APPENDIX A. POSTMARKETING REPORTS ON NSF ASSOCIATED WITH GBCA EXPOSURE

Publication Year	Targeted Class of GBCA or Specific Agents	Patient Population	Summary of Recommendations
2006[a]	All GBCAs	Patients with advanced kidney failure	First public report of NSF; after exposure to Omniscan GBCAs should be used only if necessary Consider dialysis after GBCA exposure
2007[b]	All GBCAs	All patients	Include Boxed Warning on product labelling of all GBCAs indicating NSF risk in patients with severe kidney insufficiency
2010[c]	Magnevist, Omniscan, and Optimark	Patients with impaired drug elimination (*eg*, AKI or severe CKD) (eGFR <30 mL/min)	These three GBCAs are contraindicated in these patient subgroups
2010[d]	All GBCAs	Patients with suspected impaired drug elimination	Avoid use of GBCAs unless alternative imaging modalities are unavailable Screen for risks for impaired drug elimination, including patients with CKD or AKI
2015[e]	All GBCAs	All patients	FDA commenced investigations on risks and mechanisms for retention/ accumulation of gadolinium in tissues
2017[f]	All GBCAs	All patients	FDA's review identified no evidence of adverse effects from gadolinium retention in the brain
2017[g]	All GBCAs	All patients	A required labelling update indicating gadolinium retention in the Adverse Reactions and Patient Instructions sections

[a] http://wayback.archive-it.org/7993/20170112033022/http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm053112.htm
[b] http://wayback.archive-it.org/7993/20170112033008/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108919.htm
[c] https://wayback.archive-it.org/7993/20180424232219/https://www.fda.gov/Drugs/DrugSafety/ucm223966.htm
[d] https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-gadolinium-based-contrast-agents-gbcas-are-retained-body
[e] https://wayback.archive-it.org/7993/20180424231918/https://www.fda.gov/Drugs/DrugSafety/ucm455386.htm
[f] https://wayback.archive-it.org/7993/20180424191936/https://www.fda.gov/Drugs/DrugSafety/ucm559007.htm
[g] https://wayback.archive-it.org/7993/20180424191926/https://www.fda.gov/Drugs/DrugSafety/ucm589213.htm
Abbreviations: AKI=acute kidney injury; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; GBCA=gadolinium-based contrast agent; NSF=nephrogenic systemic fibrosis

APPENDIX B. GBCA GUIDELINES

American College of Radiology – Published in 2018
ACR Manual on Contrast Media. (2018). [PDF] (10th ed.)

Gad Use Recommendation By Patient Population

General Guidance

Group II GBCAs:

- Strongly preferred [over Group I and III] for any patient at risk of NSF
- Informed consent is not recommended (deference made to local practice preferences)
- Assessment of renal function with a questionnaire or laboratory testing is optional prior to intravenous administration at standard or lower dosages
- Group II GBCAs should only be administered if deemed necessary by the supervising radiologist, and the lowest dose needed for diagnosis

Group I or III GBCAs:

- Consider patients with any of the following to be at risk for NSF: any form of dialysis, stage 4/5 CKD not on dialysis, AKI

At Risk For CKD

Inpatient

- An eGFR level should be obtained within 2 days prior to planned administration of a group I or group III GBCA
- Assess for the possibility of AKI [independent of eGFR], as eGFR calculation alone has limited accuracy for the detection of AKI

Outpatient

- If receiving group I or III GBCA, screen for conditions/factors that are associated with renal impairment (*eg*, history of renal disease, kidney transplant, single kidney, kidney surgery, h/o renal cancer, hypertension on medical therapy, diabetes)
- Patients identified to be at risk for having reduced renal function should be assessed by laboratory testing (checking results of prior laboratory tests performed within an acceptable time window, and ordering new laboratory tests only if necessary) and calculation of eGFR
- If most recent prior eGFR is 45 or above, and:

*NO risk factors and eGFR >60 or above, then no eGFR required
*WITH risk factors and/or eGFR 45-59, if most recent eGFR is within 6 weeks of the MRI, no new eGFR is needed; otherwise obtain a new eGFR

- If most recent prior eGFR 44 or below, obtain [new] eGFR within 2 days of the MRI study

AKI

- Group I agents should be avoided in patients with known or suspected AKI
- If GBCA is to be administered in this setting, a group II agent is preferred

CKD By Stage/GFR

CKD 1 or 2 (eGFR 60 to 119 ml min/1.73 m^2)

- There is no evidence that patients in these groups are at increased risk of developing NSF. Any GBCA can be administered safely to these patients

CKD 3 (eGFR 30 to 59 mL / min/1.73 m^2)

- NSF developing after GBCA administration to patients with stable eGFR30-59ml/min/1.73m2 is exceedingly rare. No special precautions are necessary in this group

CKD 4 or 5 (eGFR < 30 mL / min/1.73 m^2) not on chronic dialysis

- Group I agents are contraindicated in this setting. If a GBCA-enhanced MRI study is to be performed, a group II agent should be used

Severe or end-stage CKD(CKD4 or 5, eGFR < 30 mL/ min/1.73m^2) without dialysis

- Patients receiving group I GBCAs should be considered at risk of developing NSF

Dialysis

- Group I GBCAs contraindicated
- Group II GBCAs recommended
- Elective GBCA-enhanced MRI examinations should be performed as closely before hemodialysis as is possible
- Peritoneal dialysis may provide less NSF risk reduction compared to hemodialysis, but this has not been adequately studied

Transplant

- Considered a risk factor for renal impairment as noted above

Canadian Association of Radiologists – Published in 2019

Schieda, N., Maralani, P. J., Hurrell, C., Tsampalieros, A. K., & Hiremath, S. (2019). Updated Clinical Practice Guideline on Use of Gadolinium-Based Contrast Agents in Kidney Disease Issued by the Canadian Association of Radiologists. Canadian Association of Radiologists Journal. doi:10.1016/j.carj.2019.04.001

Schieda, N., Blaichman, J. I., Costa, A. F., Glikstein, R., Hurrell, C., James, M., Maralani, P. J., Shabana, W., Tang, A., Tsampalieros, A., van der Pol, C. B., & Hiremath, S. (2018). Gadolinium-based contrast agents in kidney disease: a comprehensive review and clinical practice guideline issued by the Canadian Association of Radiologists. Canadian Journal of Kidney Health and Disease, 5, 2054358118778573.

Gad Use Recommendation By Patient Population

General Guidance

Outpatient

- Screening for renal function in outpatients with patient questionnaires or serum creatinine at time of ordering GBCA enhanced MRI, scheduling of GBCA enhanced MRI or at the time of GBCA enhanced MRI to identify patients with possible renal dysfunction is no longer recommended when using Group II GBCAs or the Group III agent gadoxetic acid[a]

Inpatient

- Assess for potential AKI regardless of their eGFR, as eGFR is not always representative of renal function in this setting

At Risk For CKD

- Gadodiamide, gadopentetic acid, or gadoversetamide in at-risk patients absolutely contraindicated

AKI

- Should be managed similar to those with eGFR < 30 mL/min/1.73 m^2
- Delay GBCA administration when possible until renal function stabilizes or ameliorates depending on the patients underlying cause for acute renal dysfunction[a]
- Gadopentetate dimeglumine, gadodiamide, and gadoversetamide remain absolutely contraindicated
- As kidney function is not stable in patients with AKI, risk assessment for NSF should not be made on the basis of eGFR alone
- When administering Group II or III GBCAs informed consent relating to NSF is not necessary

CKD By Stage/GFR

Patients with CKD 1 or 2 (eGFR between 60 and 90 ml min/1.73 m^2)

- No special precautions should be taken in these patients

Patients with CKD 3 (eGFR between 30 and 60 mL / min/1.73 m^2)

- For patients with moderately reduced kidney function, administration of standard doses of GBCA is safe and no additional precautions are necessary
- No need for informed consent[a]

