported outcomes (*ie,* directly reported by the patient without interpretation of the patient's response).
Abbreviations: CKD=chronic kidney disease; NA=not applicable; NR=not reported

KEY QUESTION 1: When exposed to newer linear gadolinium-based contrast agents (defined as American College of Radiology Group II and III agents), what is the occurrence of nephrogenic systemic fibrosis per index GBCA exposure among:

A. All patients without restriction by kidney function

B. Patients with key risk factors for chronic kidney disease (*eg*, diabetes and hypertension)

C. Patients with any degree of kidney disease (*ie*, acute kidney injury or chronic kidney disease)

Key Points

- We identified 15 cohort studies and 1 nonrandomized controlled trial relevant to KQ 1.
- Across all 16 studies, the majority of index GBCA exposures were to ACR group II agents (n=80,715) and fewer to ACR group III agents (n=217).
- Across 3 cohort studies that included 62,544 patients without restricting enrollment to those with CKD, there were no cases of NSF reported (calculated exact upper 95% CI range 0.0001 to 0.0011).
- There were no studies that assessed NSF risk specifically in patients with risk factors for CKD, such as diabetes and hypertension.
- Across 12 studies that included 18,036 patients with any degree of kidney disease (including ESRD on dialysis), no cases of NSF were reported (calculated exact upper 95% CI range 0.0002 to 0.3085).

Description of Included Studies

Sixteen studies met our inclusion criteria for KQ 1: 8 prospective[33-40] and 7 retrospective cohort studies,[41-47] and 1 nonrandomized controlled trial.[48] Among these studies, 7 were conducted in the United States; 5 were multi-country studies spanning Europe, Asia, and the Americas; 3 were conducted in Europe, and 1 was conducted in Japan. Patients in the cohort studies had exposure to newer linear GBCAs (ACR group II) in 13 studies (gadobenate dimeglumine [n=6], gadobutrol [n=3], gadoterate meglumine [n=3], and gadoteridol [n=1]), and exposure to the macrocyclic agent gadoexetic acid (ACR group III) in 2 studies. Nine of the cohort studies reported exposures to multiple gadolinium agents,[33,35-38,40,43,46,47] and 7 reported repeated exposures to the same agents.[33-36,38-40] Eight cohort studies reported the diagnostic approach for NSF, which varied, including review of patients' medical records (n=3); clinical symptoms and examination of skin lesions (n=1); biopsy (n=1); and the Girardi criteria (n=3). Seven cohort studies were postmarketing surveillance studies funded by GBCA manufacturers.[35-40,48] In general, risk factors for NSF other than kidney disease were rarely reported.

The nonrandomized controlled trial enrolled patients with stage 3-4 CKD at 4 European sites between 2008 to 2011.[48] All patients in the exposure arm received the newer linear gadolinium

agent, gadoterate meglumine, and were followed for 3 months for the development of NSF (diagnostic approach not reported).

For each of the following KQ subquestions (A-C), we provide narrative descriptions of findings from the relevant included studies. The 13 studies that were primarily designed to identify cases of NSF after GBCA exposure are also included in the forest plot (Figure 3).

KQ 1A: Findings Among Patients Without Restriction by Kidney Function

Three cohort studies recruited patients without restricting enrollment to those who had CKD (1 high, 1 unclear, and 1 low risk of bias [ROB]).[37,39,40] All were prospective cohort studies conducted as phase 4 postmarketing surveillance studies and were funded by GBCA manufacturers, with a total of 62,544 enrolled patients of whom 1,099had at least moderate CKD (eGFR <60 mL/min/1.73m^2). Across these 3 studies, there were 27,045 patient index exposures to gadobutrol and 35,499 patient index exposures to gadoterate meglumine. All patients with moderate CKD or worse (eGFR<30 to <60 mL/min/1.73m^2) underwent a specific safety monitoring period for 3months. There were no cases of NSF reported across these 3 studies (Figure 3, Table 4, and Table 5).

KQ 1B: Findings Among Patients With Key Risk Factors for Chronic Kidney Disease

No studies specifically examined the occurrence of NSF after GBCA exposure among patients with risk factors for CKD. Of the previously described 3 cohort studies, 1 noted the prevalence of concomitant cardiac disease among the 23,708 patients eligible for inclusion to be 5.2%,[37] and a second study noted that of the 34,474 patients, 4.0% had diabetes mellitus and 4.0% had cardiovascular disease of some type.[39] The third cohort study did not describe the prevalence of any CKD risk factors.[40] We identified 1 study that enrolled 352 patients with chronic liver disease awaiting liver transplant, of which 68 had CKD and none were reported to develop NSF.[44]

KQ 1C: Findings Among Patients With Any Degree of Kidney Disease

Patients With CKD—Any Stage

For this category, we identified studies that included patients with at least some degree of kidney disease as defined by the study authors. One study rated as unclear ROB evaluated 22,897 MRI examinations in which gadoterate meglumine was administered to adults and children with normal kidney function and those with chronic kidney disease.[41] Of these exposures, there was clearly reported patient-level data for 15,377 adult patients with stage 1-5 CKD (stages 1/2 defined as eGFR levels ≥60ml/min/1.73m^2), none of whom were reported to develop NSF over a mean of 6.0 years (range 8 months to 15 years). A second phase 4 postmarketing surveillance cohort study with unclear ROB included 908 patients exposed to gadobutrol (284 with severe CKD or eGFR ≤30 ml/min/1.73m^2 and 540 with moderate CKD or eGFR ≥30 ml/min/1.73m^2 and ≤59 ml/min/1.73m^2) and reported no cases of NSF (Figure 3, Table 4).[36] One prospective cohort study with high ROB was conducted as a phase 4 study evaluating gadoexetic acid (*ie*, gadoxetate disodium) among patients with moderate to severe CKD undergoing liver MRI (n=186).[35]

Patients With CKD—Stages 3 to 5

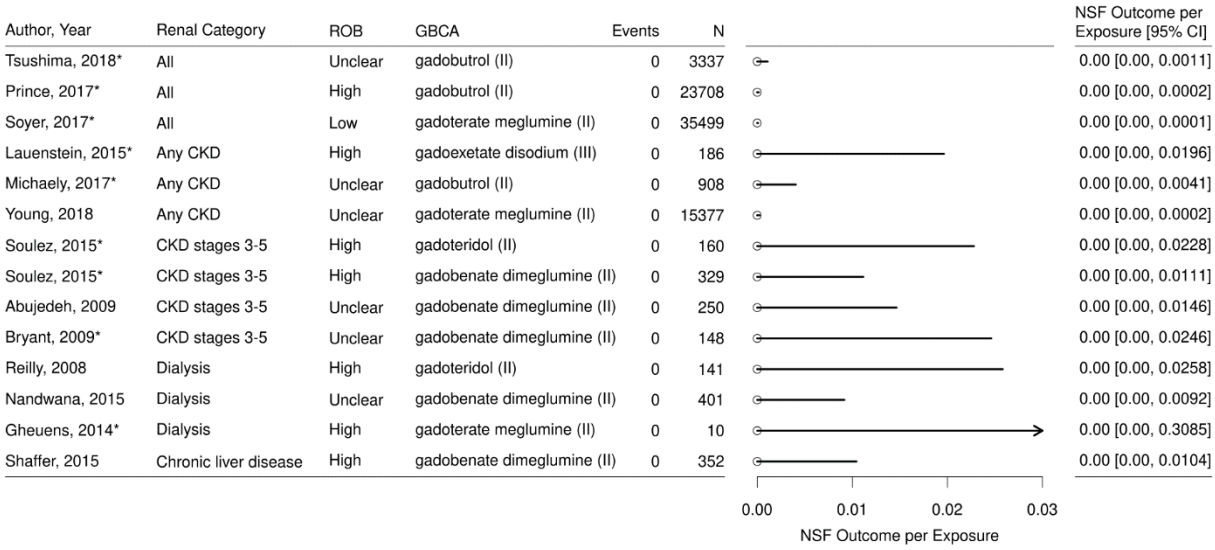
Of the 6 identified studies that enrolled patients with stage 3-5 CKD, 3 cohort studies[33,38,46] (n=887total) were designed to identify cases of NSF after GBCA exposure, and 3[42,45,48] reported the occurrence of NSF after GBCA exposure as a secondary outcome. Two studies (both with unclear ROB) sought the occurrence of NSF after index exposure to gadobenate dimeglumine at individual medical institutions, 1 among patients with stage 3 CKD only (n=148)[33] and 1 among patients with stage 3 CKD or worse (n=250).[46] A second study with high ROB combined data from 2 multicenter prospective cohort postmarketing surveillance studies in which patients with stage 3-5 CKD underwent unconfounded exposure to gadobenate dimeglumine (n=329) or gadoteridol (n=160).[38] Across the 3 studies reporting NSF as a secondary outcome (2 cohort studies, 1 nonrandomized controlled trial), 31 patients had index exposure to gadoexetic acid,[42] 25 to quarter-dose gadobenate dimeglumine,[45] and 70 to gadoterate meglumine.[48]

There were no cases of NSF reported across any of these 6 studies with 1,013 index patient exposures to newer linear or macrocyclic GBCA exposure among patients with stage 3-5 CKD (Figure 3, Table 4, Table 5).

Patients With ESRD Receiving Dialysis

In the remaining 3 studies, 2 included patients with ESRD on dialysis[34,47] and 1 included patients noted to have ESRD or who were undergoing renal transplant evaluation (75.5% were dialysis dependent).[43] One retrospective cohort study examined 141 Veterans on long-term hemodialysis at the Dallas Veterans Affairs hospital who had undergone a total of 198 exposures to gadoteridol from 2000 to 2007.[47] A second retrospective cohort study included 401 patients with ESRD or who were undergoing renal transplant evaluation and who underwent index exposure to gadobenate dimeglumine with follow up for a mean of 2.35 years.[43] Last, 1 study was a phase 1 nonrandomized prospective trial of 10 patients on hemodialysis who received exposure to gadoterate meglumine and then were monitored to identify the rapidity of gadoterate meglumine removal by dialysis and safety for up to 3 months of this GBCA post-exposure.[34] There were no cases of NSF reported among the 552 patients across these 3 studies who were exposed to newer linear or macrocyclic GBCAs among patients with ESRD or who were undergoing renal transplant evaluation (Figure 3, Table 5).

Figure 3. NSF Occurrence per GBCA Exposure[a]



*Prospective cohort studies.

[a] The study by Soulez and colleagues has 2 rows depicted, one for each GBCA.[38]

Abbreviations: CI=confidence interval; CKD=chronic kidney disease; GBCA=gadolinium-based contrast agent

Table 4. Occurrence of NSF After Index Exposure to ACR Group II and III GBCAs: Cohort Studies

Study	Range Kidney Function Included, N Patients Exposed GFR Range/CKD Stage, N Patients Exposed	Index GBCA (ACR Group)	Number of NSF Cases
All Patients Without Restriction by Kidney Function			
Tsushima, 2018[40]	All = 3,337 eGFR ≥90 mL/min = 728 eGFR ≥60-<90 mL/min = 1587 eGFR 30-59 mL/min = 427 eGFR <30 mL/min = 5	Gadobutrol (II)	0
Prince, 2017[37]	All = 23,708 eGFR 60-90 mL/min = 15 eGFR 30-59 mL/min = 100 eGFR <30 mL/min[a] = 48	Gadobutrol (II)	0
Soyer, 2017[39]	All = 35,499 eGFR 30-44 mL/min = 417 eGFR 15-30 mL/min = 58 eGFR <15 mL/min = 7	Gadoterate meglumine (II)	0
Any Degree of Kidney Disease			
Michaely, 2017[36]	Any degree kidney disease = 908 eGFR >65 mL/min = 38 eGFR >59 and ≤65 mL/min = 46 eGFR ≥30 and ≤ 59 mL/min = 540 eGFR <30 mL/min = 284	Gadobutrol (II)	0
Young, 2018[41]	Any degree kidney disease = 15,377 adults (total = 21,770 adults; 698 children)	Gadoterate meglumine (II)	0
Lauenstein, 2015[35]	Any degree kidney disease = 186[b] eGFR >65 mL/min = 47 eGFR 60-64 mL/min = 32 eGFR 30-59 mL/min = 193 eGFR <30 mL/min[b] = 85	Gadoexetic acid (III)	0
Patients With CKD—Stages 3 to 5			
de Campos, 2011[45]	CKD stages 3-5 = 24 (total 69)[c] eGFR range < 30 mL/min = 14 eGFR >30 mL/min = 10	Gadobenate dimeglumine (II)	0
Soulez, 2015[38]	CKD stages 3-5 = 329	Gadobenate dimeglumine (II)	0
	CKD stages 3-5 = 160	Gadoteridol (II)	0
Abujedeh, 2009[46]	CKD stages 3-5 = 250 Stage 3 = 243 Stage 4 = 6 Acute renal failure = 1	Gadobenate dimeglumine (II)	0
Bryant, 2009[33]	CKD stages 3-5 = 148 mean eCrCl = 50.4 mL/min (range 30-59)	Gadobenate dimeglumine (II)	0
McKinney, 2015[42]	CKD stages 3-5 = 31 Mean eGFR = 36.7 mL/min (±18.7)	Gadoexetic acid (III)	0
Patients With ESRD Receiving Dialysis			

