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EDITORIAL

Safety of Ultrasound-Enhancing Agents: Gazing Backward While Looking Forward

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Ultrasound-enhancing agents (UEAs) improve diagnostic transthoracic echocardiography (TTE) in selected cardiac patients. UEA use has been embraced by the cardiology community, and there is now an abundance of high-quality evidence supporting their safety and efficacy.[1,2] UEA administration routinely salvages nondiagnostic TTEs and can reveal otherwise undetectable cardiac pathology, allowing for timely diagnosis and reducing the need for alternative imaging modalities. It is not an exaggeration to say that much like iodinated intravenous contrast in computed tomography, UEAs unlock the full diagnostic capabilities of TTE. Unlike with iodinated intravenous contrast, however, echocardiography laboratories do not have to restrict UEA use in patients with significant renal disease and, until recently, did not routinely screen for potential cross-reactive allergies to constituent ingredients, namely, polyethylene glycol (PEG). Before 2021, many echocardiography laboratories were unaware of PEG-related hypersensitivity reactions. UEAs were administered with a sense of security, bolstered by the data-driven impression that serious adverse events (AEs) occurred infrequently after UEA exposure, estimated at 1 in 10 000 administrations.[2] The majority of AEs encountered are less serious somatic complaints like headache or flank pain, which resolve within minutes after UEA administration.[3] The ability of UEAs to improve detection of life-threating cardiac conditions like ischemic wall motion abnormality, left ventricular (LV) aneurysm or pseudoaneurysm, and LV thrombus more than justified the low risk of serious AEs, as well as the added cost to the examination.[4]

See article by Strom et al.

However, it was not always this way. In 2007, prompted by the observation of a handful of deaths and several dozen serious adverse outcomes occurring soon after UEA administration, the US Food and Drug Administration (FDA) issued a black box warning contraindicating UAE administration in severe or unstable cardiopulmonary disease including myocardial infarction, pulmonary hypertension, acute heart failure, and respiratory failure. UEA use was also contraindicated with known cardiac shunt. Additionally, this labeling mandated a 30-minute monitoring period after UEA administration in all patients.

It is now routine practice to administer UEA in all these conditions when there is inadequate visualization of the left ventricle. The American Society of Echocardiography recommends UEA administration in studies where 2 contiguous myocardial segments are not visualized, as well as in clinical scenarios like apical-variant hypertrophic cardiomyopathy where detection of LV apical aneurysm conveys prognostic

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significance.[1] Many echocardiography laboratories now consider failure to administer UEA in these situations as a quality measure that should be improved upon.

In the United States, there are currently 3 FDA-approved UEAs for use in adult echocardiography to improve LV opacification and endocardial border definition in patients with suboptimal TTE: Optison (GE Healthcare, FDA approved 1997), Definity (Lantheus Medical Imaging, FDA approved 2001), and Lumason (Bracco Diagnostics, FDA approved 2014). These UAEs consist of microbubbles composed of phospholipid or protein shells surrounding inert fluorocarbon gas designed to mimic the characteristics of red blood cells. They are injected intravenously and pass through the pulmonary circulation into the left ventricle, and they are strong reflectors of ultrasound, opacifying the LV blood pool and improving delineation of the blood–endocardial border. Two of these agents include PEG in their composition: Definity and Lumason.

It is useful to consider the historical timeline of FDA guidance regarding UEA use to fully appreciate the context of the important paper by Strom et al included in this issue of the *Journal of the American Heart Association* (*JAHA*). This timeline illustrates a remarkable story of pharmacovigilance, where signals for potential harm with UEAs were repeatedly met by dedicated investigation into the incidence of serious AEs and contributing factors. Convinced of the utility of UEAs in diagnostic TTE, several investigators rallied to produce large, high-quality studies evaluating their safety.[1,2] These studies, now comprising hundreds of thousands of administrations of UEAs, have consistently demonstrated a low event rate of serious AEs, around 1 in 10 000. Two of these studies even suggested a lower incidence of death after echocardiography with UEAs when compared with echocardiography without UEAs, after propensity score matching, in hospitalized patients with the cardiopulmonary conditions highlighted by the FDA black box warning.[5]