Patients with CKD 4 or 5 (eGFR < 30 mL / min/1.73 m^2) or Dialysis-Dependent Patients

- Alternative diagnostic tests should be considered before GBCA are prescribed
- Gadopentetate dimeglumine, gadodiamide, and gadoversetamide remain absolutely contraindicated
- When MRI is considered necessary for patient care then gadolinium enhanced examinations using Group II GBCAs (namely macrocyclic GBCA and gadobenate dimeglumine) or the Group III agent gadoxetic acid may be performed without any patient informed consent

Dialysis

- Manage as per patients with CKD 4/5 described above
- Dialysis-dependent patients should receive dialysis; HD should be performed [following] GBCA administration, ideally within 2-3 hours of MRI. However, initiating dialysis or switching from peritoneal to hemodialysis to reduce the risk of NSF is unproven[a]
- Gadopentetate dimeglumine, gadodiamide, and gadoversetamide remain absolutely contraindicated
- When administering Group II or III GBCAs informed consent relating to NSF is not necessary

Transplant

(No specific recommendations)

European Medicines Agency – Published in 2017

Gadolinium-containing contrast agents - European Medicines Agency. (2017). Retrieved from https://www.ema.europa.eu/en/medicines/human/referrals/gadolinium-containing-contrast-agents

Gad Use Recommendation	**General Guidance** • Intravenous linear agents gadoxetic acid and gadobenic acid can continue to be used for liver scans because they are taken up in the liver and meet an important diagnostic need • Gadopentetic acid given intra-articularly (into the joint) can continue to be used for joint scans because the dose of gadolinium used for joint injections is very low • All other intravenous linear products (gadodiamide, gadopentetic acid and gadoversetamide) should be suspended in the EU • Macrocyclic agents (gadobutrol, gadoteric acid and gadoteridol) are more stable and have a lower propensity to release gadolinium than linear agents. These products can continue to be used in their current indications but in the lowest doses that enhance images sufficiently and only when unenhanced body scans are not suitable

Kidney Disease: Improving Global Outcomes (KDIGO) – Published in 2013

KDIGO. (2013). KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease Clinical Practice Guidelines. Retrieved from https://www.guidelinecentral.com/summaries/kdigo-2012-clinical-practice-guideline-for-the-evaluation-and-management-of-chronic-kidney-disease/#section-date

Gad Use Recommendation By Patient Population	**CKD By Stage/GFR** • The Work Group recommends not using gadolinium-containing contrast media in people with GFR <15 ml/min/1.73 m2 (GFR category G5) unless there is no alternative appropriate test • The Work Group suggests that people with a GFR <30 ml/min/1.73 m2 (GFR categories G4–G5) who require gadolinium-containing contrast media are preferentially offered a macrocyclic chelate preparation

US Food and Drug Administration (FDA) – Published in 2018

FDA Center for Drug Evaluation and Research. (2018). New warnings for gadolinium-based contrast agents (GBCAs) for MRI. Retrieved from https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-gadolinium-based-contrast-agents-gbcas-are-retained-body

FDA Center for Drug Evaluation and Research. (2018). gadolinium-based contrast agents in patients with kidney dysfunction. Retrieved from https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-new-warnings-using-gadolinium-based-contrast-agents-patients-kidney

Gad Use Recommendation By Patient Population	**General Guidance** • Gadolinium retention has not been directly linked to adverse health effects in patients with normal kidney function, and we have concluded that the benefit of all approved GBCAs continues to outweigh any potential risks

- Health care professionals should consider the retention characteristics of each agent when choosing a GBCA for patients who may be at higher risk for gadolinium retention (see Table 1 listing GBCAs). These patients include those requiring multiple lifetime doses, pregnant women, children, and patients with inflammatory conditions. Minimize repeated GBCA imaging studies when possible, particularly closely spaced MRI studies. However, do not avoid or defer necessary GBCA MRI scans
- Linear GBCAs result in more retention and retention for a longer time than macrocyclic GBCAs. Gadolinium levels remaining in the body are higher after administration of Omniscan (gadodiamide) or OptiMARK (gadoversetamide) than after Eovist (gadoxetate disodium), Magnevist (gadopentetate dimeglumine), or Multihance (gadobenate dimeglumine). Gadolinium levels in the body are lowest after administration of Dotarem (gadoterate meglumine), Gadavist (gadobutrol), and ProHance (gadoteridol); the gadolinium levels are also similar across these agents
- Avoid use of GBCAs in patients suspected or known to have impaired drug elimination unless the need for the diagnostic information is essential and not available with non-contrasted MRI or other alternative imaging modalities
- Do not repeat administration of any GBCA during a single imaging session
- Record the specific GBCA and the dose administered to a patient
- When administering a GBCA, do not exceed the recommended dose. Prior to any re-administration, allow sufficient time for elimination of the GBCA from the body (*eg*, multiple half-lives), as described in the Pharmacokinetics section of the labeling. GBCA elimination half-lives are prolonged in patients with renal impairment; for a GBCA that involves significant hepato-biliary elimination, liver dysfunction may also prolong elimination time
- Advise patients with kidney disease to contact a healthcare professional if any of the following symptoms occurs after receiving a GBCA: burning, itching, swelling, scaling, hardening and tightening of the skin; red or dark patches on the skin; stiffness in joints with trouble moving, bending or straightening the arms, hands, legs or feet; pain in the hip bones or ribs; or muscle weakness
- Report any adverse events with GBCAs to FDA's MedWatch program

Approved Gadolinium-Based Contrast Agents

- Ablavar (gadofosveset trisodium)
- Eovist (gadoxetate disodium)
- Magnevist (gadopentetate dimeglumine)
- Multihance (gadobenate dimeglumine)
- Omniscan (gadodiamide)
- Optimark (gadoversetamide injection)
- Prohance (gadoteridol)

At Risk For CKD

- Use the clinical history to screen patients for features of AKI or risk factors for chronically reduced kidney function

AKI

- Screen patients prior to administration of a GBCA to identify those with AKI or chronic, severe, kidney disease. These patients appear to be at highest risk for NSF
- Use the clinical history to screen patients for features of AKI or risk factors for chronically reduced kidney function
- [These] patients [are] at greatest risk for developing NSF after receiving GBCAs [due to] impaired elimination of the drug. Higher than recommended doses or repeat doses of GBCAs also appear to increase the risk for NSF
- Do not use three of the GBCA drugs--Magnevist, Omniscan, and Optimark. These three GBCA drugs are contraindicated in these patients

CKD By Stage/GFR

- Screen patients prior to administration of a GBCA to identify those with AKI or chronic, severe, kidney disease. These patients appear to be at highest risk for NSF
- *(eGFR < 30 mL / min/1.73 m^2)* [These] patients [are] at greatest risk for developing NSF after receiving GBCAs [due to] impaired elimination of the drug. Higher than recommended doses or repeat doses of GBCAs also appear to increase the risk for NSF
- Do not use three of the GBCA drugs--Magnevist, Omniscan, and Optimark. These three GBCA drugs are contraindicated in these patients

Dialysis

- For patients receiving hemodialysis, physicians may consider the prompt initiation of hemodialysis following the administration of a GBCA in order to enhance the contrast agent's elimination from the body. The usefulness of hemodialysis in the prevention of NSF is unknown

[a]The guidelines have qualifying statements.