Study	Range Kidney Function Included, N Patients Exposed GFR Range/CKD Stage, N Patients Exposed	Index GBCA (ACR Group)	Number of NSF Cases
Reilly, 2008[47]	ESRD on dialysis = 141	Gadoteridol (II)	0
Nandwana, 2015[43]	ESRD = 401 ESRD not dialysis dependent = 98 ESRD on dialysis = 303	Gadobenate dimeglumine (II)	0
Gheuens, 2014[34]	ESRD on dialysis = 10	Gadoterate meglumine (II)	0
Patients With Chronic Liver Disease			
Shaffer, 2015[44]	Chronic liver disease = 352	Gadobenate dimeglumine (II)	0

[a] Includes those on dialysis.
[b] Study initially aimed to include only patients with moderate to severe renal insufficiency (eGFR <60); however, some patients had improved eGFR between screening and baseline, so additional categories added; values listed are categorized by baseline eGFR at time point that was most proximal to GBCA exposure. Only 186 of 357 patients completed the 24 month follow-up.
[c] n = 44 exposed to ½ dose of gadobenate dimeglumine but incomplete data available
Abbreviations: CKD=chronic kidney disease; eCrCl=estimated creatinine clearance; eGFR=estimated glomerular filtration rate; ESRD=end-stage renal disease; GBCA=gadolinium-based contrast agent;; NSF=nephrogenic systemic fibrosis

Table 5. Occurrence of NSF After Index Exposure to ACR Group II and III GBCAs: Nonrandomized Controlled Trial

Study (N patients)	GFR Range/CKD Stage	GBCA (ACR Group)	Number of NSF Cases
Deray, 2013[48] (n = 135)	Stage 3-4 CKD	Gadoterate meglumine (II)	0

Abbreviations: CKD=chronic kidney disease; GBCA=gadolinium-based contrast agent; GFR=glomerular filtration rate; NSF=nephrogenic systemic fibrosis

Quality of Evidence for Key Question 1

Among the cohort studies, ROB was rated high in 9 studies (60%)[34,35,37-39,42,44,45,47] and unclear in 6 studies (40%) (Figure 4).[33,36,40,41,43,46] One nonrandomized prospective trial was rated as overall high ROB (Table 6).[48] While this group of studies shared some common strengths including many being prospective, common factors contributing to higher ROB designations included inadequate or unclear exposure characterization, inadequate outcome identification, and clinically significant rates of missing data. Inadequate or unclear exposure characterization was a frequent finding as many studies did not consider coexisting exposure to GBCAs from institutions or settings outside that of the study activities. Inadequate outcome identification was often due to lack of use of definitive diagnostic criteria or limiting assessment for NSF to a subpopulation of included patients. Rates of missing data was a significant issue, since even the occurrence of a small number of NSF cases would be a clinically significant difference given the low rate of NSF. ROB ratings are shown for each study in Figure 4, Figure 5, and Table 6.

Figure 4. Risk of Bias Ratings for Included Cohort Studies in KQ 1

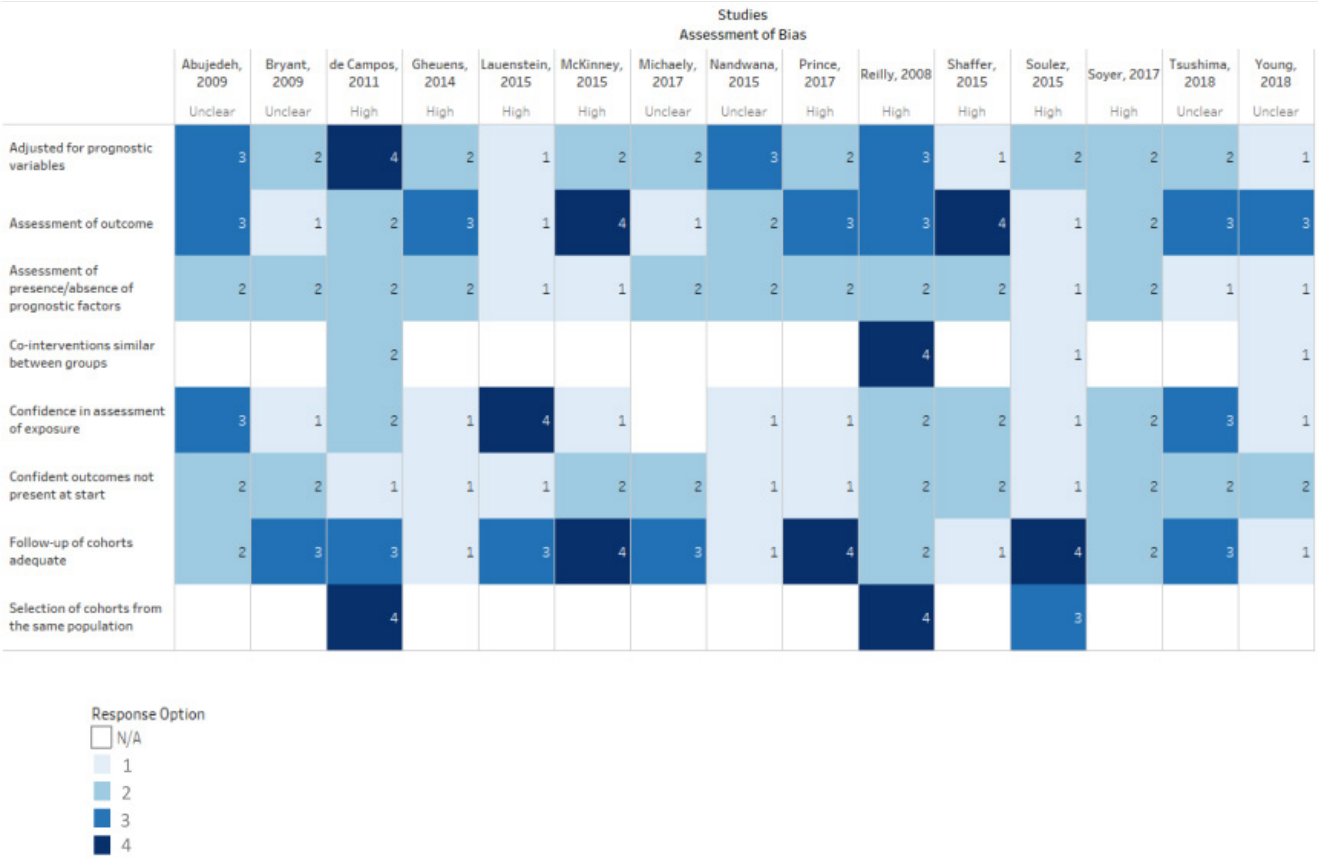


Figure 5. Risk of Bias Assessment by Question Across Included Cohort Studies in KQ 1

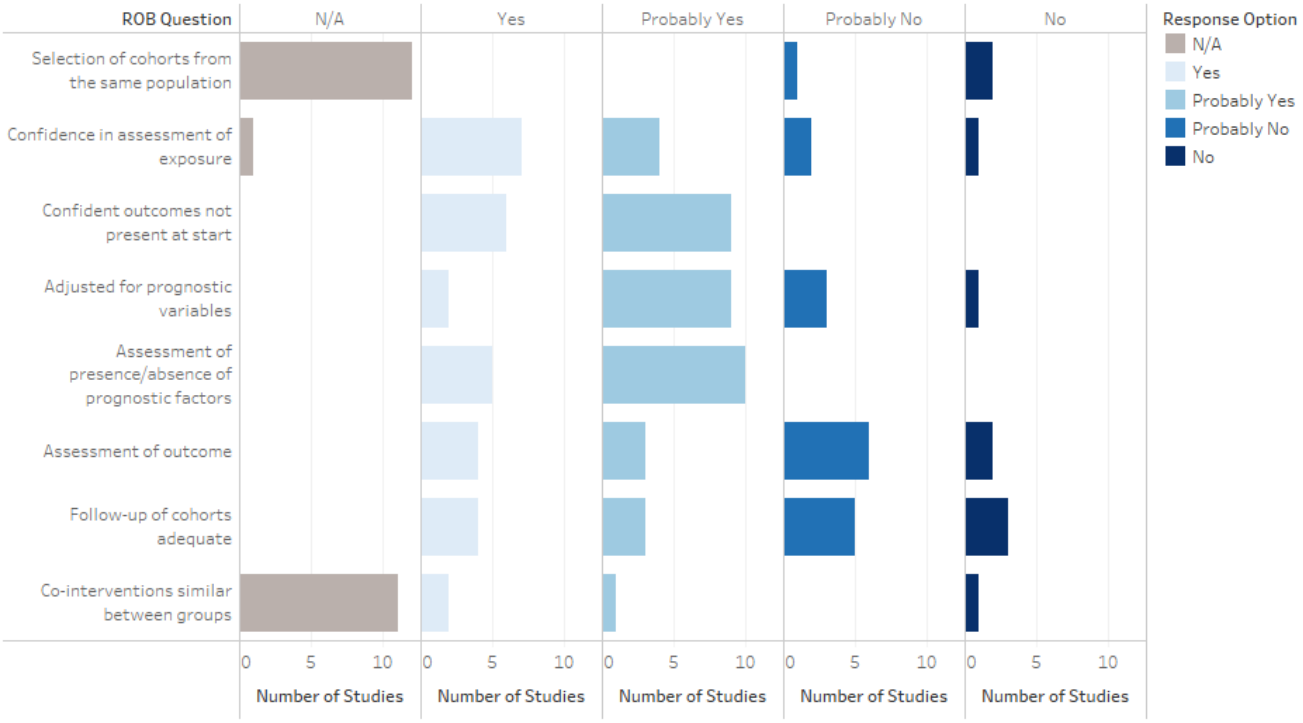


Table 6. Risk of Bias Ratings by Questions for Included Nonrandomized Controlled Trial in KQ 1

ROB Questions	ROB Rating
Random sequence generation (selection bias)	High
Allocation concealment (selection bias)	High
Were baseline OUTCOME measurements similar	Low
Were baseline PROVIDER characteristics similar	N/A
Blinding of outcome assessment (detection bias-objective outcome)	Unclear
Blinding of outcome assessment (detection bias-patient-reported outcome)	N/R
Incomplete outcome data (attrition bias)	High
Protection against contamination	Unclear
Selective reporting (reporting bias)	Low
Other bias	Unclear
Overall bias-objective	High
Overall bias-patient-reported	N/A

Summary of Findings

Overall, there were no cases of NSF reported among the 16 studies that examined the occurrence of NSF among patients exposed to newer linear and macrocyclic GBCAs (ACR groups II and III). Three cohort studies determined rates of NSF following index exposure to macrocyclic or newer linear gadolinium-based agents in all patients, without disaggregation by kidney function or risk factors for CKD (KQ 1A). There were no NSF cases reported in this subpopulation. We did not find studies that assessed NSF risk in patients with key risk factors for CKD such as diabetes and hypertension (KQ 1B). Finally, there were no cases of NSF reported in 12 studies that assessed rates of NSF specifically in patients with any degree of kidney disease (KQ 1C). Of note, among the 10 studies in patients with stage 3 CKD or worse, there were only 1,751 patients with an index ACR group II or III GBCA exposure.

KEY QUESTION 2: When compared with older gadolinium-based contrast agents (American College of Radiology group I agents), what is the occurrence of nephrogenic systemic fibrosis per index GBCA exposure for newer GBCAs among:

A. All patients without restriction by kidney function

B. Patients with key risk factors for chronic kidney disease (*eg*, diabetes and hypertension)

C. Patients with any degree of kidney disease (*ie*, acute kidney injury or chronic kidney disease)

Key Points

- We found 12 studies that examined the occurrence of NSF among patients with index exposure to American College of Radiology (ACR) group I (110,345 patients) and ACR group II GBCAs (8,499 patients), and no exposures to ACR group III GBCAs.
- Across 2 studies enrolling all patients without restriction by renal function, we found 14 cases of NSF after 108,790 ACR group I GBCA exposures (calculated exact upper 95% CI range 0.0001 to 0.0003) and 1 case of NSF after 3,646 ACR group II GBCA exposures (calculated exact upper 95% CI range 0.0018 to 0.0058).
- No studies specifically examined NSF occurrence in patients at risk for CKD.
- Across 9 cohort studies that enrolled patients with any degree of kidney disease (including ESRD on dialysis), 15 cases of NSF were reported after ACR group I GBCA exposures (calculated exact upper 95% CI range 0.0065 to 0.4593), and 0 cases NSF after ACR group II GBCA exposure (calculated exact upper 95% CI range 0.0025 to 0.9750).
- One case control study that enrolled patients with renal insufficiency reported 7 patients with NSF after ACR group I GBCA exposure and 3 after ACR group II GBCA exposure.
- Of the 4 cases of NSF after index exposure to ACR group II agents, 3 appear to be confounded with other GBCAs.