The ensuing years saw the FDA black box warning changed, the disease-state contraindications softened, the postadministration monitoring period relaxed and then removed all together, and the contraindication for UEA use in patients with a cardiac shunt dropped. From 2017 to 2021, the only contraindication to UEA use was prior hypersensitivity reaction to an individual UEA, its component gas (perflutren in the case of Optison and Definity, sodium hexafluoride in Lumason), or albumin/blood products in the case of Optison.

In 2021, in response to an FDA MedWatch alert describing hypersensitivity reactions resulting in 11 cases of anaphylaxis including 2 deaths after UEA exposure in patients with preexisting PEG allergy, the package inserts for lipid-based UEAs containing PEG (Definity and Lumason) were updated to include hypersensitivity to PEG as a contraindication for administration. The American Society of Echocardiography issued a consensus statement that now recommended routine screening for prior PEG allergy before administration of lipid-stabilized UEAs but that UEA use should not be otherwise restricted or skewed toward a specific agent. Based on available pharmacovigilance observation data, the estimated incidence of UEA hypersensitivity reactions attributable to PEG allergy remained well below the widely cited 1 in 10 000 incidence rate of serious AEs.[6] The recognition of PEG-related hypersensitivity reactions did produce a shift in thinking, however.

Considering the benign hemodynamic and rheological properties of UEAs, the majority of serious AEs after administration are attributed to immune-mediated hypersensitivity reactions. Most of these hypersensitivity reactions were previously felt to be complement activation–related pseudoanaphylaxis rather than immunoglobulin E–mediated, type 1 hypersensitivity reactions. An important distinction between the types of hypersensitivity reaction is that complement activation–related pseudoanaphylaxis reactions are felt to be sporadic and not based on prior exposure and sensitization. Additionally, complement activation–related pseudoanaphylaxis reactions may be milder or absent on repeat exposure. Immunoglobulin E–mediated hypersensitivity reactions, on the other hand, rely on prior exposure and sensitization, with reexposure resulting in mast cell degranulation and inflammatory cascade. Considering the presence of PEG in several commonly used medications including the mRNA vaccines widely administered during the COVID-19 vaccination program, the potential for cross-reactive type 1 hypersensitivity reactions based on prior exposure to PEG is a concerning development.

Recently, there have been multiple published reports probing whether there is a signal for increased incidence of serious AEs attributable to the PEG hypersensitivity hypothesis. Because of widespread implementation of PEG containing mRNA vaccines against COVID-19 starting after December 2020, this date is often used as a line of demarcation in these retrospective analyses. The studies are retrospective for several reasons: The low AE event rate associated with UEA use would require the design of large prospective trials to be adequately powered.

One of the more compelling studies, based on large sample size, was Ali et al' s 2024 paper that collected UEA administrations across 4 large health care systems from January 2010 to June 2023.[7] Data analyses were limited to the administration of lipid-stabilized UEAs, due to low volume of Optison use. AEs were stratified as mild, severe (with features of cardiopulmonary involvement), and critical (ST-segment