APPENDIX C. SEARCH STRATEGIES

MEDLINE (via PubMed)

Search date: 1/7/2019

#1	"gadolinium"[mesh] OR "gadoterate meglumine"[supplementary concept] OR "gadobutrol"[supplementary concept] OR "gadoteridol"[supplementary concept] OR "gadobenic acid"[supplementary concept] OR gadolinium[tw] OR GBCA[tw] OR GBCAs[tw] OR "gadoterate meglumine"[tw] OR "gadoteric acid"[tw] OR dotarem[tw] OR artirem[tw] OR clariscan[tw] OR gadobutrol[tw] OR gadavist[tw] OR gadovist[tw] OR gadograf[tw] OR gadoteridol[tw] OR prohance[tw] OR "gadobenate dimeglumine"[tw] OR "gadobenic acid"[tw] OR multihance[tw] OR "gadoxetate disodium"[tw] OR "gadoxetic acid"[tw] OR eovist[tw] OR primovist[tw] OR gadograf[tw]	33,757
#2	("contrast media"[mesh] OR "contrast media"[pharmacological action] OR "contrast media"[tw] OR "contrast medium"[tw] OR "contrast agent"[tw] OR "contrast agents"[tw] OR "contrast dye"[tw] OR "contrast dyes"[tw] OR "contrast enhanced"[tw]) AND ("magnetic resonance imaging"[mesh] OR "magnetic resonance imaging, interventional"[mesh] OR "magnetic resonance imaging"[tw] OR "magnetic resonance angiography"[tw] OR MRI[tw] OR MRA[tw])	48,810
#3	#1 OR #2	62,787
#4	"nephrogenic fibrosing dermopathy"[mesh] OR NSF[tw] OR NFD[tw] OR (nephrogenic[tw] AND fibros*[tw])	3,809
#5	#3 AND #4	813
#6	#5 NOT (animals[mesh] NOT humans[mesh])	771
#7	#6 NOT (Editorial[ptyp] OR Comment[ptyp])	689
#8	#7 AND English[lang]	639

EMBASE (via Elsevier)

Search date: 1/7/2019

#1	'gadolinium'/exp OR 'gadoterate meglumine'/exp OR 'gadoteric acid'/exp OR 'gadobutrol'/exp OR 'gadoteridol'/exp OR 'gadobenic acid'/exp OR 'gadobenat dimeglumine'/exp OR 'gadoxetic acid'/exp OR gadolinium:ti,ab,kw OR GBCA:ti,ab,kw OR GBCAs:ti,ab,kw OR 'gadoterate meglumine':ti,ab,kw OR 'gadoteric acid':ti,ab,kw OR dotarem:ti,ab,kw OR artirem:ti,ab,kw OR clariscan:ti,ab,kw OR gadobutrol:ti,ab,kw OR gadavist:ti,ab,kw OR gadovist:ti,ab,kw OR gadograf:ti,ab,kw OR gadoteridol:ti,ab,kw OR prohance:ti,ab,kw OR 'gadobenate dimeglumine':ti,ab,kw OR 'gadobenic acid':ti,ab,kw OR multihance:ti,ab,kw OR 'gadoxetate disodium':ti,ab,kw OR 'gadoxetic acid':ti,ab,kw OR eovist:ti,ab,kw OR primovist:ti,ab,kw OR gadograf:ti,ab,kw	61,309
#2	('contrast media'/exp OR 'contrast media':ti,ab,kw OR 'contrast medium':ti,ab,kw OR 'contrast agent':ti,ab,kw OR 'contrast agents':ti,ab,kw OR 'contrast dye':ti,ab,kw OR 'contrast dyes':ti,ab,kw OR 'contrast enhanced':ti,ab,kw) AND (' nuclear magnetic resonance imaging'/exp OR 'magnetic resonance imaging':ti,ab,kw OR 'magnetic resonance angiography':ti,ab,kw OR MRI:ti,ab,kw OR MRA:ti,ab,kw)	72,313
#3	#1 OR #2	119,975
#4	'nephrogenic systemic fibrosis'/exp OR NSF:ti,ab,kw OR NFD:ti,ab,kw OR (nephrogenic:ti,ab,kw AND fibros*:ti,ab,kw)	5,192
#5	#3 AND #4	1,405
#6	#5 AND [humans]/lim	1,242
#7	#6 NOT ('editorial'/exp OR 'letter'/exp OR 'note'/exp OR [conference abstract]/lim)	927
#8	#7 AND [english]/lim	853

Cochrane Register of Controlled Trials (via Wiley)

Search Date Within CENTRAL: 1/7/2019

#1	[mh "gadolinium"] OR gadolinium OR GBCA OR GBCAs OR "gadoterate meglumine" OR "gadoteric acid" OR dotarem OR artirem OR clariscan OR gadobutrol OR gadavist OR gadovist OR gadograf OR gadoteridol OR prohance OR "gadobenate dimeglumine" OR "gadobenic acid" OR multihance OR "gadoxetate disodium" OR "gadoxetic acid" OR eovist OR primovist OR gadograf	2,138
#2	[mh "contrast media"] OR "contrast media" OR "contrast medium" OR "contrast agent" OR "contrast agents" OR "contrast dye" OR "contrast dyes" OR "contrast enhanced"	5,789
#3	[mh "magnetic resonance imaging"] OR [mh "magnetic resonance imaging, interventional"] OR "magnetic resonance imaging" OR "magnetic resonance angiography" OR MRI OR MRA	23,641
#4	#2 AND #3	1,645
#5	#1 OR #4	3,021
#6	[mh "nephrogenic fibrosing dermopathy"] OR NSF OR NFD	124
#7	nephrogenic AND fibros*	22
#8	#6 OR #7	141
#9	#5 AND #8	18
#10	#9 limit to Trials	15

Web of Science Core Collection (via Clarivate)

Search date: 1/7/2019

#1	TS=(gadolinium OR GBCA OR GBCAs OR "gadoterate meglumine" OR "gadoteric acid" OR dotarem OR artirem OR clariscan OR gadobutrol OR gadavist OR gadovist OR gadograf OR gadoteridol OR prohance OR "gadobenate dimeglumine" OR "gadobenic acid" OR multihance OR "gadoxetate disodium" OR "gadoxetic acid" OR eovist OR primovist OR gadograf)	38,662
#2	TS=("contrast media" OR "contrast medium" OR "contrast agent" OR "contrast agents" OR "contrast dye" OR "contrast dyes" OR "contrast enhanced")	89,925
#3	TS=("magnetic resonance imaging" OR "magnetic resonance imaging, interventional" OR "magnetic resonance imaging" OR "magnetic resonance angiography" OR MRI OR MRA)	410,317
#4	#2 AND #3	35,768
#5	#1 OR #4	66,398
#6	TS=(nephrogenic AND fibros*)	2,257
#7	#5 AND #6	1,592
#8	#7 AND [Restrict to English language]	1,540
#9	#8 AND [Restrict to Article OR Review]	1,355

APPENDIX D. EXCLUDED STUDIES

Excluded references are listed following this table.

	Exclusion Reason				
Study	**Not full publication**	**Not population of interest**	**Not eligible intervention**	**Not eligible design**	**Not eligible outcome**
Abujudeh, 2010[1]					X
Aggarwal, 2011[2]			X		
Aires, 2007[3]			X		
Al Habeeb, 2009[4]			X		
Alhadad, 2012[5]			X		
Altun, 2009[6]			X		
Aluma, 2007[7]			X		
Amuluru, 2009[8]			X		
Anavekar, 2008[9]			X		
Andrews, 2008[10]	X				
Anonymous, 2007[11]	X				
Anonymous, 2010[12]	X				
Anonymous, 2010[13]	X				
Anzalone, 2011[14]	X				
Auron, 2006[15]			X		
Azzouz, 2014[16]			X		
Bahrami, 2009[17]			X		
Bainotti, 2008[18]			X		
Bangsgaard, 2011[19]			X		
Bangsgaard, 2009[20]			X		
Barker-Griffith, 2011[21]			X		
Baron, 2003[22]			X		
Baumgarten, 2008[23]	X				
Bayliss, 2008[24]			X		