Description of Included Studies

To address KQ 2, we searched the literature for studies including patients exposed to older linear GBCAs (ACR group I agents) and patients exposed to macrocyclic or newer linear GBCAs (ACR group II and III agents). In total, we found 12 studies that met this criteria (118,844 patients).[49-60] One was a nested case-control study of NSF cases compared with GBCA-exposed controls. We found 2 retrospective cohort studies that compared the risk of NSF after exposure to gadodiamide (ACR group I) versus gadobenate dimeglumine (ACR group II) before and after multifaceted health care system-level changes to reduce occurrence of NSF; examples of such changes include changing the standard gadolinium agent used and education of ordering providers.[49,54] All other studies identified were cohort studies that included index exposures to 3 or more GBCAs. Two of these studies were prospective,[51,60] and 7 were retrospective.[50,52,55-59] The retrospective cohort studies were primarily audits of existing patient data in the medical records of a given clinical institution (*ie*, dialysis unit, health care system). Eight studies included patients with index exposures one of 3 or more GBCAs across ACR groups I and II,[50-52,56-60] and 1 study included index exposures to ACR groups I and II GBCAs and a GBCA no longer in use (gadofosveset).[55] Four studies addressing KQ 2 were conducted within the United States,[49,50,54,59] 1 was conducted in China,[56] and the rest were conducted within Europe. Of note, 1 study was not designed to assess the risk of NSF after GBCA exposure; instead, incident NSF cases were collected as a secondary outcome.[60]

Across these 12 studies, there were index exposures to all ACR group II GBCAs, with a total of 8,499 patients in ACR group II GBCA index exposures compared with 110,345 patients in the ACR group I index exposures. The most common group II GBCA was gadobenate dimeglumine (7% of index exposures). We found no index exposures to the ACR group III agent gadoexetic acid (*ie*, gadoxetate disodium). There were 5 exposures to a now-discontinued GBCA, gadofosveset. Diagnosis of NSF was generally established though triangulation of medical record chart reviews or database analyses focusing on ICD codes, documentation of symptoms and exam findings, and sometimes pathology reports from skin biopsies. In addition, some studies surveyed local nephrology and dermatology providers for known NSF cases.[49] Ten cohort studies reported the diagnostic approach for NSF, which varied and consisted of review of patients' medical records (n=1); clinical symptoms and examination of skin (n=1); biopsy (n=7); and other clinical criteria (*ie,* Cowper criteria[61] [n=1]).[49-52,54-59] The follow-up of patients in observation for the development of evidence of NSF after index GBCA exposure ranged from 60 days to 10 years with a median of 28 months. Next, we report findings across the 12 included studies grouped by kidney disease status.

KQ 2A: Findings Among All Patients Without Restriction by Kidney Function

Two retrospective cohort studies (1 high and 1 unclear ROB) reviewed the dermatopathology records across all patients at a total of 3 hospitals (2 in the United States[59] and 1 in China[56]) for NSF or similar histopathologic diagnoses. The US-based study examined the records of 83,121 patients who had received a GBCA-enhanced magnetic resonance imaging (MRI) at 2 large medical centers in New York State: 71,441 gadodiamide (ACR group I), 8,669 gadopentetate dimeglumine (ACR group I), 2,785 gadobenate dimeglumine (ACR group II), and 226 gadoteridol (ACR group II).[59] That study found 31 NSF cases, of which 15 had received documented high-dose GBCA exposure at 1 of the 2 institutions prior to the development of NSF; the other 16 cases either received GBCA exposures at a different institution or had no available information on GBCA exposure (see Figure 6 for cases by GBCA index exposure across studies). Fourteen of the NSF cases occurred in patients exposed to gadodiamide (ACR group I) and 1 in a patient exposed to gadobenate dimeglumine (ACR group II). That patient developed NSF after 2 exposures to high-dose gadobenate dimeglumine but also had received an unknown GBCA at another medical facility within 60 days of symptom onset. All 15 cases of NSF occurred in patients with impaired renal function at the time of GBCA exposure (3 on chronic dialysis or continuous veno-venous hemofiltration [CVVH] and 12 with eGFR range 5-22 ml/min). This cohort included 131 patients with AKI, which accounted for 11 of the 15 NSF cases (including the case with gadobenate dimeglumine).

The other study examined records in a single military hospital in Beijing, China, and found 0 cases of NSF among 29,315 patient index exposures (28,680 exposed to gadopentetate dimeglumine [ACR group 1] and 635 exposed to gadobenate dimeglumine [ACR group II]) over a 44-month period.[56] This cohort included 118 patients with CKD or AKI and 33 patients on hemodialysis with GBCA exposure (which agent was not reported). See Table 7 for additional details.

KQ 2B: Findings Among Patients With Key Risk Factors for Chronic Kidney Disease

No studies specifically examined the occurrence of NSF after GBCA exposure among patients with risk factors for CKD. Neither of the 2 cohorts described above that examined NSF occurrence across an entire medical center reported the prevalence of risk factors for CKD among those exposed.

One study with high ROB examined the occurrence of NSF after GBCA exposure among a cohort of 1,167 patients with chronic liver disease (843 patients with eGFR<90 ml/min/1.73m^2) receiving care at a tertiary liver center.[50] In this cohort, 186 patients with CKD were exposed to multiple GBCAs, and the index exposure could not be determined. Otherwise, 675 patients received gadobenate dimeglumine (ACR group II), 301 gadoversetamide (ACR group I), and 5 to gadopentetate dimeglumine (ACR group I). There were no cases of NSF reported.

KQ 2C: Findings Among Patients With Any Degree of Kidney Disease

Patients With CKD—Any Stage

For this category, we identified 1 cohort study[58] and 1 case-control study[53] that included patients exposed to ACR group I and II GBCAs. We found a second cohort study that also included patients exposed to a now-discontinued agent, gadofosveset.[55] All studies involved retrospective data collection and were found to have a high ROB. The 2 cohort studies mostly consisted of patients with stage 3 CKD or higher (91.9%[58] and 80.8%[55]). Both had a majority of ACR group II exposures (179[58] and 1,486[55]) compared with ACR group I exposures (53[58] and 562[55]). There were only 5 gadofosveset index patient exposures in the one cohort.[55] Neither cohort study identified any cases of NSF (Figure 6, Table 7). The case-control study included 7 NSF cases with ACR group I index exposure (1 gadopentetate dimeglumine, 6 gadodiamide) and 3 cases with ACR group II index exposures (2 gadobutrol and 1 gadoterate megumine) (Table 8).[53]

Patients With CKD—Stages 3 to 5

Two retrospective cohort studies examined GBCA exposures among patients with CKD stage 3 or higher.[49,57] One study at high ROB compared patients pre- and post-educational and policy changes at an academic medical facility in the United States during which the agent given to patients with eGFR ≤30 was changed from gadodiamide (ACR group I) to gadobenate dimeglumine (ACR group II).[49] That study found 6 NSF cases among 246 patients with index exposure to gadodiamide and 0 cases among 1,423 patients exposed to gadobenate dimeglumine. The other study was a retrospective cohort at low ROB with 27 patients with stage 3 CKD or higher (median stage 4) who had received GBCA as an alternative contrast agent for conventional angiography (1 exposed to ACR group II agent, 26 exposed to ACR group I agent).[57] That study found 1 case of NSF in a patient with index exposure to gadodiamide (ACR group I) confounded by 8 additional GBCA exposures (3 of which were with ACR group II agents and 5 were other ACR group I GBCAs).

Patients With ESRD Receiving Dialysis

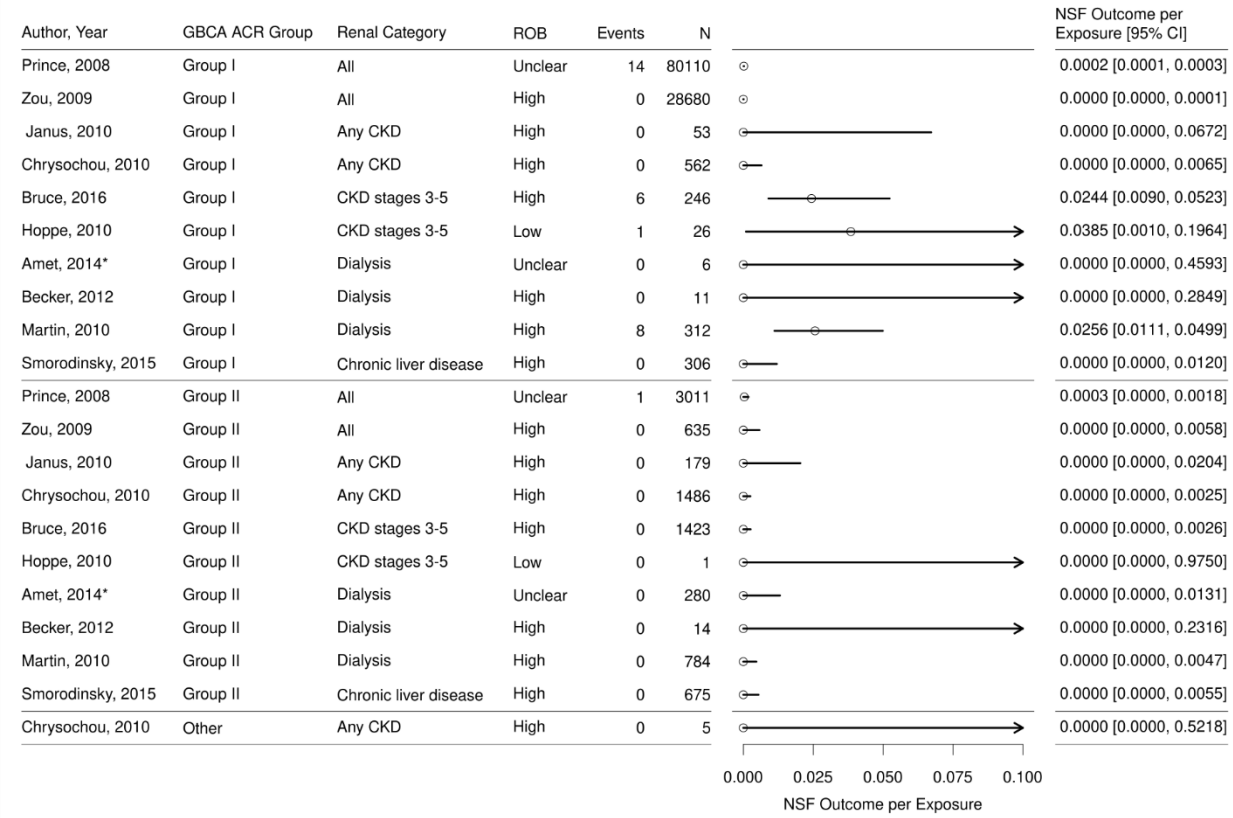
Four studies (2 prospective[51,60] and 2 retrospective[52,54]) focused specifically on patients receiving dialysis. One study conducted a prospective cohort study (571 patients; unclear ROB) for the French drug regulatory agency among patients on chronic dialysis (both hemodialysis and

peritoneal dialysis) for at least 3 months who were scheduled for an MRI with or without GBCA contrast.[51] Of the 280 patients in this cohort who received an identified GBCA, 6 patients received an ACR group I agent (5 gadopentetate dimeglumine and 1 gadodiamide) and 280 received an ACR group II agent (255 gadoterate meglumine, 12 gadobenate dimeglumine, 11 gadobutrol, and 2 gadoteridol). Patients self-monitored for symptoms of dermatologic changes and were systematically evaluated if symptoms arose. Authors also sought potential cases of NSF and/or dermatologic events from treating nephrologists and regional pharmacovigilance centers. No cases of NSF were identified.

