Gadolinium is an optimal contrast agent for magnetic resonance imaging (MRI). However, gadolinium is a lanthanide metal that is toxic in its free form (1). To counteract this toxicity, gadolinium-based contrast media (GBCMs) utilize different chelating ligands to enhance stability of gadolinium and are classified according to the type of chelating agent used (2). The most well-known adverse effect of GBCMs is nephrogenic systemic fibrosis (NSF), a debilitating condition associated with GBCM exposure that was first recognized in the early 2000s. Most likely due to the kidney’s role in clearing GBCMs, the presence of kidney disease is a strong risk factor for NSF, and almost all cases have occurred in patients with advanced kidney disease (2). Although not universally fatal and relatively rare, the disease is severely debilitating, and there remains no cure to date. The recognition of a causal relationship between GBCMs and NSF led the Food and Drug Administration to issue a black box warning in 2007 that advised avoiding GBCM administration to patients at risk (3); since then, there has been a near-complete prohibition of gadolinium-enhanced imaging for patients with advanced CKD. Additionally, innovative use of nongadolinium-containing contrast agents, such as iron-based agents (4), has been developed to improve the diagnostic yield of some MRI procedures among patients at risk. Collectively, these measures have largely led to a disappearance of new NSF cases, although given the long latency of disease occurrence after exposure (up to 5 years after exposure), some sporadic cases have been reported (5).

The strength and stability of the ligand-gadolinium complex is thought to be a key factor in the risk of GBCM toxicity, and newer GBCM compounds that provide greater stability of the ligand bond theoretically afford increased protection against adverse effects. Indeed, experimental models comparing the tissue effects of older versus newer GBCMs in rodents have suggested that older agents induce more skin fibrosis and gadolinium tissue accumulation; however, widespread gadolinium accumulation was still observed even with newer agents (6). With the rarity of new NSF cases reported, some, but not all, advisory boards, including the American College of Radiology (ACR), have advised liberalized use of these newer classes of GBCMs with removal of restrictions for class 2 GBCM in patients with kidney disease, going as far as to recommend that preadministration renal function testing and informed consent for patients should be considered optional (7).

In Veterans Health Administration (VHA) facilities, GBCM administration continues to be undertaken with caution. Signature informed consent is a requirement for intravascular administration of contrast agents in “high-risk” patients (limited exceptions may be made in cases of time-sensitive medical emergencies). This requirement applies to intravascular injection of GBCM in patients at risk of NSF (e.g., those with severe renal failure) (8). It is recommended that patients with eGFR < 30 ml/ min per 1.73 m², with AKI, or who are on dialysis be considered for examination with an alternative modality or reduced-dose GBCM protocol; however, there is no absolute contraindication for administration of ACR group 2 GBCM in these patients (9).

To reconcile the variance in recommendations about liberalization of newer GBCM use in patients with severe CKD and to develop an informed response to these recommendations, the VHA Renal Field Advisory Council, a multidisciplinary group of nephrology subject matter experts, commissioned the VHA Evidence Synthesis Program to conduct a systematic review of all available evidence on the risk of NSF associated with newer GBCMs, particularly among patients with kidney disease. These findings were recently published (10). From 3254 studies published up to March 5, 2020, 32 were selected on the basis of the inclusion criteria of containing documented exposure to newer (ACR class 2 or 3) GBCM agents, containing assessment of confirmed or suspected NSF occurrence after exposure, and meeting study design criteria (randomized, controlled trial; cohort or patient-control; patient series; or patient reports). Studies were excluded that were non-English published, lacked quantitative reporting of GBCM-exposed patients, or had follow-up after index GBCM exposure of <2 weeks.