	Exclusion Reason				
Study	**Not full publication**	**Not population of interest**	**Not eligible intervention**	**Not eligible design**	**Not eligible outcome**
Bernstein, 2014[25]			X		
Bhaskaran, 2010[26]			X		
Blankholm, 2013[27]			X		
Bridges, 2009[28]			X		
Broome, 2007[29]			X		
Burke, 2016[30]					X
Cassis, 2006[31]			X		
Chan, 2009[32]			X		
Chandran, 2009[33]			X		
Chao, 2008[34]			X		
Chen, 2009[35]			X		
Cheng, 2007[36]			X		
Chiu, 2004[37]			X		
Choi, 2011[38]	X				
Chow, 2011[39]			X		
Christensen, 2011[40]			X		
Chung, 2004[41]			X		
Clorius, 2007[42]			X		
Collidge, 2007[43]			X		
Cowper, 2006[44]	X				
Cowper, 2000[45]			X		
Craig, 2011[46]			X		
Cubero-Gomez, 2017[47]					X
Cuende, 2009[48]			X		
Cuffy, 2011[49]			X		
Daram, 2005[50]			X		
Dawn, 2004[51]			X		
de Kerviler, 2016[52]				X	

	Exclusion Reason				
Study	**Not full publication**	**Not population of interest**	**Not eligible intervention**	**Not eligible design**	**Not eligible outcome**
Deng, 2010[53]			X		
Deng, 2008[54]			X		
Deo, 2007[55]			X		
Dewan, 2016[56]			X		
Dhungel, 2008[57]	X				
Do, 2012[58]			X		
Duffy, 2008[59]			X		
Dundova, 2005[60]			X		
Dupont, 2005[61]			X		
Edgar, 2010[62]			X		
Edsall, 2004[63]			X		
Edward, 2010[64]			X		
Elmholdt, 2010[65]				X	
Endrikat, 2015[66]					X
Endrikat, 2016[67]				X	
Evenepoel, 2004[68]			X		
Ferner, 2011[69]				X	
Fingerhut, 2018[70]			X		
Firoz, 2008[71]			X		
Foss, 2009[72]			X		
Friedman, 2012[73]				X	
Fuah, 2017[74]			X		
Gambichler, 2004[75]			X		
George, 2006[76]			X		
Gharacholou, 2011[77]			X		
Gibson, 2006[78]			X		
Giersig, 2007[79]	X				
Gilliet, 2005[80]			X		

	Exclusion Reason				
Study	**Not full publication**	**Not population of interest**	**Not eligible intervention**	**Not eligible design**	**Not eligible outcome**
Glaich, 2005[81]			X		
Goddard, 2007[82]			X		
Granata, 2016[83]					X
Grand, 2012[84]			X		
Grebe, 2008[85]			X		
Grobner, 2006[86]			X		
Gulati, 2008[87]			X		
Gutierrez, 2012[88]				X	
Gutierrez, 2015[89]					X
Gutierrez, 2015[90]					X
Hall, 2012[91]				X	
Haller, 2011[92]	X				
Halteh, 2017[93]			X		
Hamilton, 2011[94]					X
Hanna, 2014[95]			X		
Hashemi, 2013[96]			X		
Hauser, 2004[97]			X		
He, 2016[98]			X		
Hedley, 2007[99]	X				
Hedley, 2007[100]	X				
Heinz-Peer, 2010[101]			X		
Hickson, 2010[102]			X		
Hidalgo Parra, 2008[103]			X		
High, 2007[104]			X		
High, 2007[105]			X		
Hodnett, 2011[106]			X		
Homayoon, 2014[107]					X
Hong, 2011[108]	X				

	Exclusion Reason				
Study	**Not full publication**	**Not population of interest**	**Not eligible intervention**	**Not eligible design**	**Not eligible outcome**
Hope, 2009[109]			X		
Hubbard, 2003[110]			X		
Hurley, 2012[111]					X
Introcaso, 2008[112]			X		
Introcaso, 2007[113]			X		
Ishiguchi, 2010[114]					X
Jalandhara, 2011[115]				X	
Jan, 2008[116]	X				
Jan, 2003[117]			X		
Jikki, 2008[118]	X				
Kafi, 2004[119]			X		
Kalisz, 2011[120]			X		
Kanda, 2015[121]					X
Kartono, 2011[122]			X		
Kaul, 2012[123]				X	
Kay, 2008[124]			X		
Kay, 2008[125]			X		
Kelly, 2008[126]			X		
Kendrick-Jones, 2011[127]			X		
Kennedy, 2010[128]			X		
Khor, 2013[129]	X				
Khurana, 2008[130]			X		
Khurram, 2007[131]			X		
Kim, 2006[132]			X		
Kitaura, 2010[133]			X		
Knapp, 2010[134]			X		
Koratala, 2017[135]			X		
Koreishi, 2009[136]			X		

	Exclusion Reason				
Study	**Not full publication**	**Not population of interest**	**Not eligible intervention**	**Not eligible design**	**Not eligible outcome**
Kraetschmer, 2009[137]	X				
Kramer, 2011[138]					X
Kreuter, 2008[139]			X		
Krishnamurthy, 2011[140]				X	
Kroshinsky, 2009[141]			X		
Krous, 2007[142]			X		
Kucher, 2006[143]			X		
Kunst, 2011[144]				X	
Larson, 2015[145]			X		
Lauenstein, 2007[146]			X		
Learned, 2013[147]			X		
LeBoit, 2003[148]	X				
Lee, 2009[149]				X	
Lee, 2012[150]				X	
Leiner, 2009[151]	X				
Lemy, 2010[152]			X		
Leung, 2009[153]			X		
Levine, 2004[154]			X		
Lewis, 2006[155]			X		
Lim, 2007[156]			X		
Lu, 2009[157]			X		
Mackay-Wiggan, 2003[158]			X		
Marckmann, 2008[159]			X		
Markus, 2005[160]			X		
Martin, 2008[161]	X				
Martin, 2018[162]					X
Mathur, 2008[163]			X		
Matich, 2014[164]	X				

	Exclusion Reason				
Study	**Not full publication**	**Not population of interest**	**Not eligible intervention**	**Not eligible design**	**Not eligible outcome**
Matsumoto, 2012[165]			X		
Mavrogeni, 2011[166]				X	
Mazhar, 2009[167]			X		
McNeill, 2002[168]			X		
Mendoza, 2006[169]			X		
Mihai, 2011[170]				X	
Miyamoto, 2011[171]			X		
Mohidin, 2018[172]			X		
Morcos, 2011[173]		X			
Moreno-Romero, 2007[174]			X		
Moschella, 2004[175]			X		
Murata, 2016[176]					X
Nakai, 2009[177]			X		
Nardone, 2014[178]			X		
Nazarian, 2011[179]			X		
Nguyen, 2014[180]			X		
Nielsen, 2010[181]	X				
Obermoser, 2004[182]			X		
Okada, 2001[183]			X		
Ota, 2012[184]	X				
Othersen, 2007[185]			X		
Pagel, 2011[186]				X	
Panda, 2006[187]			X		
Panesar, 2008[188]			X		
Pao, 2009[189]			X		
Penfield, 2008[190]	X				
Perazella, 2007[191]				X	
Perazella, 2003[192]			X		

	Exclusion Reason				
Study	**Not full publication**	**Not population of interest**	**Not eligible intervention**	**Not eligible design**	**Not eligible outcome**
Perazella, 2007[193]			X		
Perez-Rodriguez, 2009[194]			X		
Pieringer, 2008[195]	X				
Prince, 2011[196]					X
Pryor, 2007[197]			X		
Radbruch, 2015[198]					X
Ray, 2016[199]			X		
Riccabona, 2008[200]	X				
Roberts, 2016[201]				X	
Robinson, 2011[202]	X				
Rodby, 2011[203]	X				
Ross, 2015[204]			X		
Ruiz-Genao, 2005[205]			X		
Rydahl, 2008[206]			X		
Saenz, 2006[207]			X		
Sambol, 2011[208]			X		
Sanchez-Ross, 2007[209]			X		
Sanyal, 2011[210]			X		
Saussereau, 2008[211]			X		
Schieren, 2009[212]			X		
Schietinger, 2008[213]			X		
Schleichert, 2012[214]			X		
Schmiedl, 2009[215]			X		
Schmook, 2005[216]			X		
Schneider, 2007[217]					X
Schroeder, 2008[218]			X		
Sego, 2008[219]			X		
Semelka, 2016[220]				X	