The 2 retrospective studies of patients on chronic dialysis were rated as high ROB. One reported occurrence of NSF before and after a policy-based change in GBCA usage among patients on dialysis (full-dose gadodiamide to half-dose gadobenate dimeglumine) at a large academic institution.[54] That study found 8 cases of NSF out of 312 patients who received gadodiamide (ACR group I) compared with 0 cases among 784 patients who received gadobenate dimeglumine (ACR group II). The other study reported on 508 hemodialysis patients in Germany, of whom 25 had undergone GBCA exposure (11 ACR group I, 14 ACR group II), and found 0 cases of NSF.[52]

Last, 1 study included a secondary safety analysis at unclear ROB with 38 hemodialysis patients from a prospective parent cardiovascular study in combination with GBCA-exposed patients for clinical reasons.[60] That study identified 1 confounded case of NSF in a patient with index exposure to an ACR group I agent and a total of 6 GBCA-enhanced MRIs (5 with gadopentetate dimeglumine and 1 with gadobenate dimeglumine).

Figure 6. NSF Occurrence per GBCA Exposure[a]



* Prospective cohort studies.
Abbreviations: ACR=American College of Radiology; CI=confidence interval; CKD=chronic kidney disease; GBCA=gadolinium-based contrast agent; NSF=nephrogenic systemic fibrosis; ROB=risk of bias

Table 7. Cases of NSF After Index Exposure to ACR Group II vs ACR Group I: Cohort Studies

Study	Range Renal Function Included, N Patients Exposed GFR Range/CKD Stage, N Patients Exposed	Index GBCA (ACR Group)	Number of NSF Cases
All Patients Without Restriction by Kidney Function			
Prince, 2008[59]	All = 83,121 eGFR 15-30: 387 eGFR <15: 114	Gadodiamide (I) = 71,441 Gadopentetate dimeglumine (I) = 8,669 Gadobenate dimeglumine (II) = 2,785 Gadoteridol (II) = 226	1 confounded case after gadobenate dimeglumine index exposure vs 14 cases after exposure to gadodiamide
Zou, 2009[56]	All = 29,315 eGFR 15 to < ~30: 92	Gadopentetate dimeglumine (I) [Bayer] 17,491 + [Beijing Beilu] 11,189 = 28,680 Gadobenate dimeglumine (II) = 635	0

Study	Range Renal Function Included, N Patients Exposed GFR Range/CKD Stage, N Patients Exposed	Index GBCA (ACR Group)	Number of NSF Cases
Any Degree of Kidney Disease			
Chrysochou, 2010[55]	Any CKD = 2053 eGFR ≥90: 89 eGFR 60-90: 305 eGFR 45-59/30-44: 918 eGFR 15-30: 491 eGFR <15: 250	Gadopentetate dimeglumine (I) = 522 Gadodiamide (I) = 40 Gadoterate meglumine (II) = 86 Gadobutrol (II) = 69 Gadobenate dimeglumine (II) = 1331 Gadofosveset trisodium (NA) = 5	0
Janus, 2010[58]	Any CKD = 232 (308 total) eGFR 60-90: 22 eGFR 45-59: 56 eGFR 15-30: 62 eGFR <15: 165	Gadopentetate dimeglumine (I) 46 Gadodiamide (I) 7 Gadobenate dimeglumine (II) 3 Gadoterate meglumine (II) 176	0
Patients With CKD—Stages 3 to 5			
Bruce, 2016[49]	CKD stages 3-5 = 1669	Gadodiamide (I) 246 Gadobenate dimeglumine (II) 1423	6/246 cases gadodiamide vs 0/1423 cases gadobenate dimeglumine
Hoppe, 2010[57]	CKD stages 3-5 =27	Gadodiamide (I) 25 Gadopentetate dimeglumine (I) 1 Gadobutrol (II) 1	1 confounded NSF case after exposure to gadodiamide, gadoteridol, gadopentetate dimeglumine
Patients With ESRD Receiving Dialysis			
Amet, 2014[51]	ESRD on dialysis = 287 (571 total)	Gadopentetate dimeglumine (I) 5 Gadodiamide (I) 1 Gadoterate meglumine (II) 255 Gadobenate dimeglumine (II) 12 Gadobutrol (II) 11 Gadoteridol (II) 2	0
Becker, 2012[52]	ESRD on dialysis = 25 (508 total)	Gadodiamide (I) 4 Gadopentetate dimeglumine (I) 7 Gadoterate meglumine (II) 5 Gadobutrol (II) 4 Gadoteridol (II) 5	0
Martin, 2010[54]	ESRD dialysis = 1,096	Gadodiamide (I) 312 Gadobenate dimeglumine (II) 784	8/312 gadodiamide vs 0/784 gadobenate dimeglumine
Schieren, 2008[60]	ESRD on dialysis = 20 (38 total)	Gadopentetate dimeglumine (I) 19 Gadobutrol (II) 1 Gadopentetate /Gadobutrol 18	1 gadopentetate dimeglumine

Study	Range Renal Function Included, N Patients Exposed GFR Range/CKD Stage, N Patients Exposed	Index GBCA (ACR Group)	Number of NSF Cases
Patients With Chronic Liver Disease			
Smorodinsky, 2015[50]	Chronic liver disease = 981 (1167 total)	Gadopentetate dimeglumine (I) 5 Gadobenate dimeglumine (II) 675 gadoversetamide 301	0

Abbreviations: ACR=American College of Radiology; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; ESRD=end-stage renal disease; GBCA=gadolinium-based contrast agent; NSF=nephrogenic systemic fibrosis

Table 8. Cases of NSF After Index Exposure to ACR Group II: Case-Control Studies

Study	Range Kidney Function Included, N Patients Exposed GFR Range/CKD Stage, N Patients Exposed	Index GBCA (ACR Group)	Number of NSF Cases
Elmholt, 2011[53]	Any degree kidney disease = 17 cases NSF (17 controls)	• Mix of agents • 2 control groups (exposed, unexposed) • 10 cases and controls exposures NR	• 2 cases gadobutrol (1 possibly confounded) • 1 case gadoterate meglumine (1 possibly confounded) • 7 cases group I or unknown

Abbreviations: ACR=American College of Radiology; CKD=chronic kidney disease; GBCA=gadolinium-based contrast agent; GFR=glomerular filtration rate; NSF=nephrogenic systemic fibrosis; NR=not reported

Summary of NSF Cases from Studies

Across the included studies that examined patients exposed to ACR group II and ACR group I GBCA (188,819 patients), 41 patients were found to have NSF. All but 4 patients had some reported exposure to ACR group I agents (index or otherwise). The degree of renal impairment was not clear across these 4 cases, but all had CKD of some stage and 2 had eGFR <30 or were on dialysis. Of the 4 patients found to have NSF after an index exposure to ACR group II agents, 1 patient had received an unknown GBCA within 2 weeks prior to the index exposure of gadobenate dimeglumine,[59] 2 received gadobutrol (1 with potential confounding),[53] and 1 received gadoterate meglumine (also with potential confounding).[53] Thus, there was one unconfounded case of NSF after index exposure to an ACR group II agents.

Quality of Evidence for Key Question 2

For the 12 included studies, we found the ROB for occurrence of NSF to be low for 1 study,[57] unclear for 4 studies,[51,53,59,60] and high for 7 studies.[49,50,52,54-56,58] Similar to KQ 1, the most common methodologic issues that led to findings of higher ROB included inadequate or unclear exposure characterization (n=5); inadequate outcome identification (n=9); and higher rates of missing data (n=7). ROB ratings are shown for each study in Figures 7-9.

Figure 7. Risk of Bias Ratings for Included Cohort Studies in KQ 2

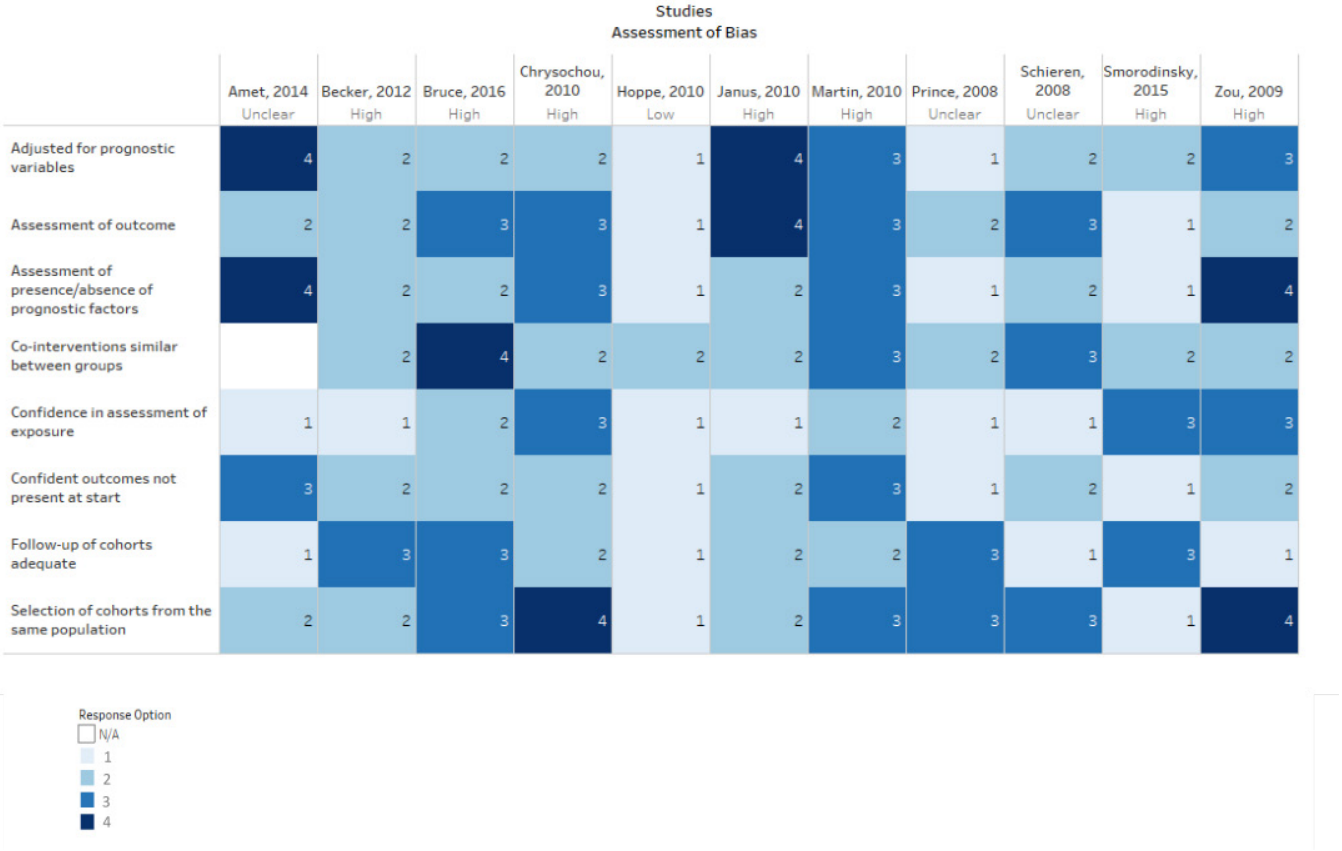
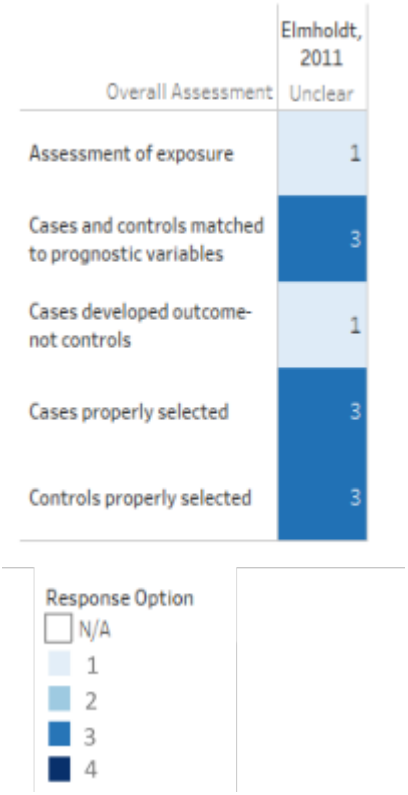


Figure 8. Risk of Bias Assessment Across Included Cohort Studies in KQ 2

Figure 9. Risk of Bias Ratings for Included Case-Control Study in KQ 2



Summary of Findings

Across the 12 studies (1 low ROB, 4 unclear ROB, 7 high ROB), a total of 110,345 patients had index GBCA exposures to ACR group I agents and 8,499 to ACR group II agents. Forty-one cases of NSF were reported with a clearly identified GBCA exposure, of which 37 had a reported exposure to an ACR group I agent and 4 had an index exposure to an ACR group II agent. There were no index exposures to the single ACR group III agent, Gadoexetic acid. Only 1 study included prospective data collection among patients with GBCA exposures,[51] while the rest assessed GBCA exposure and NSF cases from previously existing chart records and recall of involved providers. While most of the included studies examined occurrence of NSF after index exposure to GBCA among patients with CKD, most of the patient-level GBCA exposures were from the general population studies, which did not restrict enrollment to those with kidney disease. We did not find any studies that focused specifically on patients at risk for CKD, and risk factors for CKD were not reported among patients in cohorts involving undifferentiated general populations.

