Ultrasound Enhancing Agents: Recommended Laboratory Practices from ASE
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**Contributors**

Jonathan R. Lindner, MD, FASE (Chair)  
*Oregon Health & Science University*

James Hodovan, MS, RDCS (AE, PE), CVT  
*Oregon Health & Science University*

Sharon Mulvagh, MD, FASE, FRCP(C), FACC  
*Queen Elizabeth II Health Sciences Centre*

Margaret M. Park, BS, ACS, RDCS, RVT, FSDMS, FASE  
*Cleveland Clinic*

Thomas R. Porter, MD, FASE  
*University of Nebraska Medical Center*

G. Monet Strachan, ACS, RDACS, FASE  
*University of California San Diego*

Kevin S. Wei, MD, FASE  
*Oregon Health & Science University*

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ASE gratefully acknowledges the support of the following industry partners in the publication of this resource. There was no industry influence on the content.
INTRODUCTION

Contrast echocardiography is a cardiac ultrasound imaging technique that relies on the detection of FDA-approved ultrasound enhancing agents (UEAs) that are composed of encapsulated microbubbles that reside within the blood pool. While the technique requires dedicated education on the part of the sonographer and physician imaging team, it is no longer considered to be an “advanced” technique for specialized laboratories. Instead, contrast echocardiography is now considered by the American Society of Echocardiography (ASE) and imaging societies worldwide to be an indispensable part of the practice of echocardiography. This priority statement is based on extensive data demonstrating the ability of contrast echocardiography to: (i) improve the quality of echocardiography and reduce error, (ii) detect life-threatening conditions, (iii) improve laboratory efficiency and cost-effectiveness, (iv) reduce interobserver variability in interpretation, and (v) provide information on disease processes that would not be possible without the use of UEAs. The importance of the technique is also underscored by mandates for contrast echocardiography components in the curriculum for accredited sonographer and physician training programs, for laboratory accreditation, and for board certification in Adult Cardiology and Echocardiography.

ASE first introduced guidelines for the use of UEAs in contrast echocardiography in 2008. A second guideline document was released in 2018. The latest guideline document is comprehensive in its description of indications, methods, and laboratory policies related to the use of UEAs. The focused document provided here contains a synopsis of information that experts in the field of echocardiography view to be important for facilitating laboratory, clinic, or hospital policy decisions regarding the practice of contrast echocardiography. Information is provided on contrast storage, administration, consent policies, billing, and safety.
1. Enhancing Agents

There are three commercially available UEAs approved for use in the United States for cardiac imaging: Optison, Definity (Luminity in Europe), and Lumason (Sonovue outside the USA). All contain a high molecular weight gas that is low in terms of solubility and diffusivity in order to optimize their in vivo stability and reduce surface tension. The shell of Optison is composed of human serum albumin, whereas Definity and Lumason possess a phospholipid shell. Optison and Definity have a gas core composed of octafluoropropane (perfluor) gas whereas Lumason contains sulfur hexafluoride gas. The specific lipid composition and charge differ between Lumason and Definity. Optison and Definity require refrigeration before use, whereas Lumason is stored as a dry lyophilized powder without refrigeration. Preparation requirements for each of the agents differ: Definity requires activation with a mechanical agitator, Optison requires a resuspension of the bubbles by hand, and Lumason requires mixing and hand agitation. All agents should be vented prior to withdrawal to prevent pressure-related degradation of the agent.

There are currently three commercially available UEAs that differ in their composition and concentration.
Storage recommendations and the physical preparation of the UEAs differ between the agents.
UEAs are indicated to enhance the cardiac blood pool in order to better assess ventricular borders, ventricular function, masses, and other intracavitary or myocardial pathology.
UEAs can be used off-label to assess perfusion.

2. Availability and Storage of Ultrasound Enhancing Agents

The immediate availability of UEAs for practitioners of echocardiography influences whether contrast echocardiography is used according to ASE and American College of Cardiology (ACC) guidelines. Post-program surveys from ASE Scientific Sessions and from major educational meetings have clearly and consistently established that one of the major obstacles to the adoption of guideline-directed use of contrast echocardiography is the time and effort required for access to UEAs. Accordingly, experts in echocardiography have advocated that UEAs be ordered through established pharmacy protocols, but stored in the Echocardiography Laboratory and in other areas where sonographers have immediate access to their use. In particular, it is important that UEAs be readily availability for use in areas of hospitals where patients who are most likely to have technically challenging acoustic windows, such as the intensive care units. These policies are used by many leading academic and clinical healthcare institutions in the United States, and do not differ from those practiced by other imaging laboratories that routinely utilize contrast agents (cardiac catheterization laboratory, CT and MRI radiology services, etc.). Key concepts for the efficient use of UEAs are:

- UEAs should be stored in echocardiography laboratories and intensive care units where they are available for immediate use by sonographers.
- Echo labs in hospitals or clinics should coordinate with Pharmacy Services to ensure compliance with all policies and procedures (including information on batch/lot data) and reporting of adverse events.
- For agents that require refrigeration, a dedicated refrigerator within the echo lab for drug storage is required for optimizing efficiency through immediate access to UEAs.
- Consent policies are governed individually by each medical institution. Requirement for written consent is viewed as an unnecessary obstacle, is contrary to policies for other radiologic services, and can be avoided by including UEAs in the procedure order set.
3. Administration and Imaging:
All UEAs require the placement of an intravenous catheter (IV). Training for IV placement and administration of agents are governed by the policies of each institution. However, the American Society of Echocardiography (ASE) recommends the training of sonographers for the placement and safe maintenance of IVs for outpatient administration.1,2 This approach has been used successfully by many echocardiography laboratories in the United States that have implemented contrast echocardiography with high efficiency. The ASE also recommends policies that support physician-sonographer communication and laboratory policies for identification of patients who are most likely to benefit from contrast echocardiography.

Optison and Definity have been given as either small bolus injections or as diluted infusions in normal saline (10% and 3-5%, respectively), while Lumason has been primarily used as small 0.5 milliliter bolus injections followed by slow 5-10 ml saline flushes to avoid LV cavity shadowing. Intravenous enhancing agents are approved to enhance LV opacification in adults, although Lumason has also recently been approved by the FDA for pediatric use. Although not specifically approved for stress testing, UEAs have been shown to improve the detection of regional wall motion abnormalities at rest and during stress testing, to provide a greater likelihood for a diagnostic study, and to improve reader confidence.3,4

The signals obtained from UEAs are dependent on many machine-related factors. ASE recommends the use of real-time very-low mechanical index techniques which are available on nearly all commercially-available ultrasound imaging systems, but often require optional software. These contrast-specific multi-pulse sequence schemes permit the enhanced detection of microbubbles within the IV cavity and myocardium, and thus permit improved assessments of regional wall motion, cavity volumes, and myocardial perfusion.

Sonographers performing contrast echocardiography should be trained in the following practices:

- Contrast-specific methods (pulse inversion, power modulation, harmonic imaging) and other standard setting adjustments (gain, focus, mechanical index, frame rate, dynamic range) are required to optimize UEA signal-to-noise ratio.
- Sonographers must conform to policies including documentation in the patient's electronic health record of:
  1) no history of known or suspected hypersensitivity to UEA or its components, 2) UEA administration (agent, dose), and 3) any adverse reactions.
- Sonographers should be trained in the safety of UEAs, including adverse event recognition, and must be trained to contact healthcare workers that are licensed to treat rare reactions.

4. Billing
Specific codes for hospital outpatient (HOPPS) and Physicians office use of contrast are displayed in the Table. Note that enhancing agent use codes are available for resting echocardiograms, Doppler enhancement, stress echocardiograms, and for myocardial perfusion. However, the myocardial perfusion add-on code (0439T) is not currently reimbursed by Medicare (as of January 2021).
### CY2020 Coding and Payment for Contrast Enhanced Echocardiography

The tables below and on the next page, address coding and payment for contrast enhanced ultrasound services. The payment rates detailed are Medicare national averages for CY2020. Actual payment rates are site-specific and will likely differ from the illustrative amounts noted below. Providers are solely responsible for exercising clinical judgement in selecting the appropriate coding for services provided. Inclusion in this document does not guarantee coverage or reimbursement. ASE strongly encourages all providers to communicate with individual payers for specific details.