	Exclusion Reason				
Study	**Not full publication**	**Not population of interest**	**Not eligible intervention**	**Not eligible design**	**Not eligible outcome**
Shabana, 2008[221]			X		
Shah, 2017[222]				X	
Sharfuddin, 2011[223]			X		
Sharma, 2008[224]			X		
Shimoji, 2012[225]			X		
Singh, 2008[226]			X		
So, 2009[227]			X		
Solomon, 2007[228]			X		
Soulez, 2008[229]					X
Steen, 2009[230]			X		
Streams, 2003[231]			X		
Su, 2009[232]			X		
Su, 2009[233]			X		
Swaminathan, 2008[234]			X		
Tan, 2004[235]			X		
Tanaka, 2016[236]					X
Thakral, 2009[237]			X		
Thakral, 2007[238]			X		
Thomsen, 2006[239]	X				
Thomsen, 2008[240]	X				
Thomsen, 2010[241]				X	
Thomsen, 2006[242]	X				
Thomson, 2015[243]			X		
Thurnher, 2007[244]				X	
Ting, 2003[245]			X		
Todd, 2007[246]			X		
Tsai, 2007[247]			X		
Tsushima, 2008[248]	X				

	Exclusion Reason				
Study	**Not full publication**	**Not population of interest**	**Not eligible intervention**	**Not eligible design**	**Not eligible outcome**
Ustuner, 2011[249]			X		
Valsangiacomo Buechel, 2011[250]				X	
Voth, 2011[251]					X
Wahba, 2007[252]			X		
Wang, 2011[253]			X		
Weigle, 2008[254]			X		
Weiss, 2007[255]			X		
Weller, 2014[256]				X	
Wertman, 2008[257]			X		
Wiginton, 2008[258]			X		
Wilford, 2010[259]			X		
Wilson, 2017[260]			X		
Winship, 2013[261]			X		
Woodard, 2012[262]					X
Yerram, 2007[263]			X		
Yoldez, 2018[264]	X				
Zelasko, 2008[265]			X		
Zhang, 2015[266]				X	
Zhang, 2017[267]			X		
Zou, 2011[268]				X	

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APPENDIX E. RISK OF BIAS ASSESSMENT TOOL

Risk of Bias Assessment Tool Citation

For documentation and tools for assessing risk of bias (ROB), refer to Evidence Partners' Methodological Resources at https://www.evidencepartners.com/resources/methodological-resources/.

ROB IN CASE CONTROL STUDIES

1.Can we be confident in the assessment of exposure?

- ○ Definitely yes (low risk of bias)
- ○ Probably yes
- ○ Probably no
- ◉ Definitely no (high risk of bias)

What is your justification for the response above?

Examples of low risk of bias: Evidence of **gadolinium** exposure comes from previously created records **(e.g. electronic medical records)** and data abstractors are unaware of the study hypothesis

Examples of higher risk of bias: Evidence of **gadolinium** exposure is acquired by patient interview, but interviewers are blinded to patient status and memory of exposure unlikely to be influenced by occurrence of the outcome

Examples of high risk of bias: Evidence of **gadolinium** exposure is acquired by patient interview, data collectors are not blinded to patient status or the study hypothesis. Memory of exposure is likely to be influenced by the occurrence of the outcome.

3.Can we be confident that cases had developed the outcome of interest and controls had not?

- ○ Definitely yes (low risk of bias)
- ○ Probably yes
- ○ Probably no
- ○ Definitely no (high risk of bias)

What is your justification for the response above?

Examples of low risk of bias: Cases and controls undergo valid and reliable diagnostic procedures **(e.g. use of Girardi 2011 scoring criteria and/or skin biopsy)**. Surveillance for the outcome of interest clearly unrelated to the exposure of interest

Examples of higher risk of bias: The outcome of interest is acquired by subjective methods (e.g. patient interview); however, reasonable steps are taken to independently validate results (e.g. independent validation by >1 person). Surveillance for the outcome of interest possibly related to the exposure of interest **(e.g. monitoring dialysis patients who have undergone gadolinium-enhanced MRI)**

Examples of high risk of bias: No description, cases are established with diagnostic procedures associated with high rates of false positive results, or controls are established with diagnostic procedures associated with high rates of false negative results. Surveillance for the outcome of interest clearly related to the exposure of interest **(e.g. no use of standardized diagnostic criteria and/or no skin biopsy)**

Were the cases (those who were exposed and developed the outcome of interest) properly 5.selected?

- Definitely yes (low risk of bias)
- Probably yes
- Probably no
- Definitely no (high risk of bias)

What is your justification for the response above?

Examples of low risk of bias: All eligible cases are enrolled in a defined catchment area over a defined period of time during which diagnostic procedures would be unlikely to have changed, or a random sample of those cases

Examples of higher risk of bias: All eligible cases in a defined catchment area over a defined period of time **(e.g. before and after first case of NSF defined ~2006)** during which diagnostic procedures would be likely to have changed, or a random sample of those cases

Examples of high risk of bias: Not reported

Were the controls (those who were exposed and did not develop the outcome of interest) 7.properly selected?

- Definitely yes (low risk of bias)
- Mostly yes
- Mostly no
- Definitely no (high risk of bias)

What is your justification for the response above?

Examples of low risk of bias: Controls clearly selected from the same underlying population as the cases and equally at risk of exposure to **gadolinium**

Examples of higher risk of bias: Differences in sampling frame of cases and controls that may be related to the exposure of interest

Examples of high risk of bias: Difference in sampling frame of cases and controls clearly related to the exposure of interest

Were cases and controls matched according to important prognostic variables or was statistical 9.adjustment carried out for those variables?

- Definitely yes (low risk of bias)
- Probably yes
- Probably no
- Definitely no (high risk of bias)

What is your justification for the response above?

Examples of low risk of bias: comprehensive matching or adjustment for all plausible prognostic variables **(e.g. stage CKD/GFR, risk factors for CKD)**

Examples of higher risk of bias: matching or adjustment for most plausible prognostic variables **(e.g. stage CKD/GFR, risk factors for CKD)**

Examples of high risk of bias: matching or adjustment for a minority of plausible prognostic variables **(e.g. stage CKD/GFR, risk factors for CKD)**, or no matching or adjustment at all. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability

11.Assessment of Bias (Automatically Generated)

- Low risk of bias for all key domains.
- (•) Unclear risk of bias for one or more key domains.
- High risk of bias for one or more key domains.

Clear Response

Comments on overall rating for the responses above?

What was the funding source for this study?

Was there any pharmaceutical affiliation/association with the study?

Did the first or last author declare any conflict of interest? (if so, please explain)

ROB IN COHORT STUDIES

1.Was selection of exposed and non-exposed cohorts drawn from the same population?

- Definitely yes (low risk of bias)
- Probably yes
- Probably no
- Definitely no (high risk of bias)
- Not applicable

What is your justification for the response above?

Examples of low risk of bias: Exposed and unexposed drawn for same administrative database of patients presenting at same points of care **(e.g. same renal or dialysis unit)** over the same time frame

Examples of high risk of bias: exposed and unexposed presenting to different points of care or over a different time frame

3.Can we be confident in the assessment of exposure?

- Definitely yes (low risk of bias)
- Probably yes
- Probably no
- Definitely no (high risk of bias)

What is your justification for the response above?