CASE REPORTS AND CASE SERIES: NSF AFTER EXPOSURE TO NEWER GBCAs

Key Point

- We identified 18 cases of NSF after exposure to ACR group II or III GBCAs reported across included case reports and case series; in total 9 cases were unconfounded and occurred after exposure to gadobutrol (n=6) and gadobenate dimeglumine (n=3).

In addition to the above included studies for KQ 1 and KQ 2, we also included case reports and case series of patients diagnosed with NSF after exposure to a newer GBCA (ACR group II or III). While these study designs are generally less rigorous and would not support the determination of the rate of occurrence of NSF after exposure to certain GBCAs, they are described here to provide context for a possible signal of association in the published literature. Table 9 shows aspects of the 18 cases of NSF described in the 10 identified case reports and case series.[62-71] Nine of the 18 cases were reported to be unconfounded (gadobutrol, n=6; gadobenate dimeglumine, n=3). The other 9 cases included a described confounding with an older GBCA known to be associated with NSF. All but 2 of the cases described reported diagnosis at least in part due to a skin biopsy, though specific diagnostic criteria were generally not reported. Renal function at the time of GBCA exposure was inconsistently reported. We did not conduct a quality assessment of case reports and case series.

Table 9. Case Reports and Case Series of NSF After Index Exposure to Newer GBCAs

Study	Number of NSF Cases	GBCA	Age Gender	Kidney Function[a]	Diagnostic Criteria/Biopsy	Confounded?	Notes
Endrikat, 2018[62]	3	Gadobutrol	NR	NR	Cowper/Girardi diagnostic (x2) Cowper/Girardi consistent with (x1)	N	Pharmacovigilance database
Lohani, 2017[63]	1	Gadobenate dimeglumine	57, F	eGFR 64 mL/min/1.73m^2→ CrCl 22.7mL/min	Skin biopsy	N	Comorbid hypertension; likely inaccurate initial GFR estimation
Barbieri, 2016[64]	2	Multi-agent	52, F	eGFR 30.3 mL/min/1.73m^2	Skin biopsy	Y Gadodiamide, Gadoteridol*, Gadopentetate dimeglumine, Gadobutrol*	Renal transplant; cumulative GBCA dose 1.26mmol/kg (0.68mmol/kg older linear GBCAs)
		Multi-agent	61, F	Unknown	Skin biopsy	Y Gadodiamide, Gadoteridol, Gadoterate meglumine*	Renal transplant; cumulative GBCA dose 0.81 mmol/kg (0.45mmol/kg older linear GBCAs)
Birka, 2015[65]	1	Multi-agent	25, F	Dialysis	Skin biopsy	Y Gadopentetate dimeglumine, Gadoteridol	Renal transplant
Elmholdt, 2013[66]	3 (of 64 total)	Gadobutrol (2) Gadobenate dimeglumine (1)	Unknown	Unknown	Skin biopsy	N	Nationwide investigation (Denmark)
Wollanka, 2009[68]	1	Gadobutrol	69, M	Dialysis	Skin biopsy	N	Hyperphosphatemia, anemia, arteriosclerosis

Study	Number of NSF Cases	GBCA	Age Gender	Kidney Function[a]	Diagnostic Criteria/Biopsy	Confounded?	Notes
Shin, 2008[69]	1	Multi-agent	60, F	eGFR ~30ml/min/1.73m^2	Skin biopsy	Y Gadobenate dimeglumine (105ml total); gadopentetate dimeglumine dimeglumine (60ml total)	Hypertension, diabetes mellitus, coronary artery disease
Sadowski, 2007[70]	1 (of 13 total)	Multi-agent	Unknown, F	eGFR 21.6-23.9 ml/min/1.73m^2	Skin biopsy	Y Gadodiamide; Gadobenate dimeglumine	Liver transplant, angiosarcoma, portal vein thrombosis
Semelka, 2016[71]	3 (of 4 total)	Multi-agent	43, F	"Normal renal function"	"Subcutaneous lesions, skin tightness, and shiny appearance of skin over fingers"	Y Gadoversetamide; gadoexetic acid; gadobutrol	Exam 3.5 months after GBCA exposure; h/o Guillain-Barre syndrome
		Gadobenate dimeglumine	58, F	"Normal renal function"	Skin biopsy	Gadobenate dimeglumine	Exam 7 years after GBCA exposure
		Multi-agent	55, F	"Normal renal function"	"Skin and subcutaneous tissues of her hands and feet were thickened and red with a doughy consistency"	Gadodiamide; Gadobenate dimeglumine	Exam 8 years after GBCA exposure
Becker, 2010[67]	2 (of 23 total)	Multi-agent	Unknown	Unknown	Skin biopsy	Y Gadobutrol; Gadopentetate dimeglumine	German registry
		Multi-agent	Unknown	Unknown	Skin biopsy	Y Gadoterate meglumine;	

Study	Number of NSF Cases	GBCA	Age Gender	Kidney Function[a]	Diagnostic Criteria/Biopsy	Confounded?	Notes
						unspecified older linear	

[a] At time of GBCA exposure.
*Most proximal to diagnosis of NSF.
Abbreviations: eGFR=estimated glomerular filtration rate; F=female; GBCA=gadolinium-based contrast agent; M=male; N=no; Y=yes

SUMMARY AND DISCUSSION

Magnetic resonance imaging (MRI) has become an essential tool in the diagnosis and management of a myriad of medical conditions, with 118 MRIs per 1,000 people conducted annually in the United States.[72] Because the preferred contrast medium for MRIs is a gadolinium-based contrast agent (GBCA), there has been widespread exposure to GBCAs across the population. However, with the recognition of the association of GBCA exposure with the rare, but devastating, condition of nephrogenic systemic fibrosis (NSF) among patients with impaired kidney function, swift restrictions were placed on GBCA use for at-risk patients. Currently, GBCA-enhanced MRIs are contraindicated for individuals with acute kidney injury, estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2, and those requiring renal replacement (*ie*, peritoneal dialysis or hemodialysis) (see Appendix B for guidelines). Fortunately, transition to macrocyclic and newer linear agents, caution with dosing, and judicious use among at-risk individuals have resulted in a dramatically reduced NSF incidence.[73] However, clinicians caring for patients with kidney disease now face a difficult dilemma. When a patient with impaired renal function could benefit from a GBCA-enhanced MRI and a reasonable alternative is not available, the patient and clinician must determine if the clinical benefit outweighs the small but serious risk of NSF. Given the relative paucity of information about risk of NSF with newer GBCAs in patients with CKD, uncertainty about current restrictions has arisen. Thus, we sought to assess the occurrence of NSF in patients after index exposure to this group of newer, seemingly safer, group of GBCAs.

Among older GBCAs, NSF is a rare adverse event in the range of 36.5 per 100,000 exposures.[74] However, since the FDA and other international governing bodies issued warnings on the use of these older ACR group I gadolinium agents, there has been a dramatic reduction in NSF occurrence.[1] While this represents a marked policy success, a resulting implication of this wholesale practice change is that there are fewer opportunities for cases to occur[1] and less data from which to determine the pools of patients who are at greatest risk and those who can undergo exposure with less risk. Studying adverse events in general can be challenging as they are usually not subjected to the same rigor and systematic collection as other outcomes in clinical trials.[75,76] Infrequent adverse events, such as NSF, are particularly unlikely to be adequately captured in the context of a trial.

To assess the risk of NSF after exposure to newer linear and macrocyclic GBCAs, we cast a wide net for study types that could provide evidence to explore our key questions, with a primary focus on studies that allowed for calculation of risk with a clear numerator and denominator. However, we also included case series and case reports to provide information about a potential signal for NSF risk not otherwise captured in the identified observational studies. In total, we identified 28 studies for this review. Sixteen studies evaluated only the newer linear or macrocyclic GBCAs (ACR groups II and III) and were included in the analysis to address KQ 1. Twelve studies included patients exposed to both the newer and older linear GBCAs and thus were included in the analysis for KQ 2.

SUMMARY OF EVIDENCE BY KEY QUESTION

Key Question 1 Summary

The primary objective of KQ 1 was to identify the occurrence of NSF following index exposure to the presumably safer macrocyclic and newer linear GBCAs (ACR groups II and III). Additionally, our secondary objective was to identify the occurrence of NSF within specific subpopulations: all patients without restriction by kidney function; patients with CKD or AKI; and patients with CKD risk factors such as hypertension and diabetes. We included 16 eligible studies consisting of 15 cohort studies, and 1 nonrandomized controlled trial. Across these studies, ROB was mostly high or unclear. The pooled patient population in the mostly prospective cohort studies was 80,932. Index GBCA exposure was to the newer linear GCBAs in most studies (n=13) and less so to macrocyclic agents (n=2). However, 9 studies reported that patients were exposed to multiple GBCAs, including a mix of macrocyclic and newer linear agents.

Across these studies, there were no cases of NSF reported following exposure to the macrocyclic or newer linear GBCAs (ACR group II and III) or a mix of these agents. While these findings were consistent even within patient subpopulations, such as among all patients or those with CKD and AKI, the majority of patients exposed across all 16 studies did not have kidney disease of any type. In fact, less than 10% of patients across these studies were identified to have CKD. In addition, none of the included studies assessed NSF occurrence specifically among patients with CKD risk factors such as hypertension and diabetes, and acute renal failure was inconsistently reported. In summary, we found no evidence of occurrence of NSF across 80,932 patient index exposures to macrocyclic or newer linear GBCAs among patients mostly with normal or near normal renal function. As shown in the forest plot (Figure 3), the exact upper 95% CI for the estimate of NSF occurrence per exposure ranged from 0.0001 to 0.3085. Thus, rare events remain possible in understudied populations (*eg*, CKD, AKI, and patients at risk for CKD).

This review focused on the development of NSF after index exposure to an ACR group II or III GBCA (KQ 1), and when possible, in comparison to ACR group I GBCAs (KQ 2). For these outcomes, we assessed our degree of confidence in our summary findings using certainty of evidence (COE) ratings. Similar to our analysis, for rating the COE we focused on those studies which were primarily designed to identify NSF after GBCA exposure. We present the COE for each patient population of interest across both KQs. These ratings are summarized below with supporting information provided in Table 10.

- We found *low* COE due to ROB that there are no cases of NSF after index exposure to ACR group II GBCAs among patients in the general population without restriction by kidney function.
- We found *low* COE due to ROB that there are no cases of NSF after index exposure to ACR group II GBCAs among patients with any level of kidney disease.
- We found *very low* COE due to ROB that there are no cases of NSF after index exposure to ACR group II or III GBCAs among patients with stage 3-5 CKD.
- We found *low* COE due to ROB that there are no cases of NSF after index exposure to ACR group II GBCAs among patients with ESRD on dialysis.

Because we found no studies in patient populations with risk factors for CKD, we did not rate the certainty of evidence for this question. In addition, the only patient population in which a study used the ACR group III agent, gadoexetic acid, was CKD stage 3-5, thus that is the only COE rating that includes mention of ACR group III GBCAs.