#### Physician Office / IDTF

<table>
<thead>
<tr>
<th>Ultrasound Microbubble CPT codes</th>
<th>Final 2021 Professional Payment</th>
<th>Final 2021 Technical Payment</th>
<th>Final 2021 Global Payment</th>
</tr>
</thead>
<tbody>
<tr>
<td>76978 Ultrasound, microbubble contrast, initial lesion</td>
<td>$79.90</td>
<td>$243.88</td>
<td>$323.78</td>
</tr>
<tr>
<td>76979 add on code Ultrasound, microbubble contrast, each additional lesion w/ separate injection</td>
<td>$41.87</td>
<td>$178.99</td>
<td>$220.85</td>
</tr>
</tbody>
</table>

#### Transthoracic Echocardiography (TTE) CPT

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
<th>Final 2021 Professional Payment</th>
<th>Final 2021 Technical Payment</th>
<th>Final 2021 Global Payment</th>
</tr>
</thead>
<tbody>
<tr>
<td>93303 TTE, congenital complete</td>
<td>$65.32</td>
<td>$172.15</td>
<td>$237.47</td>
<td></td>
</tr>
<tr>
<td>93304 TTE, congenital limited</td>
<td>$36.98</td>
<td>$129.79</td>
<td>$166.77</td>
<td></td>
</tr>
<tr>
<td>93306 TTE, complete</td>
<td>$70.83</td>
<td>$137.12</td>
<td>$207.94</td>
<td></td>
</tr>
<tr>
<td>93307 TTE limited</td>
<td>$45.36</td>
<td>$101.53</td>
<td>$146.89</td>
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</table>

#### Transesophageal Echocardiography (TEE) CPT

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
<th>Final 2021 Professional Payment</th>
<th>Final 2021 Technical Payment</th>
<th>Final 2021 Global Payment</th>
</tr>
</thead>
<tbody>
<tr>
<td>93312 TEE probe placement, image acquisition, interpretation and report</td>
<td>$109.21</td>
<td>$143.05</td>
<td>$252.25</td>
<td></td>
</tr>
<tr>
<td>93315 TEE Congenital, probe placement, image acquisition, interpretation and report</td>
<td>$128.74</td>
<td>$-</td>
<td>$-</td>
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</tbody>
</table>

#### Stress Echocardiography CPT

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
<th>Final 2021 Professional Payment</th>
<th>Final 2021 Technical Payment</th>
<th>Final 2021 Global Payment</th>
</tr>
</thead>
<tbody>
<tr>
<td>93350 Stress TTE with interpretation and report</td>
<td>$70.83</td>
<td>$125.95</td>
<td>$196.78</td>
<td></td>
</tr>
<tr>
<td>93351 Stress TTE complete</td>
<td>$84.43</td>
<td>$158.74</td>
<td>$243.18</td>
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<tr>
<td>93352 Admin ECG contrast agent</td>
<td>$-</td>
<td>$-</td>
<td>$34.19</td>
<td></td>
</tr>
<tr>
<td>0439T Contrast perfusion</td>
<td>Carrier Priced</td>
<td>Carrier Priced</td>
<td>Carrier Priced</td>
<td></td>
</tr>
</tbody>
</table>

#### Contrast Agents* 

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
<th>Final 2021 Professional Payment</th>
<th>Final 2021 Technical Payment</th>
<th>Final 2021 Global Payment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q9950 - Lumason Injection sulfur hexafluoride lipid microspheres, mil (1 mil dosage)</td>
<td>N/A</td>
<td>N/A</td>
<td>$18.23</td>
<td></td>
</tr>
<tr>
<td>Q9956 - Optison Injection, perflutren lipid microspheres, mil (1 mil dosage)</td>
<td>N/A</td>
<td>N/A</td>
<td>$31.37</td>
<td></td>
</tr>
<tr>
<td>Q9957 - Definity Injection, perflutren lipid microspheres, mil (1 mil dosage)</td>
<td>N/A</td>
<td>N/A</td>
<td>$47.06</td>
<td></td>
</tr>
</tbody>
</table>

*Fee Schedule for January – March 2021 noted above; Average Sales Price (ASP) updated quarterly.
Source - CMS CY2021 Final Medicare Physician Fee Schedule - https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PhysicianFeeSched/PFS-Relative-Value-Files
## Hospital Outpatient Prospective Payment System (HOPPS)

**Note:** Hospital Outpatient Departments bill Medicare C-codes for Contrast Echocardiography. Commercial payers may accept C-codes; if not, refer to CPT 933XX codes.