Note: pay attention to certainty about specific gadolinium agent used and potential for patients to undergo gadolinium-enhanced MRIs in another system
Examples of low risk of bias: Secure record [e.g. surgical records, pharmacy records]
Examples of higher risk of bias: Structured interview at a single point in time; Written self-report; Individuals who are asked to retrospectively confirm their exposure status may be subject to recall bias – less likely to recall an exposure if they have not developed an adverse outcome, and more likely to recall an exposure (whether an exposure occurred or not) if they have developed an adverse outcome.
Examples of high risk of bias: uncertain how exposure information obtained

5.Can we be confident that the outcome of interest was not present at start of study?

- Definitely yes (low risk of bias)
- Probably yes

- Probably no
- Definitely no (high risk of bias)

What is your justification for the response above?

Note: did any of the patients have NSF at the beginning of the cohort time frame? This is particularly tricky for retrospective studies.

Did the study match exposed and unexposed for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables?
If no comparator: Did the study examine one or more relevant confounders/risk factors,
7. **using acceptable statistical techniques such as stratification or adjustment?**

- Definitely yes (low risk of bias)
- Mostly yes
- Mostly no
- Definitely no (high risk of bias)

What is your justification for the response above?

Examples of low risk of bias: comprehensive matching or adjustment for all plausible prognostic variables **(e.g. stage CKD/GFR, risk factors for CKD)**
Examples of higher risk of bias: matching or adjustment for most plausible prognostic variables **(e.g. stage CKD/GFR, risk factors for CKD)**
Examples of high risk of bias: matching or adjustment for a minority of plausible prognostic variables **(e.g. stage CKD/GFR, risk factors for CKD)**, or no matching or adjustment at all. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability.

9. Can we be confident in the assessment of the presence or absence of prognostic factors?

- Definitely yes (low risk of bias)
- Probably yes
- Probably no
- Definitely no (high risk of bias)

What is your justification for the response above?

Examples of low risk of bias: Interview of all participants; self-completed survey from all participants; review of charts with reproducibility demonstrated; from database with documentation of accuracy of abstraction of prognostic data **(e.g. stage CKD/GFR, risk factors for CKD)**
Examples of higher risk of bias: Chart review without demonstration of reproducibility; database with uncertain quality of abstraction of prognostic information **(e.g. stage CKD/GFR, risk factors for CKD)**

Examples of high risk of bias: Prognostic information from database with no available documentation of quality of abstraction of prognostic variables **(e.g. stage CKD/GFR, risk factors for CKD)**

11.Can we be confident in the assessment of outcome?

- Definitely yes (low risk of bias)
- Probably yes
- Probably no
- Definitely no (high risk of bias)

What is your justification for the response above?

Examples of low risk of bias: Independent blind assessment; Record linkage; For some outcomes (e.g. fractured hip), reference to the medical record is sufficient to satisfy the requirement for confirmation of the fracture.
(e.g. did authors use standardized diagnostic criteria and/or require skin biopsy)
Examples of higher risk of bias: Independent assessment unblinded; self-report; For some outcomes (e.g. vertebral fracture where reference to x-rays would be required) reference to the medical record would not be adequate outcomes.
Examples of high risk of bias: Authors did not use standardized diagnostic criteria for NSF and/or require skin biopsy

13.Was the follow up of cohorts adequate?

- Definitely yes (low risk of bias)
- Probably yes
- Probably no
- Definitely no (high risk of bias)

What is your justification for the response above?

Note: at least 2 weeks of follow up after gadolinium exposure is required
Examples of low risk of bias: (less than 5-10% for prospective cohorts) No missing outcome data; Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring is unlikely to introduce bias); Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk is not enough to have a important impact on the intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes is not large enough to have an important impact on the observed effect size; Missing data have been imputed using appropriate methods.
Examples of high risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk is enough to induce important bias in intervention effect estimate; For continuous outcome data,

plausible effect size (difference in means or standardized difference in means) among missing outcomes is large enough to induce clinically relevant bias in the observed effect size.

15.Were co-Interventions similar between groups?

- Definitely yes (low risk of bias)
- Probably yes
- Probably no
- Definitely no (high risk of bias)
- Not applicable

What is your justification for the response above?

Examples of low risk of bias: Most or all relevant co-interventions that might influence the outcome of interest are documented to be similar in the exposed and unexposed.
Examples of high risk of bias: Few or no relevant co-interventions that might influence the outcome of interest are documented to be similar in the exposed and unexposed. **e.g. if exposures were self-reported, did the patients undergo many different imaging tests?**

17.Assessment of Bias **(not auto-generated)**

- Low risk of bias for all key domains.
- Unclear risk of bias for one or more key domains.
- High risk of bias for one or more key domains.

Clear Response

What was the funding source for this study?

Was there any pharmaceutical affiliation/association with the study?

Did the first or last author declare any conflict of interest? (if so, please explain)

Comments on overall rating for the responses above?

APPENDIX F. PEER REVIEW COMMENTS AND RESPONSE TABLE

Question Text	Reviewer Number	Comment	Response
Are the objectives, scope, and methods for this review clearly described?	1	Yes	Acknowledged
	4	Yes	Acknowledged
	5	Yes	Acknowledged
Is there any indication of bias in our synthesis of the evidence?	1	No	Acknowledged
	4	No	Acknowledged
	5	No	Acknowledged
Are there any published or unpublished studies that we may have overlooked?	1	No	Acknowledged
	4	No	Acknowledged
	5	No	Acknowledged
Additional suggestions or comments can be provided below. If applicable, please indicate the page and line numbers from the draft report.	1	Include narrative or table of FDA post marketing reports on NSF associated with GBCA that may not have been published	This is an excellent suggestion, and we have made the addition as Appendix A.
	4	Overall excellent review. Below *xxxxx* is used to indicate suggested additions or changes. Page 4, line 22. Please clarify if all patients reported in KQ2 studies had exposure to both Group 1 and Group 2 agents, or if some or most patients had exposure to just one or the other. Page 6, line 50. "… patients with *advanced* renal insufficiency." Page 8, line 23. As a diagnostic tool *and depending on clinical indication*, … Page 15, line 11. Definition of 'index GBCA exposure' is somewhat buried here. Recommend including this definition	Thank you, we have made the suggested changes and added clarifications in the final report. A sentence has been added to the Executive Summary under the KQ2 Results section to clarify exposures to Group I and Group II.

Question Text	Reviewer Number	Comment	Response
		in Executive Summary section. Page 53—59. Use of periods in table bullet points is inconsistent. Page 55, line 20. Correct spacing between serum and creatinine. Page 55, line 26 (and others). Remove footnote indicators if footnotes not included in table. Page 56, line 31. HD should be performed *following* GBCA administration, ideally within 2—3 hours... [The actual guidelines say "the same day as," however 'following' is a clearer restatement of the intent.] Page 59, line 21. *Do* not use… Page 59, line 34. *Do*not use…	A sentence has been added to the Executive Summary under the Data Synthesis and Analysis section to clarify index exposure.
	5	Please review terminology used to describe chronic kidney disease throughout document. In accordance with current accepted terminology, Acute renal insufficiency should be changed to Acute Kidney Injury; chronic renal insufficiency should be changed to chronic kidney disease.	Thank you, we have made these changes in the final report.

APPENDIX G. STUDY CHARACTERISTICS

For full study citations in this appendix, please refer to the report's main reference list.