Table 10. Certainty of Evidence for Occurrence of NSF After Index Exposure to ACR Group II and III GBCAs

Outcome	Number of Studies (Number of Patients)	Range of CI	Certainty of Evidence Rating (Rationale)
Cases of NSF in all levels of kidney function	3 cohort studies (62,544)	0 cases of NSF Upper limit 95% CI range: 0.0001 to 0.0011	**0 Cases of NSF – Low COE** (rated down for serious risk of bias)
Cases of NSF in patients with key risk factors for CKD	0 studies	-	-
Cases of NSF in patients with any level kidney disease	3 cohort studies (16,471)	0 cases of NSF Upper limit 95% CI range: 0.0002 to 0.0196	**0 Cases of NSF – Low COE** (rated down for serious risk of bias)
Cases of NSF in patients with CKD stage 3-5[a]	6 observational studies[b] (1,8036)	0 cases of NSF Upper limit CI range: 0.0111 to 0.0246[b]	**0 Cases of NSF – Very Low COE** (rated down for very serious risk of bias)
Cases of NSF in patients on dialysis	3 cohort studies (552)	0 cases of NSF Upper limit CI range: 0.0092 to 0.0385	**0 Cases of NSF – Low COE** (rated down for serious risk of bias)

[a] Includes one study with 186 patients with index exposure to ACR group III agent.
[b] Includes 2 cohort studies and 1 nonrandomized controlled study, which are not included in the upper limit 95% CI ranges.
Abbreviations: CI=confidence interval; COE=certainty of evidence; NSF=nephrogenic systemic fibrosis; ROB=risk of bias

Key Question 2 Summary

We also assessed the occurrence of NSF among patients after index exposure to macrocyclic or newer linear GBCAs (ACR group II/III) compared with older linear GBCAs (ACR group I). Due to heterogeneity of patient populations, methodology, and time frame, we did not conduct meta-analyses or calculate risk ratios. Thus, we conducted a narrative synthesis of the 12 included studies for KQ 2, including 1 nested case-control study and 11 cohort studies. Across these studies, there were 110,345 patient index exposures to ACR group I GBCAs, 8,499 patient index exposures to ACR group II GBCAs, and no patient index exposures to the single ACR group III GBCA, gadoxetic acid. Most cohort studies were retrospective and reviewed existing chart records and administrative databases with occasional supplementation by provider recall. The majority of the patient-level index exposures across these 12 studies occurred in general patient populations with mostly normal kidney function (112,436 of 118,844, 94.6%). Those studies focused on patients with CKD were grouped by general stage of CKD with 3 studies looking at

NSF across any CKD stage, 2 studies focused on patients with stage 3-5 CKD, and 4 studies examining patients on dialysis only (5,427 patient index GBCA exposures). No studies specifically examined patients at risk for CKD.

Of the 41 cases of NSF identified in these 12 studies, only 4 cases were among ACR group II agents, of which 3 appear to be confounded with other unspecified GBCAs. The rest of the NSF cases occurred among patients with reported exposure to ACR group I agents. Among the 4 cases of NSF that occurred after index exposure to ACR group II agents, all had CKD of some stage and 2 had eGFR <30 or were on dialysis. Thus, across studies with 8,499 index exposures to ACR group II patients there was 1 reported unconfounded case of NSF (though this case came from a study that did not report exposures received outside the study institution). The exact upper 95% CI for NSF occurrence per index GBCA exposure for ACR group I agents ranged from 0.0001 to 0.4593 compared to ACR group II agents which ranged from 0.0018 to 0.9750 (see Figure 6). Thus, incident NSF is rare but the confidence intervals for ACR group I and group II agents are similar. The relatively scarce data among patients with CKD and among patients with exposures to the single ACR group III agent limit conclusions that can be drawn about safety and risk in these populations.

As noted above, we also present the COE rating for each patient population of interest. These ratings are summarized below with supporting information provided in Table 11.

- We found *very low* COE due to ROB and inconsistency that there are 14 cases of NSF after 108,790 index exposures to ACR group I GBCAs compared to 1 case of NSF after 3,646 ACR group II GBCAs among patients in all patients without restriction by renal function.
- We found *very low* COE due to ROB that there are 7 cases of NSF after 629 index exposures to ACR group I or and 3 after 1,675 index exposures group II GBCAs among patients with any level of renal insufficiency.
- We found *very low* COE due to ROB and inconsistency that there are 7 cases of NSF after 272 index exposures to ACR group I and no cases of NSF after 1,424 index exposure to ACR group II GBCAs among patients with stage 3-5 CKD.
- We found *very low* COE due to ROB that there are 9 cases of NSF after 348 index exposures to ACR group I GBCAs compared to 0 cases of NSF after 1,079 index exposures to ACR group II GBCAs among patients with ESRD on dialysis.

Similar to KQ 1, we found no studies in patient populations with risk factors for CKD, we did not rate the certainty of evidence for this question. We also did not find any studies that included exposures to ACR group III GBCAs.

Table 11. Certainty of Evidence for Occurrence of NSF After Index Exposure to ACR Group II Compared With ACR Group I GBCAs

Outcome	Number of Studies (Number of Patients)	Number of Cases NSF Range of CI	Certainty of Evidence Rating (Rationale)
Cases of NSF in all patients	2 cohort studies (112,436)	14 cases NSF after 108,790 ACR group I GBCA exposures Upper limit CI range: 0.0001 to 0.0003	**Very Low COE** (rated down for very serious risk of bias and inconsistency)
		1 case NSF after 3,646 ACR group II GBCA exposures Upper limit CI range 0.0018 to 0.0058	
Cases of NSF in patients with key risk factors for CKD	0 studies	-	-
Cases of NSF in patients with any level of kidney disease	3 observational studies (2,304)	7 cases NSF after 629 ACR group I GBCA exposures[a] Upper limit CI range: 0.0065 to 0.0672	**Very Low COE** (rated down for very serious risk of bias)
		3 case NSF after 1,675 ACR group II GBCA exposures[a] Upper limit CI range 0.0025 to 0.0204	
Cases of NSF in patients with CKD stage 3-5	2 cohort studies (1,696)	7 cases NSF after 272 ACR group I GBCA exposures Upper limit CI range:0.0523 to 0.1964	**Very Low COE** (rated down for very serious risk of bias and inconsistency)
		0 case NSF after 1,424 ACR group II GBCA exposures Upper limit CI range 0.0026 to 0.9750	
Cases of NSF in patients on dialysis	4 cohort studies (1,427)	9 cases NSF after 348 ACR group I GBCA exposures Upper limit CI range: 0.0499 to 0.4593[b]	**Very Low COE** (rated down for very serious risk of bias)
		0 case NSF after 1,079 ACR group II GBCA exposures Upper limit CI range 0.0047 to 0.2316	

[a] All 10 were from the case-control study,[53] which were not included in the upper limit 95% CI ranges.
[b] One case of NSF was reported in a cohort study where NSF was not a primary outcome,[59] which were not included in the upper limit 95% CI ranges.

Abbreviations: CI=confidence interval; COE=certainty of evidence; NSF=nephrogenic systemic fibrosis; ROB=risk of bias

Prior Systematic Reviews

Our findings are generally consistent with prior reviews of NSF risk and GBCA exposure. A recent review by Attari and colleagues (2019)[73] examined clinical features and risk factors of confirmed NSF cases in addition to comparing the incidence of NSF before and after 2008 (date FDA issued the boxed warning). They derived the denominator for incidence rate calculations from assumptions about market share for GBCAs by ACR group. An accompanying editorial noted the importance of use of a reliable exposure denominator and control group in order to apply data to clinical decision making.[77] In this project, we prioritized studies that included a clear denominator for patient exposure by GBCA (both KQ 1 and KQ 2) and those that included a comparison to ACR group I GBCAs (KQ 2). (Of note, Attari and colleagues reported 2 cases of unconfounded NSF after ACR group II GBCA exposure, both of which were included in our review under the case report/case series section as well.)

The work by Schieda and colleagues (2019)[7] as part of the Clinical Practice Guideline from the Canadian Association of Radiologists included a thorough review of reported data around cases of NSF after exposure to individual GBCAs, though it did not summarize the denominator of exposure by agent or group. A review by Zhang and colleagues (2015)[1] focused on the association between GBCA exposure generally and NSF occurrence and found an odds ratio of 16.504 (95% CI 7.455 to 36.533), which decreased from before 2007 to after 2007. Of their included studies, data by specific individual agents (only gadodiamide, gadopentetate dimeglumine, and gadoterate meglumine) or multiple unspecified agents. Our review included data across all ACR group II and III agents, though we found particularly limited data from ACR group III agents, which is likely a consequence of the restricted indications for its use.[7] We note that we reviewed the references from identified systematic reviews (those mentioned here and others) as part of our hand-search to supplement those articles identified by our formal search strategy.

CLINICAL AND POLICY IMPLICATIONS

Across 28 studies, we identified few cases—primarily confounded cases—in which group II or III agents were implicated in the development of NSF. Notably, the included studies we identified were heterogeneous in patient population, follow-up length, and overall quality. The majority of patients index GBCA exposures occurred in patients with normal or near normal renal function, and there was relatively little data on other patient populations of interest. Specifically, although several studies included individuals on dialysis, very few adequately reported on acute kidney injury, a known NSF risk factor from prior studies. In addition, there were no studies that specifically examined NSF occurrence among patients at risk for CKD, and few studies provided details on other potential risk factors for NSF development such as modality of renal replacement or inflammation status, among others. Consistent with (guidelines, current VA practice, *etc*) caution remains prudent in the use of GBCA among individuals with severely impaired renal function (*ie*, those with eGFR < 30) or fluctuating severe dysfunction and acute kidney injury, as the exact clinical factors contributing to NSF risk in these populations remains unknown (*ie*, hyperphosphatemia). Further investigation is also warranted to investigate the risk of GBCAs among individuals with kidney transplant and allograft dysfunction.

Canadian guidelines have suggested that individuals with AKI should be managed "similar to those with eGFR <30, with the caveat that if GBCA administration can be delayed it should be until renal function stabilizes or ameliorates."[7] Clinical equipoise may be most appropriate during the administration of GBCAs among individuals with AKI given the absence of comprehensive data evaluating NSF risk in this group.

LIMITATIONS

This review has a number of important strengths that provide notable contributions to the literature. First, we used an *a priori* publicly registered protocol, a comprehensive literature search, and a thorough quality assessment. Second, we focused our review on higher-order evidence that could provide risk calculations. However, in doing so, we may have excluded studies that reported information about NSF cases that may have been related to gadolinium exposure but from which we could not identify a clear numerator and/or denominator. Upon review of excluded studies, the only unconfounded cases of NSF come from 2 papers[78,79] that describe NSF or NSF-like cases reported to the postmarketing surveillance system of the manufacturer of gadobutrol. While it appears there may be overlap between these papers, together they report 2 to 7 unconfounded cases of NSF (2 of which were already captured in an included study [53] and 1 in our case reports [68]). In addition, while we included case reports among patients with NSF who were exposed to GBCAs of interest in order to identify a signal for potential risk, we did not include a search of the FDA Adverse Event Reporting database for case reporting.[80] In addition, it is important to note that this review is not a comprehensive review of all potential harms associated with gadolinium exposure. Of late there has been a growing awareness and concern about the long-term deposition of gadolinium in brain and other tissues among patients with normal renal function.[3,5] Thus, regardless of the risk of NSF development among certain patient populations, there are other concerns associated with the use of gadolinium that will necessarily inform shared decision-making with patients in need of advanced imaging modalities.

Study Quality

This report is also limited by the quality of the existing literature. Overall, the risk of bias for included studies was high or unclear primarily due to a few common issues. First, due to both the rarity and severity of NSF, ethical barriers will prevent study of this condition in randomized controlled trials and thus observational studies were the appropriate predominant design of choice for these investigations. Second, assessment of gadolinium exposure was often incomplete due to lack of investigation and accounting for exposures outside the healthcare setting of the study authors. This is particularly problematic in health care contexts such as the United States where patients could potentially receive medical care, and thus contrast-enhanced imaging, in multiple systems simultaneously. If patients had received more gadolinium exposure than captured by the included studies—in particular, if a patient had been exposed to older gadolinium agents with a well-documented risk for NSF—then we would expect that this bias would lead to overestimation of NSF cases. Third, missing data was a common issue. Given the rarity of expected events, if even a few patients who were lost to follow-up had developed NSF, the impact on outcomes would be significant. Thus, incomplete efforts to minimize missing data was a significant quality limitation in some studies and could lead to underestimation of risk of NSF with the agents in question. Fourth, many of the larger, single-agent observational studies included in this review were conducted by the manufacturers of the studied gadolinium agents.[35-

[40] As noted above, most of these studies were conducted in response to an FDA mandate for postmarketing surveillance and were powered based on expected incidence rates that turned out to be greater than those observed. This issue was further complicated by the fact that the FDA removed the postmarketing surveillance requirement in the midst of the conduct of some studies and recruitment was subsequently stopped early. Thus, a significant portion of the identified prospective, single-agent observational cohort studies were ultimately underpowered and terminated earlier than planned.