Twenty of the included studies examined the occurrence of NSF per exposure to newer GBCMs among
83,291 patients with index GBCM exposure and reported no cases of NSF. However, most of the patients in these studies did not have kidney disease. In fact, only a trivial number of patients had CKD stage 3 or greater (3236 of 80,952 [4%]), with only 1% (886 of 80,952) of patients receiving maintenance dialysis. Furthermore, the majority of studies and patients with CKD stages 3–5 or on dialysis (five of nine [56%] and 2454 of 3236 [75%], respectively) were exposed to a unique class 2 GBCM that enjoys hepatic as well as renal clearance (gadobenate dimeglumine), which may have reduced NSF occurrence.

The remaining 12 studies directly compared the occurrence of NSF between older and newer GBCMs among patients with or without CKD and reported 37 and four cases of NSF among those exposed to older and newer agents from a pool of 11,0345 and 8499 patients, respectively. Although the rarity of NSF with newer GBCMs use is reassuring, experience with these newer agents has only accumulated well after the practice of restricting and prohibiting exposure among patients with kidney disease was put in place, making risk estimates difficult, if not impossible, to ascertain among this highest-risk group. To illustrate this point, only 3123 (3%) patients of the patient population studied in this second part of the systemic review were identified as having CKD stage 3 or worse, with only 1427 (1%) receiving dialysis. Although no unconfounded cases of NSF were reported in these subgroups, because of the small sample size, the upper 95% confidence interval of risk was reported to be as high as 0.258 events per newer GBCM exposure among patients receiving dialysis, which approximated that reported for class 1 GBCMs.
Additionally, no studies were identified that specifically addressed exposure risk among patients with AKI. Certainty about the safety of newer GBCMs is further limited by the high risk of bias for many of the included studies resulting from GBCM industry funding and the lack of standardized NSF identification criteria and substantial missing data, which may result in under-reporting of NSF cases.

An earlier systematic review of the literature published up to January 2019 by Woolen et al. (11) also reported no unconfounded cases of NSF among 4931 patients with CKD stage 4/5 (eGFR<30 ml/min per 1.73 m²) exposed to newer GBCM agents but similarly reported a wide range of the upper bound of risk between populations exposed to different specific GBCM agents. Unfortunately, the review did not describe whether patients on dialysis constituted part of the overall patient pool for analysis. It also highlighted the uncertainty of the data posed by nonuniformity of NSF case definitions used by the different studies, ranging from histologic diagnosis to patient-reported questionnaire to electronic health record of the MRI facility to a lack of description.

What do these recent studies tell us about how to manage the current risks of GBCM administration among patients with CKD? Although the fact that no unconfounded NSF cases occurred among >80,000 index exposures to newer GBCMs should certainly give us some reassurance that risks remain small for the general population without significant kidney disease, it is sobering to recognize that the population most at risk for NSF was signiﬁcantly under-represented in these studies. Our understanding of the risk of harm of newer GBCMs is further constrained by the complete lack of safety data for patients with AKI as well as for those with severe CKD undergoing repeated GBCM administration. Caution is also warranted in generalizing safety evidence derived predominantly from a single new GBCM to all class 2 GBCMs, particularly when the specific GBCM examined may offer an additional protective advantage against NSF due to its potential for hepatic clearance (Figure 1).

In conclusion, given the uncertainty of the evidence and lingering concerns about gadolinium tissue accumulation from animal models, it is premature to conclude that all newer GBCMs are safe for administration to people with severe kidney dysfunction. Paraphrasing from Altman and Bland (12) in their landmark editorial, in the absence of clear evidence we should refrain from interpreting that there is trivial or no risk, and likewise, where public health is concerned, we should hesitate to use an absence of evidence to justify inaction. There is simply not enough evidence to throw caution to the wind; prudence would dictate that informed consent, where possible, should remain the standard for those with severe CKD if an alternate imaging procedure will not suffice.

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Author Contributions

S.T. Crowley and P.H. Pun wrote the original draft and reviewed and edited the manuscript.

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See related debate, “Group II GBCM Can Be Used Safely for Imaging in Stage 4/5 CKD Patients: PRO,” and commentary, “Group II GBCM Can Be Used Safely for Imaging in Stage 4/5 CKD Patients: COMMENTARY,” on pages 10–12 and 16–19, respectively.