elevation, loss of pulse or consciousness) and had to occur within 30 minutes of UEA exposure. A total of 201 834 Definity administrations and 84 943 Lumason administrations were included in the analyses. Serious AEs occurred, with an event rate of 0.0114% (1.14 per 10 000) with Definity and 0.0848% (8.5 per 10 000) with Lumason. The critical AE event rate with Definity was 0.1 per 10 000 administrations versus 3.3 per 10 000 with Lumason. The rate of serious AEs reported by Ali et al is higher than the historically cited frequency of 1 in 10 000; however, this may reflect a broader definition of serious AEs by the investigators compared with prior studies.[8] Assuming consistent adjudication of events across the study population, there was a higher incidence of AEs observed with Lumason compared with Definity. Additionally, the AE rate broken down by year appeared to increase from 2019 to 2023 with Lumason, while remaining relatively flat with Definity. It is important to note that analysis of the AE rate after UEAs occurring after introduction of the COVID-19 vaccine was limited to the patients receiving Lumason. Patients with AEs after Lumason were more likely to be vaccinated than unvaccinated (88% versus 75%), an observation without clear statistical significance (P=0.05). Patients with AEs after Lumason that occurred after December 2020 were more likely to have received the Moderna vaccine (71%) than the Pfizer-BioNTech vaccine (26%), a different trend than that seen in the matched control group (the majority of whom received Pfizer-BioNTech vaccine). Whether the divergence in AE rate after 2020 is due to nascent hypersensitivity to PEG as influenced by UEA type or mRNA vaccine exposure is speculative. It is undeniable, though, that the FDA MedWatch report and American Society of Echocardiography Consensus Statement on hypersensitivity reactions to PEG issued in 2021 could have influenced the observation and adjudication of UEA reactions during the later study period.[8]

In this issue of *JAHA*, Strom et al report on a large cohort of patients who underwent TTE or stress echocardiography (SE), with or without a UEA, over a period from 2018 to 2022.[9] The retrospective analysis spans the period before and after the introduction of the COVID-19 vaccination by design. The study population reflects a "real-world" cohort with the only selection bias being continuous enrollment in health insurance and having undergone TTE or SE. The investigators accomplish this by querying a national database of closed insurance claims representing >140 million patients. They included all adult patients with at least 1 closed claim for TTE or SE during the study window along with continuous enrollment in benefits from 1 year before the index TTE or SE through at least 48 hours after. Patients with a closed claim for TTE or SE with UAE and a billing event for a specific UAE were included in the UAE-exposed arm. COVID vaccination status was extracted from the closed claims data along with multiple cardiovascular comorbidity covariates. Only the first TTE or SE with UEA exposure during the study window was included in the analysis. Thirty-two percent of the TTE or SE events analyzed occurred after the introduction of commercially available COVID vaccines. The study population ultimately included 11.4 million TTE or SE examinations, of which 500 073 (4.4%) were performed with a specific UEA. The 3 commercially available UAE agents were well represented in the study population, with Definity use being the most common (81%). More than 50 000 Lumason and 40 000 Optison administrations were included in the analysis.

The authors set out to determine if UEA use was associated with a higher rate of AEs within 2 days of exposure compared with echocardiography without UEA use. Another aim was to determine if any individual UEA was observed to have a greater-than-expected AE rate. The final aim was to determine if there was increasing risk for AEs later in the study, ostensibly after population-level exposure to the mRNA vaccine beginning in December 2020. The primary end point measured was death within 48 hours after TTE or SE. The study uses a unique method to determine if death occurred. The deidentified data set did not include a subject-specific death date; rather, it included only month of death along with the completed insurance claims for a subject. Patients were determined to have died on the basis of month of death combined with cessation of new claims 48 hours after TTE or SE. Secondary end points (based on *International Classification of Diseases* [*ICD-10*] coding) included anaphylaxis, myocardial infarction, ventricular tachycardia, and cardiac arrest. The secondary outcomes were determined to have occurred if there were claims containing *ICD-10* code corresponding to these diagnoses within 48 hours of TTE or SE.

In this study, the observed death rate was lower in patients receiving UAEs compared with those who did not (0.02% versus 0.14%). After propensity matching, the observed death rate within 48 hours was 0.02% with UEAs and 0.07% without UEAs. Rates of anaphylaxis in the 2 days after TTE/SE were equivalently low in both the UEA and non-UEA groups (0.01% or 1 in 10 000). Cardiac arrest occurred in 0.12% of patients receiving UEAs but was observed with greater frequency in both the matched and unmatched cohort not receiving UEAs. The odds ratio of death was lower in patients who received UEAs compared with those who did not, an interesting finding also observed in prior large studies[5]; this observation was consistent across the individual UEA brands. The crude incidence of anaphylaxis with Lumason was 0.03% compared with 0.02% in TTE or SE without a UAE, which is notably lower than the serious AE rate with Lumason

reported by Ali et al.[7] Finally, the crude death rate broken down by UEA brand and study year did not appear to demonstrate an increasing trend after 2020, either in aggregate or by UEA type, also different from the previously mentioned study.