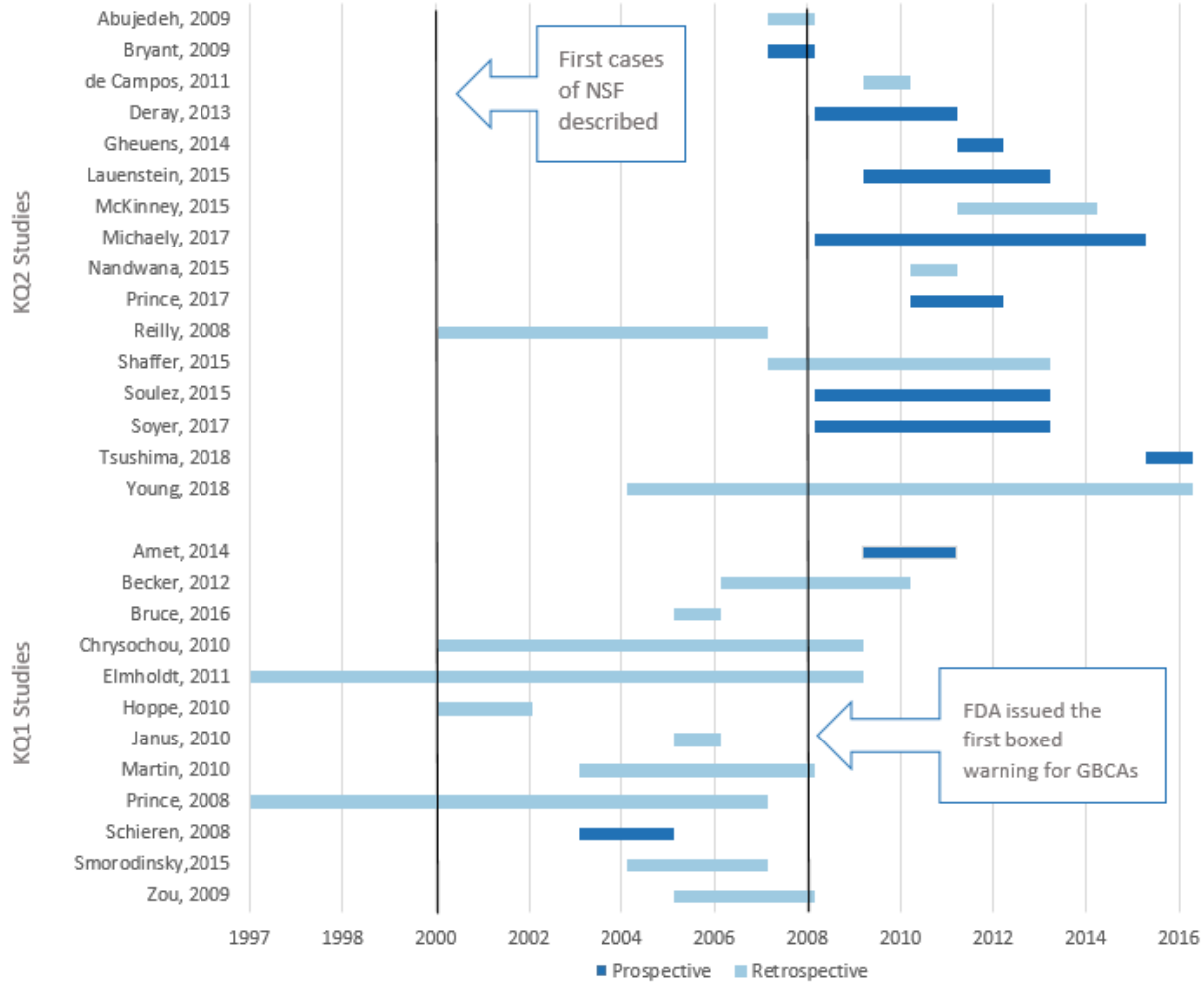
Publication Bias

Publication bias in the context of rare adverse events can be difficult to identify due to the reliance on observational studies, which are not consistently registered in ClinicalTrials.gov. Entities with a commercial interest in the use of certain gadolinium agents may play a role in potential publication bias—a role that typically is presumed to bias toward publication of favorable results[81] (or fewer cases of NSF). In the case of GBCA exposure, this risk is somewhat ameliorated by past FDA requirements for such entities to conduct postmarketing surveillance studies, at least some of which resulted in publications identified for this report.[35-40]

Heterogeneity

In general, the findings across the included studies were consistent with zero or very few cases of NSF reported. This consistency was found despite differences in study design and methodology. Examples of study variability include the severity of renal disease among included patients, country of study conduct, differences in study follow-up duration (see Appendix I), and timing of patient data collection relative to the clinical diagnosis (*ie*, retrospective vs prospective cohorts). Differences in timing of data collection could be potentially important as some studies obtained data about patient events which occurred before knowledge of NSF was widespread. This timing issue could increase the likelihood of missed or wrong diagnoses. However, Figure 10 shows that the majority of studies reflect patient data from after the initial case reports of NSF.

Figure 10. Study Window Timeline for Included Studies



Applicability of Findings to the VA Population

Because the currently recognized major determining factors in the pathophysiology of NSF are biological in nature, the results in this report are presumed to be readily applicable to the VA population. In fact, we purposely chose to make eligible those studies that included pediatric populations as we felt that the pathophysiology of NSF would be similar enough to adult populations to provide useful evidence. However, we did find 1 study conducted solely in a VA setting.[47]

RESEARCH GAPS/FUTURE RESEARCH

We identified several gaps in the existing literature that warrant further consideration. To systematically identify the existence of, and reason for, these gaps, we used an existing framework (Table 12). Robinson et al[82] propose the identification of gaps categorically using the PICOTS framework (population, intervention, comparator, outcome, timing, and setting) and classification by reason (insufficient or imprecise information, biased information, inconsistency and/or not the right information).

Table 12. Evidence Gaps and Future Research

Evidence Gap	Reason	Types of Studies to Consider
Population		
• No studies conducted specifically among patients with known risk factors for CKD • Little data among patients with acute kidney injury • Little data specifically about patients with earlier stage CKD (*ie*, stage 1-2 CKD) • Need for use of current CKD staging categories (*ie*, stage 3a/3b) • Only 1 study that specifically focused on Veterans	• Insufficient information • Not the right information	• Prospective cohort studies • Retrospective cohort studies • Postmarket surveillance studies
Interventions		
• Understudied GBCAs, specifically gadoexetic acid (Eovist) • Routine and detailed collection of GBCA-exposed history per individual and total cumulative dose per patient • Consideration of GBCA exposure across health care systems	• Insufficient information • Biased information	• Prospective cohort studies • Postmarket surveillance studies
Comparators		
• Continued collection of data allowing comparison across different GBCA types (Appendix J)	• Insufficient information	• Prospective cohort studies • Retrospective cohort studies • Postmarket surveillance studies
Outcomes		
• Consistent use of standardized diagnostic criteria for NSF	• Biased information	• Prospective cohort studies • Postmarket surveillance studies
Setting		
• Large, comprehensive health care systems likely to capture majority or all GBCA exposures	• Insufficient information	• Prospective cohort studies • Retrospective cohort studies

Of note, if there is continued movement to liberalize the use of newer gadolinium agents, prospective monitoring for the development of NSF could support future research on populations at potential risk but who have not previously undergone unrestricted exposure. In addition, the consistent collection of detailed information about potential risk modifiers (*eg*, inflammatory states,[3] gadolinium dose, comorbid medication administration) could provide needed data for the identification of factors that promote the development of NSF in some patients with renal disease over others. In particular, prior work has noted that acute kidney injury is a particularly significant risk factor for NSF development. Unfortunately, acute kidney injury was rarely reported across studies and future work may benefit from careful phenotyping of AKI by severity and etiology. Comprehensive national health care systems such as the VA, which provide the majority if not all of an individual patient's health care, are well-suited to conduct high quality observational studies which capture needed details of gadolinium exposure, relevant risk factors, and use a comprehensive NSF case identification approach including populations of concern such as those with CKD, risk factors for CKD, and AKI.

CONCLUSIONS

Nephrogenic systemic fibrosis is a rare but devastating and usually lethal disease occurring in patients who have received a gadolinium-based contrast agent. Over the last decade, incidence of NSF dropped off dramatically after formal restrictions limited the use of older linear GBCAs, particularly in patients with advanced kidney disease. However, patients with kidney disease and their providers need evidence to guide shared decision-making about the use of newer and seemingly safer GBCAs when MRIs are warranted for clinical care. We found very few cases of NSF reported after index exposures to newer linear and macrocyclic GBCAs. Most reported cases are of uncertain value since they occurred in patients who had also been exposed to other, often older, GBCAs around the same time. Generally, we found little data to inform the care of patients who are at risk for developing CKD or those with acute kidney injury. In addition, most of the data exists among patients with normal renal function and rare cases of NSF cannot be excluded in patients with significant kidney disease.

REFERENCES

1. Zhang B, Liang L, Chen W, et al. An Updated Study to Determine Association between Gadolinium-Based Contrast Agents and Nephrogenic Systemic Fibrosis. *PLoS One*. 2015;10(6):e0129720.
2. Nephrogenic Fibrosing Dermopathy Associated With Exposure to Gadolinium-Containing Contrast Agents—St. Louis, Missouri, 2002-2006. MMWR. 2007;56:137-141. *JAMA*. 2007;297(14):1542-1544.
3. Leyba K, Wagner B. Gadolinium-based contrast agents: why nephrologists need to be concerned. *Curr Opin Nephrol Hypertens*. 2019;28(2):154-162.
4. U.S. Food and Drug Administration. FDA Drug Safety Communication: New warnings for using gadolinium-based contrast agents in patients with kidney dysfunction. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-new-warnings-using-gadolinium-based-contrast-agents-patients-kidney#sa. Accessed July 30, 2019.
5. McDonald RJ, Levine D, Weinreb J, et al. Gadolinium Retention: A Research Roadmap from the 2018 NIH/ACR/RSNA Workshop on Gadolinium Chelates. *Radiology*. 2018;289(2):517-534.
6. Bernstein EJ, Schmidt-Lauber C, Kay J. Nephrogenic systemic fibrosis: a systemic fibrosing disease resulting from gadolinium exposure. *Best Pract Res Clin Rheumatol*. 2012;26(4):489-503.
7. Schieda N, Maralani PJ, Hurrell C, et al. Updated Clinical Practice Guideline on Use of Gadolinium-Based Contrast Agents in Kidney Disease Issued by the Canadian Association of Radiologists. *Can Assoc Radiol J*. 2019;70(3):226-232.
8. Grebe SO, Borrmann M, Altenburg A, et al. Chronic inflammation and accelerated atherosclerosis as important cofactors in nephrogenic systemic fibrosis following intravenous gadolinium exposure. *Clin Exp Nephrol*. 2008;12(5):403-406.
9. American College of Radiology. Manual on Contrast Media [online]. Available at: https://www.acr.org/Clinical-Resources/Contrast-Manual. Accessed July 30, 2019.
10. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097.
11. Runge VM. Dechelation (Transmetalation): Consequences and Safety Concerns With the Linear Gadolinium-Based Contrast Agents, In View of Recent Health Care Rulings by the EMA (Europe), FDA (United States), and PMDA (Japan). *Invest Radiol*. 2018;53(10):571-578.
12. Scott LJ. Gadobutrol: A Review in Contrast-Enhanced MRI and MRA. *Clin Drug Investig*. 2018;38(8):773-784.
13. Beam AS, Moore KG, Gillis SN, et al. GBCAs and Risk for Nephrogenic Systemic Fibrosis: A Literature Review. *Radiol Technol*. 2017;88(6):583-589.
14. Kitajima K, Maeda T, Watanabe S, et al. Recent topics related to nephrogenic systemic fibrosis associated with gadolinium-based contrast agents. *Int J Urol*. 2012;19(9):806-11.
15. Zou Z, Zhang HL, Roditi GH, et al. Nephrogenic systemic fibrosis: review of 370 biopsy-confirmed cases. *JACC Cardiovasc Imaging*. 2011;4(11):1206-16.
16. Hellman RN. Gadolinium-induced nephrogenic systemic fibrosis. *Semin Nephrol*. 2011;31(3):310-6.
17. Abu-Alfa AK. Nephrogenic systemic fibrosis and gadolinium-based contrast agents. *Adv Chronic Kidney Dis*. 2011;18(3):188-98.