Study Country (Companion Study)	N Patients GBCA-Exposed (Total Study N)	GBCA (N)	Study Period	GFR Range/CKD	NSF Diagnostic Criteria	Follow-up	Risk of Bias
Nonrandomized controlled trial (KQ 1)							
Deray, 2013[48] Belgium, France, Italy, Spain	70 (70)	Gadoterate meglumine (70)	2008-2011	CKD stages 3-5	NR	3 months	High Pharmaceutical affiliated
Case-control study (KQ 2)							
Elmholdt, 2011[53] Denmark (Elmholdt, 2010[83])	565 (4648)	Gadobutrol (2) Gadoteric acid (8)	1997-2009	Any CKD	NR	NR; mean time from NSF symptom onset to time of diagnosing NSF was 5 ± 3 years (range 0-11)	Unclear
Cohort studies (single agent, KQ 1)							
Abujedeh, 2009[46] USA	92 (250)	Gadobenate dimeglumine (250)	2007-2008	CKD stages 3-5	Non-biopsy: skin exams were done on 183 patients	Mean 108 ± 60 days (range 3-253 days)	Unclear
Bryant, 2009[33] USA (California)	148 (168)	Gadobenate dimeglumine (168)	2007-2008	CKD stages 3-5	Biopsy; specific criteria not specified	6 months	Unclear
de Campos, 2011[45] USA (North Carolina)	2 (69)	Gadobenate dimeglumine (25 quarter-dose; 44 half-dose)	2009-2010	CKD stages 3-5	NR	Mean 8 months (range 4-12 months)	High
Gheuens, 2014[34]	10 (10)	Gadoteric acid (10)	2011-2012	Dialysis	NR	Up to 3 months	High

Study Country (Companion Study)	N Patients GBCA-Exposed (Total Study N)	GBCA (N)	Study Period	GFR Range/CKD	NSF Diagnostic Criteria	Follow-up	Risk of Bias
Belgium							Pharmaceutical affiliated
Lauenstein, 2015[35] Multinational	186 (357)	Gadoexetate disodium (357)	2009-2013	Any CKD	Girardi criteria	Up to 24 months patients with mild renal impairment were not included in follow-up	High Pharmaceutical affiliated
McKinney, 2015[42] USA (Minnesota)	31 (31)	Gadoxetate disodium (31)	2011-2014	CKD stages 3-5	NR	Mean 13.2 months, SD 11.5 (range 1.1-43 months)	High
Michaely, 2017[36] Germany [18 centers], Italy [10], Spain [3], Austria [6], Switzerland [1], Canada [5], Australia [2], South Korea [8], and Thailand [2]	908 (927)	Gadobutrol (908)	2008-2015	Any CKD	Girardi criteria	24 months; patients with mild renal impairment were not included in the follow-up	Unclear Pharmaceutical affiliated
Nandwana, 2015[43] USA (Georgia)	401 (401)	Gadobenate dimeglumine (401)	1/2010-12/2010	Dialysis	Patient's electronic medical record	Mean 2.35 years ± 1.61, (range 0-4.61)	Unclear
Prince, 2017[37] China, Kazakhstan, Kyrgyzstan, Korea, Taiwan,	23,708 (23,708)	Gadobutrol (23708)	2010-2013	All	NR	Up to 3 months	High Pharmaceutical affiliated

Study Country (Companion Study)	N Patients GBCA-Exposed (Total Study N)	GBCA (N)	Study Period	GFR Range/CKD	NSF Diagnostic Criteria	Follow-up	Risk of Bias
Thailand, Bosnia, Herzegovina, Czech Republic, France, Germany, Greece, Hungary, Italy, Russia, Spain, Canada, South Africa (Glutig, 2016[84])							
Reilly, 2008[47] USA (Texas)	141 (141)	Gadoteridol (141)	2000-2007	Dialysis	NR	Mean 570 days (SD 474)	High
Shaffer, 2015[44] USA (Georgia)	352 (352)	Gadobenate dimeglumine (352)	2007-2013	Chronic liver disease	Examination of the patient medical record	Median 17 months (IQR 41.0)	High
Soulez, 2015[38] USA, Canada, Europe	534 (947)	Gadobenate dimeglumine (329) Gadoteridol (160)	2008-2013	CKD stages 3-5	Girardi criteria	2 years	High Pharmaceutical affiliated
Soyer, 2017[39] Argentina, Austria, China, France, Germany, India, Italy, Saudi Arabia, Spain, UK	35499 (35499)	Gadoterate meglumine (35499)	2008-2013	All	NR	Mean 148 days, (range 3 months to 996 days) followed up only patients with impaired renal function	Low Pharmaceutical affiliated

Study Country (Companion Study)	N Patients GBCA-Exposed (Total Study N)	GBCA (N)	Study Period	GFR Range/CKD	NSF Diagnostic Criteria	Follow-up	Risk of Bias
Tsushima, 2018[40] Japan	3337 (3337)	Gadobutrol (3337)	2015-2017	All	NR	3-25 months in patients with eGFR <30	Unclear Pharmaceutical affiliated
Young, 2018[41] Scotland	15,377 (22,468)	Gadoterate meglumine (22,325 adults; 572 pediatric)	2004-2016	Any CKD	Diagnosis determined only via dermatology records	Mean 6.0 years ± 2.5 (range 8 months-15 years) (adults); 6.2 years ± 2.4 (1-10 years) (pediatrics)	Unclear
Cohort studies (multiple agents, KQ 2)							
Amet, 2014[51] France	(n=571)	Gadoteric acid (255) Gadobenate (12) Gadobutrol (11) Gadopentetate (5) Gadoteridol (2) Gadodiamide (1)	2009-2011	Dialysis	Biopsy; criteria NR	At least 4 months	Unclear
Becker, 2012[52] Germany	25 (508)	Gadodiamide (4) Gadopentetate (7) Gadoterate (5) Gadobutrol (4) Gadoteridol (5)	2006-2010	Dialysis	Biopsy; criteria NR	4 years	High
Bruce, 2016[49] USA (Wisconsin)	1669 (1669)	Gadobenate dimeglumine (1423) Gadodiamide (246)		CKD stages 3-5	Clinical symptoms + deep skin biopsy	Not defined; up to 9 years for gadodiamide earlier cohort	High
Chrysochou, 2010[55] UK	2053 (2053)	Gadopentetate (572) Gadoterate (86) Gadodiamide (40) Gadobutrol (69) Vasovist (5)	2000-2009	Any CKD	Includes biopsy findings, reasons for derm/rheum referral as outcomes	Mean 28.6 ± 18.2 months	High

Study Country (Companion Study)	N Patients GBCA-Exposed (Total Study N)	GBCA (N)	Study Period	GFR Range/CKD	NSF Diagnostic Criteria	Follow-up	Risk of Bias
		Gadobenate (1321)					
Hoppe, 2010[57] Switzerland	27 (27)	Gadodiamide (25) Gadopentetate (1) Gadobutrol (1)	2000-2002	CKD stages 3-5	Biopsy, dermatology reports	Mean 28 months (± 29.5); range 1-84 months	Low
Janus, 2010[58] France	232 (308)	Gadoterate (176) Gadopentetate (46) Gadodiamide (7) Gadobenate (3)	2005-2006	Any CKD	Non-biopsy; clinician diagnosis	4 months	High
Martin, 2010[54] USA (Georgia)	1096 (1096)	Gadobenate dimeglumine (784) Gadodiamide (312)	10/2003 - 1/2007	Dialysis	Biopsy; criteria NR	6 months or more	High
Prince, 2008[59] USA (New York)	82,804 (83,121)	Gadodiamide (71441) Gadopentetate (8669) Gadobenate (2785) Gadoteridol (226)	1997-2007	All	Biopsy; criteria NR	Unclear; 10 year retrospective study	Unclear
Schieren, 2008[60] Germany	20 (38)	Gadopentetate (37) confounded with Gadobutrol (25)	2003-2005	Dialysis	Unclear "clinical follow-up"	1 year	Unclear
Smorodinsky, 2015[50] USA (California)	981 (1,167)	Gadobenate (675) Gadoversetamide (301) Gadopentetate (5) Confounded (186)	2004-2007	Chronic liver disease	As per chart in dermatopath records, chart notes, discharge summaries or ICD-9 codes	At least 60 days; mean 1505 days (range 61-3400)	High

Study Country (Companion Study)	N Patients GBCA-Exposed (Total Study N)	GBCA (N)	Study Period	GFR Range/CKD	NSF Diagnostic Criteria	Follow-up	Risk of Bias
Zou, 2009[56] China	29,315 (29,315)	Gadopentetate [Bayer] (17,491) + [Beijing Beilu] (11,189) Gadobenate (635)	2005-2008	All	Non-biopsy	3 months	High

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

APPENDIX H. GLOSSARY

For full study citations in this appendix, please refer to the report's main reference list.