The primary strength of the study by Strom et al is the large and unselected nature of the study population. The data are drawn from a nationwide claims database; though limited to the United States, it is a geographically diverse data set representing a broad swath of the country as opposed to a single heath care system or region. The overall rate of UAE use with echocardiography was 4.4%, well below the generally cited rate of 10% to 15% of studies impacted by suboptimal LV visualization. This finding reflects the real-world nature of the study and is not entirely surprising, as there are often pragmatic reasons driving underuse of UEAs: TTE and SE are often performed in an outpatient or ambulatory setting, which can present certain barriers to UEA use.

There are some limitations of the study, acknowledged by the authors. One criticism is that the primary outcome measured (death within 48 hours of TTE or SE) was determined by analysis of claims data without the actual death date. The authors suggest that their method may overestimate rate of death. One could also argue that it may fail to identify death occurring within 48 hours. This lack of granularity is hopefully buffered by the very large sample size and scope of the study population. The reliance on *ICD-10* codes to adjudicate secondary outcome AEs occurring within 48 hours of TTE or SE could plausibly lead to under- or overestimates of the true event rate, influenced by the clinical setting of AEs or the accuracy of coding. The authors point out that most AEs associated with UEA administration occur within 30 minutes of exposure, which likely increases clinical identification and diagnostic capture. Though the paper explicitly investigates the incidence of AEs after presumed exposure to PEG through COVID-19 vaccination, the investigators intentionally limit analysis to only the first exposure to UAE during the study period, excluding subsequent or serial exposures to UEA from analysis. Considering the PEG hypersensitivity hypothesis, including serial exposure to UEAs may have generated useful information.

It is important to state that event rate, even in a large study, does not imply causality. Consider the 14/10 000 unadjusted death rate observed in those undergoing TTE or SE without UEAs in this paper. This does not imply that cardiac ultrasound itself has a low rate of lethality. Patients undergoing routine TTE include hospitalized inpatients, patients being treated with surgery or chemotherapy, and patients with critical or advanced illness: a heterogenous population that would be expected to have a higher rate of AEs than all-comers.

Ultimately, Strom et al have delivered an important and effective article that deserves a place among the seminal papers evaluating UEA safety. It is also a timely paper, arriving at a time when serious questions have been raised about AE rates in PEG-containing lipid-based UEAs. This article did not redemonstrate a significantly greater AE rate with a specific lipid-based UEA brand, nor did it show a higher rate of serious AEs over time. Using a nationwide data set to capture a real-world population, Strom et al have demonstrated a low rate of death, anaphylaxis, or cardiac arrest after echocardiography with a UAE. AE rate is not increased compared with echocardiography without a UEA, and UEA use in fact appears to be associated with a lower odds ratio for death, similar to prior large studies in more selected critical care or hospitalized populations.[5]

It should be mentioned that this study was supported by a research grant from Bracco Diagnostics, the maker of Lumason. That should not diminish its contribution to the field. Some of the foundational papers that resulted in relaxation of the FDA black box warning and removal of disease-based contraindications to UEA administration were also supported by research grants from UEA manufacturers.[5] Responsible pharmacovigilance is a 3-legged stool that relies on the partnership and combined efforts of clinician investigators, the FDA, and our industry partners. We are all stakeholders when it comes to better understanding any potential risk to our patients while striving to provide the best diagnostic imaging possible.

ARTICLE INFORMATION

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Disclosures

None.

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