18. Mazhar SM, Shiehmorteza M, Kohl CA, et al. Nephrogenic systemic fibrosis in liver disease: a systematic review. *J Magn Reson Imaging*. 2009;30(6):1313-22.
19. Chrysochou C, Buckley DL, Dark P, et al. Gadolinium-enhanced magnetic resonance imaging for renovascular disease and nephrogenic systemic fibrosis: critical review of the literature and UK experience. *J Magn Reson Imaging*. 2009;29(4):887-94.
20. Runge VM. Advances in magnetic resonance (2008). *Invest Radiol*. 2008;43(12):893-8.
21. Agarwal R, Brunelli SM, Williams K, et al. Gadolinium-based contrast agents and nephrogenic systemic fibrosis: a systematic review and meta-analysis. *Nephrol Dial Transplant*. 2009;24(3):856-63.
22. Nainani N, Panesar M. Nephrogenic systemic fibrosis. *Am J Nephrol*. 2009;29(1):1-9.
23. Bhave G, Lewis JB, Chang SS. Association of gadolinium based magnetic resonance imaging contrast agents and nephrogenic systemic fibrosis. *J Urol*. 2008;180(3):830-5; discussion 835.
24. Idee JM, Port M, Medina C, et al. Possible involvement of gadolinium chelates in the pathophysiology of nephrogenic systemic fibrosis: a critical review. *Toxicology*. 2008;248(2-3):77-88.
25. Marckmann P. Nephrogenic systemic fibrosis: epidemiology update. *Curr Opin Nephrol Hypertens*. 2008;17(3):315-9.
26. Anzalone N, Essig M, Lee SK, et al. Optimizing contrast-enhanced magnetic resonance imaging characterization of brain metastases: Relevance to stereotactic radiosurgery. *Neurosurgery*. 2013;72(5):691-701.
27. European Medicines Agency. Gadolinium-containing contrast agents. Available at: https://www.ema.europa.eu/en/medicines/human/referrals/gadolinium-containing-contrast-agents. Accessed September 5, 2019.
28. Evidence Partners Inc. DistillerAI website. Available at: https://www.evidencepartners.com/distiller-ai/. Accessed October 12, 2018.
29. Cochrane Effective Practice and Organisation of Care (EPOC). Suggested risk of bias criteria for EPOC reviews. EPOC Resources for review authors, 2017. Available at: http://epoc.cochrane.org/resources/epoc-resources-review-authors Accessed May 17, 2018.
30. Evidence Partners. Methods Commentary: Risk of Bias in Cohort Studies. Available at: https://www.evidencepartners.com/resources/methodological-resources/risk-of-bias-in-cohort-studies/. Accessed July 30, 2019.
31. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika*. 1934;26(4):404-413.
32. Hultcrantz M, Rind D, Akl EA, et al. The GRADE Working Group clarifies the construct of certainty of evidence. *J Clin Epidemiol*. 2017;87:4-13.
33. Bryant BJ, 2nd, Im K, Broome DR. Evaluation of the incidence of nephrogenic systemic fibrosis in patients with moderate renal insufficiency administered gadobenate dimeglumine for MRI. *Clin Radiol*. 2009;64(7):706-13.
34. Gheuens E, Daelemans R, Mesens S. Dialysability of gadoteric acid in patients with end-stage renal disease undergoing hemodialysis. *Invest Radiol*. 2014;49(8):505-8.
35. 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(6):416-22.

36. Michaely HJ, Aschauer M, Deutschmann H, et al. Gadobutrol in Renally Impaired Patients: Results of the GRIP Study. *Invest Radiol*. 2017;52(1):55-60.
37. 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(1):286-295.
38. 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(3):469-78.
39. 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(4):988-997.
40. Tsushima Y, Awai K, Shinoda G, et al. Post-marketing surveillance of gadobutrol for contrast-enhanced magnetic resonance imaging in Japan. *Jpn J Radiol*. 2018;36(11):676-685.
41. Young LK, Matthew SZ, Houston JG. Absence of potential gadolinium toxicity symptoms following 22,897 gadoteric acid (Dotarem(R)) examinations, including 3,209 performed on renally insufficient individuals. *Eur Radiol*. 2018.
42. McKinney AM, Gawande R, Pezeshk P, et al. Preliminary experience with intravenous gadoxetate disodium as a craniospinal MR contrast agent. *Eur J Radiol*. 2015;84(12):2539-47.
43. Nandwana SB, Moreno CC, Osipow MT, et al. Gadobenate Dimeglumine Administration and Nephrogenic Systemic Fibrosis: Is There a Real Risk in Patients with Impaired Renal Function? *Radiology*. 2015;276(3):741-7.
44. Shaffer KM, Parikh MR, Runge TM, et al. Renal safety of intravenous gadolinium-enhanced magnetic resonance imaging in patients awaiting liver transplantation. *Liver Transpl*. 2015;21(11):1340-6.
45. de Campos RO, Heredia V, Ramalho M, et al. Quarter-dose (0.025 mmol/kg) gadobenate dimeglumine for abdominal MRI in patients at risk for nephrogenic systemic fibrosis: preliminary observations. *AJR Am J Roentgenol*. 2011;196(3):545-52.
46. Abujudeh HH, Rolls H, Kaewlai R, et al. Retrospective assessment of prevalence of nephrogenic systemic fibrosis (NSF) after implementation of a new guideline for the use of gadobenate dimeglumine as a sole contrast agent for magnetic resonance examination in renally impaired patients. *J Magn Reson Imaging*. 2009;30(6):1335-40.
47. Reilly RF. Risk for nephrogenic systemic fibrosis with gadoteridol (ProHance) in patients who are on long-term hemodialysis. *Clin J Am Soc Nephrol*. 2008;3(3):747-51.
48. Deray G, Rouviere O, Bacigalupo L, et al. Safety of meglumine gadoterate (Gd-DOTA)-enhanced MRI compared to unenhanced MRI in patients with chronic kidney disease (RESCUE study). *Eur Radiol*. 2013;23(5):1250-9.
49. 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(11):701-705.
50. Smorodinsky E, Ansdell DS, Foster ZW, et al. Risk of nephrogenic systemic fibrosis is low in patients with chronic liver disease exposed to gadolinium-based contrast agents. *J Magn Reson Imaging*. 2015;41(5):1259-67.
51. Amet S, Launay-Vacher V, Clement O, et al. Incidence of nephrogenic systemic fibrosis in patients undergoing dialysis after contrast-enhanced magnetic resonance imaging with

gadolinium-based contrast agents: the Prospective Fibrose Nephrogenique Systemique study. *Invest Radiol*. 2014;49(2):109-15.
52. Becker S, Walter S, Witzke O, et al. Application of gadolinium-based contrast agents and prevalence of nephrogenic systemic fibrosis in a cohort of end-stage renal disease patients on hemodialysis. *Nephron Clin Pract*. 2012;121(1-2):c91-4.
53. Elmholdt TR, Pedersen M, Jorgensen B, et al. Nephrogenic systemic fibrosis is found only among gadolinium-exposed patients with renal insufficiency: a case-control study from Denmark. *Br J Dermatol*. 2011;165(4):828-36.
54. Martin DR, Krishnamoorthy SK, Kalb B, et al. Decreased incidence of NSF in patients on dialysis after changing gadolinium contrast-enhanced MRI protocols. *J Magn Reson Imaging*. 2010;31(2):440-6.
55. Chrysochou C, Power A, Shurrab AE, et al. Low risk for nephrogenic systemic fibrosis in nondialysis patients who have chronic kidney disease and are investigated with gadolinium-enhanced magnetic resonance imaging. *Clin J Am Soc Nephrol*. 2010;5(3):484-9.
56. Zou Z, Ma L, Li H. Incidence of nephrogenic systemic fibrosis at Chinese PLA General Hospital. *J Magn Reson Imaging*. 2009;30(6):1309-12.
57. Hoppe H, Spagnuolo S, Froehlich JM, et al. Retrospective analysis of patients for development of nephrogenic systemic fibrosis following conventional angiography using gadolinium-based contrast agents. *Eur Radiol*. 2010;20(3):595-603.
58. Janus N, Launay-Vacher V, Karie S, et al. Prevalence of nephrogenic systemic fibrosis in renal insufficiency patients: results of the FINEST study. *Eur J Radiol*. 2010;73(2):357-9.
59. Prince MR, Zhang H, Morris M, et al. Incidence of nephrogenic systemic fibrosis at two large medical centers. *Radiology*. 2008;248(3):807-16.
60. Schieren G, Tokmak F, Lefringhausen L, et al. C-reactive protein levels and clinical symptoms following gadolinium administration in hemodialysis patients. *Am J Kidney Dis*. 2008;51(6):976-86.
61. Cowper SE, Rabach M, Girardi M. Clinical and histological findings in nephrogenic systemic fibrosis. *Eur J Radiol*. 2008;66(2):191-9.
62. Endrikat J, Dohanish S, Schleyer N, et al. 10 Years of Nephrogenic Systemic Fibrosis: A Comprehensive Analysis of Nephrogenic Systemic Fibrosis Reports Received by a Pharmaceutical Company from 2006 to 2016. *Invest Radiol*. 2018;53(9):541-550.
63. Lohani S, Golenbiewski J, Swami A, et al. A unique case of nephrogenic systemic fibrosis from gadolinium exposure in a patient with normal eGFR. *BMJ Case Rep*. 2017;2017.
64. Barbieri S, Schroeder C, Froehlich JM, et al. High signal intensity in dentate nucleus and globus pallidus on unenhanced T1-weighted MR images in three patients with impaired renal function and vascular calcification. *Contrast Media Mol Imaging*. 2016;11(3):245-50.
65. Birka M, Wentker KS, Lusmoller E, et al. Diagnosis of nephrogenic systemic fibrosis by means of elemental bioimaging and speciation analysis. *Anal Chem*. 2015;87(6):3321-8.
66. Elmholdt TR, Olesen AB, Jorgensen B, et al. Nephrogenic systemic fibrosis in Denmark--a nationwide investigation. *PLoS One*. 2013;8(12):e82037.
67. Becker S, Walter S, Witzke O, et al. The German registry for nephrogenic systemic fibrosis: findings from 23 patients. *Clin Nephrol*. 2010;73(6):426-30.
68. Wollanka H, Weidenmaier W, Giersig C. NSF after Gadovist exposure: a case report and hypothesis of NSF development. *Nephrol Dial Transplant*. 2009;24(12):3882-4.

69. Shin K, Granter SR, Coblyn JS, et al. Progressive arm and leg stiffness in a patient with chronic renal impairment. *Nat Clin Pract Rheumatol*. 2008;4(10):557-62.
70. Sadowski EA, Bennett LK, Chan MR, et al. Nephrogenic systemic fibrosis: risk factors and incidence estimation. *Radiology*. 2007;243(1):148-57.
71. Semelka RC, Commander CW, Jay M, et al. Presumed Gadolinium Toxicity in Subjects With Normal Renal Function: A Report of 4 Cases. *Invest Radiol*. 2016;51(10):661-5.
72. Papanicolas I, Woskie LR, Jha AK. Health Care Spending in the United States and Other High-Income Countries. *JAMA*. 2018;319(10):1024-1039.
73. Attari H, Cao Y, Elmholdt TR, et al. A Systematic Review of 639 Patients with Biopsy-confirmed Nephrogenic Systemic Fibrosis. *Radiology*. 2019;292(2):376-386.
74. Perez-Rodriguez J, Lai S, Ehst BD, et al. Nephrogenic systemic fibrosis: incidence, associations, and effect of risk factor assessment--report of 33 cases. *Radiology*. 2009;250(2):371-7.
75. Chou R, Helfand M. Challenges in systematic reviews that assess treatment harms. *Ann Intern Med*. 2005;142(12 Pt 2):1090-9.
76. Chou R, Aronson N, Atkins D, et al. AHRQ series paper 4: assessing harms when comparing medical interventions: AHRQ and the effective health-care program. *J Clin Epidemiol*. 2010;63(5):502-12.
77. Davenport MS. Virtual Elimination of Nephrogenic Systemic Fibrosis: A Medical Success Story with a Small Asterisk. *Radiology*. 2019;292(2):387-389.
78. Endrikat J, Vogtlaender K, Dohanish S, et al. Safety of Gadobutrol: Results From 42 Clinical Phase II to IV Studies and Postmarketing Surveillance After 29 Million Applications. *Invest Radiol*. 2016;51(9):537-43.
79. Voth M, Rosenberg M, Breuer J. Safety of gadobutrol, a new generation of contrast agents: experience from clinical trials and postmarketing surveillance. *Invest Radiol*. 2011;46(11):663-71.
80. U.S. Food and Drug Administration. FDA Adverse Event Reporting System (FAERS) Public Dashboard. Available at: https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard. Accessed August 23, 2019.
81. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration. Chapter 8: Assessing risk of bias in included studies. Available at: https://handbook-5-1.cochrane.org/chapter_8/8_assessing_risk_of_bias_in_included_studies.htm. Accessed September 5, 2019.
82. Robinson KA, Saldanha IJ, McKoy NA. Development of a framework to identify research gaps from systematic reviews. *J Clin Epidemiol*. 2011;64(12):1325-30.
83. Elmholdt TR, Jorgensen B, Ramsing M, et al. Two cases of nephrogenic systemic fibrosis after exposure to the macrocyclic compound gadobutrol. *NDT Plus*. 2010;3(3):285-287.
84. Glutig K, Bhargava R, Hahn G, et al. Safety of gadobutrol in more than 1,000 pediatric patients: subanalysis of the GARDIAN study, a global multicenter prospective non-interventional study. *Pediatr Radiol*. 2016;46(9):1317-23.