Term | **Definition**

Certainty of evidence (COE)

We assessed COE using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[32] for 4 domains:

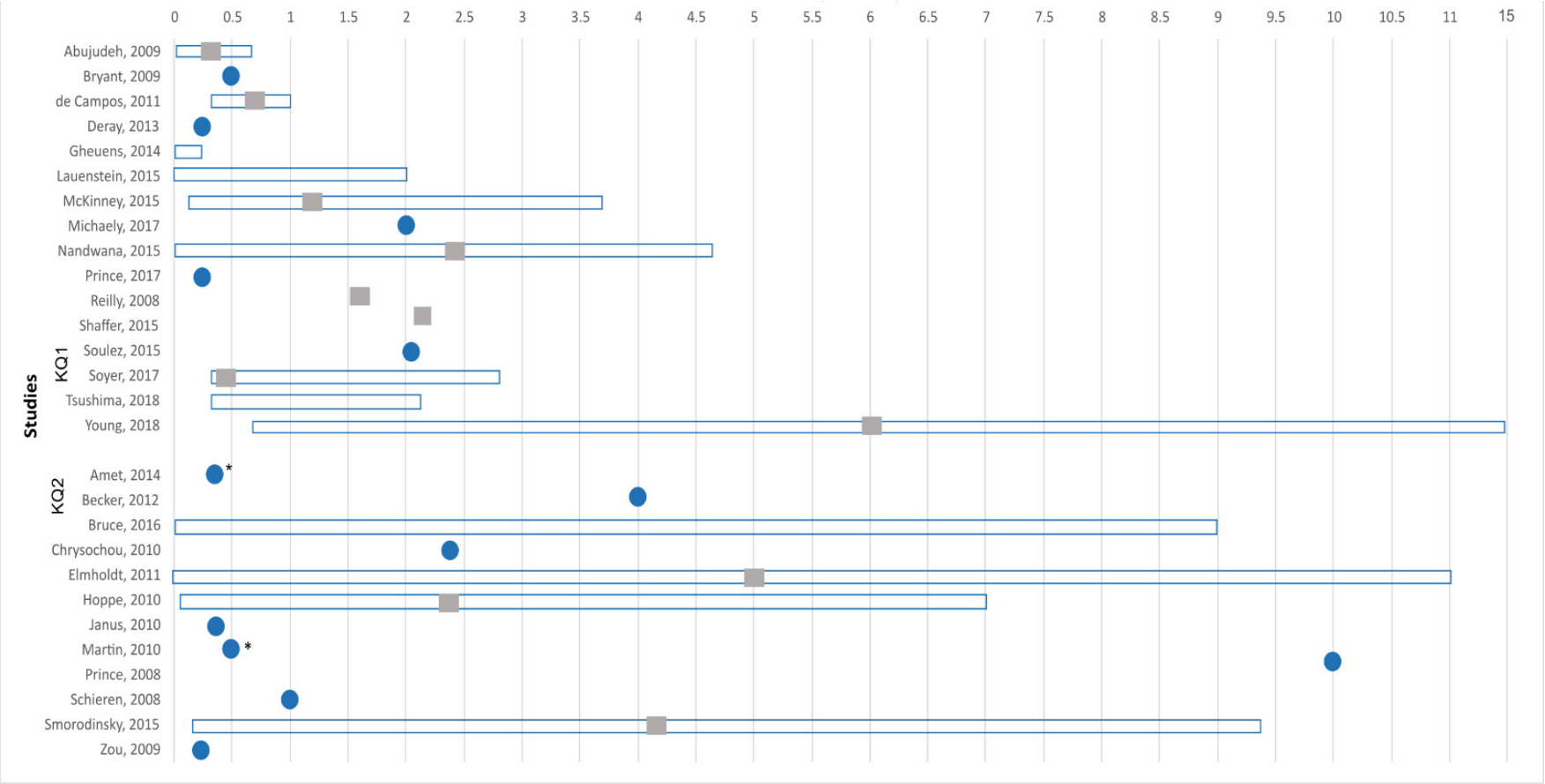
Domain	*Rating*	*How Assessed*
Risk of bias	Low Unclear High	Assessed primarily through study design and aggregate study quality
Consistency	Not serious inconsistency Serious inconsistency Very serious inconsistency	Assessed primarily through whether effect sizes are generally on the same side of "no effect," the overall range of effect sizes, and statistical measures of heterogeneity
Directness	Not indirect Serious indirectness Very serious indirectness	Assessed by whether the evidence involves direct comparisons or indirect comparisons through use of surrogate outcomes or use of separate bodies of evidence
Precision	Not serious imprecision Serious imprecision Very serious imprecision	Based primarily on the size of the confidence intervals of effect estimates, the optimal information size and considerations of whether the confidence interval crossed a clinical decision threshold

Summary COE ratings for a body of evidence:

- High—High confidence that the true effect lies close to that of the estimate of the effect.
- Moderate—Moderate confidence in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low—Limited confidence in the effect estimate. The true effect may be substantially different from the estimate of the effect.
- Very low—Very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.
- Insufficient—Impossible or imprudent to rate. In these situations, a rating of insufficient is assigned.

Term	Definition
Chronic kidney disease stages	• Stage 1 with normal or high estimated glomerular filtration rate (eGFR): eGFR >90 mL/min • Stage 2 Mild CKD: eGFR = 60-89 mL/min • Stage 3A Moderate CKD: eGFR = 45-59 mL/min • Stage 3B Moderate CKD: eGFR = 30-44 mL/min • Stage 4 Severe CKD: eGFR = 15-29 mL/min • Stage 5 End-Stage CKD: eGFR <15 mL/min
Index exposure	The only gadolinium contrast agent exposure as reported by the study, or the primary exposure for studies in which patients were exposed to multiple gadolinium-based contrast agents (*ie*, confounded exposures).
Objective outcomes (*ie*, non–patient-reported outcomes)	Outcomes that are not subject to a large degree of individual interpretation and are likely to be reliably measured across patients in a study, by different health care providers, and over time.
Patient-reported outcomes	Outcomes that are directly reported by the patient without interpretation of the patient's response by a clinician or anyone else and pertains to the patient's health, quality of life, or functional status associated with health care or treatment.
Risk of bias (ROB)	An assessment of study quality. In this report, we used the Cochrane EPOC ROB tool, which is applicable to randomized and nonrandomized studies[29]: • Randomization and allocation concealment • Comparability of groups at baseline • Blinded outcomes assessment • Completeness of follow-up and differential loss to follow-up • Whether incomplete data were addressed appropriately • Protection against contamination • Selective outcomes reporting • Intervention independent from other changes (specific to interrupted time series) • Intervention pre-specified (specific to interrupted time series) • Intervention affect on data collection (specific to interrupted time series) Summary ROB ratings for a study: • Low ROB—Bias, if present, is unlikely to alter the results seriously • Unclear ROB—Bias that raises some doubts about the results • High ROB—Bias that may alter the results seriously For observational cohort and case-control studies, we adapted the Newcastle-Ottawa ROB scale (from the version modified by Guyatt and colleagues). For documentation and tools, refer to Evidence Partners' Methodological Resources at https://www.evidencepartners.com/resources/methodological-resources/.

APPENDIX I. FOLLOW-UP TIME IN YEARS



APPENDIX J. INDEX GBCA EXPOSURES ACROSS STUDIES