### Ultrasound Microbubble APCs

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>2021 Payment</th>
<th>2021 APC</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>76978</td>
<td>Ultrasound, microbubble contrast, initial lesion</td>
<td>$182.22</td>
<td>5571</td>
<td>Level Imaging with Contrast</td>
</tr>
<tr>
<td>76979</td>
<td>Ultrasound, microbubble contrast, each additional lesion with separate injection</td>
<td>$-</td>
<td>N/A</td>
<td>Packaged</td>
</tr>
</tbody>
</table>

### Contrast Echocardiography APCs

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>2021 Payment</th>
<th>2021 APC</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C8921</td>
<td>TTE with contrast, or without contrast followed by with contrast, for congenital cardiac anomalies; complete</td>
<td>$715.18</td>
<td>5573</td>
<td>Level 3 Imaging with Contrast</td>
</tr>
<tr>
<td>C8922</td>
<td>TTE with contrast, or without contrast followed by with contrast, for congenital cardiac anomalies; follow-up or limited study</td>
<td>$715.18</td>
<td>5573</td>
<td>Level 3 Imaging with Contrast</td>
</tr>
<tr>
<td>C8923</td>
<td>2D TTE with contrast, or without contrast followed by with contrast, real-time with image documentation (2d), includes m-mode recording, when performed, complete, without spectral or color doppler echocardiography</td>
<td>$715.18</td>
<td>5573</td>
<td>Level 3 Imaging with Contrast</td>
</tr>
<tr>
<td>C8924</td>
<td>2D TTE with contrast, or without contrast followed by with contrast, real-time with image documentation (2d), includes m-mode recording, when performed, follow-up or limited study</td>
<td>$368.12</td>
<td>5572</td>
<td>Level 2 Imaging with Contrast</td>
</tr>
<tr>
<td>C8925</td>
<td>2D TEE with contrast, or without contrast followed by with contrast, real time with image documentation (2d) (with or without m-mode recording); including probe placement, image acquisition, interpretation and report</td>
<td>$715.18</td>
<td>5573</td>
<td>Level 3 Imaging with Contrast</td>
</tr>
<tr>
<td>C8926</td>
<td>TEE with contrast, or without contrast followed by with contrast, for congenital cardiac anomalies; including probe placement, image acquisition, interpretation and report</td>
<td>$715.18</td>
<td>5573</td>
<td>Level 3 Imaging with Contrast</td>
</tr>
<tr>
<td>C8927</td>
<td>TEE with contrast, or without contrast followed by with contrast, for monitoring purposes, including probe placement, real time 2-dimensional image acquisition and interpretation leading to ongoing (continuous) assessment of (dynamically changing) cardiac pumping function and to therapeutic measures on an immediate time basis</td>
<td>$715.18</td>
<td>5573</td>
<td>Level 3 Imaging with Contrast</td>
</tr>
<tr>
<td>C8928</td>
<td>TTE with contrast, or without contrast followed by with contrast, real-time with image documentation (2d), includes m-mode recording, when performed, during rest and cardiovascular stress test using treadmill, bicycle exercise and/or pharmacologically induced stress, with interpretation and report</td>
<td>$715.18</td>
<td>5573</td>
<td>Level 3 Imaging with Contrast</td>
</tr>
<tr>
<td>C8929</td>
<td>TTE with contrast, or without contrast followed by with contrast, real-time with image documentation (2d), includes m-mode recording, when performed, complete, with spectral doppler echocardiography, and with color flow doppler echocardiography</td>
<td>$715.18</td>
<td>5573</td>
<td>Level 3 Imaging with Contrast</td>
</tr>
<tr>
<td>C8930</td>
<td>TTE with contrast, or without contrast followed by with contrast, real-time with image documentation (2d), includes m-mode recording, when performed, during rest and cardiovascular stress test using treadmill, bicycle exercise and/or pharmacologically induced stress, with interpretation and report; including performance of continuous electrocardiographic monitoring, with physician supervision</td>
<td>$715.18</td>
<td>5573</td>
<td>Level 3 Imaging with Contrast</td>
</tr>
</tbody>
</table>

### Contrast Agents

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>2021 Payment</th>
<th>2021 APC</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q9950*</td>
<td>Injection sulfur hexafluoride lipid microspheres ($101.75 per 5 ml vial)</td>
<td>$-</td>
<td>N/A</td>
<td>Packaged</td>
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<tr>
<td>Q9955</td>
<td>Injection, octafluoropropane microspheres, per ml</td>
<td>$-</td>
<td>N/A</td>
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<tr>
<td>Q9956</td>
<td>Injection, perfluorin lipid microspheres, per ml</td>
<td>$-</td>
<td>N/A</td>
<td>Packaged</td>
</tr>
</tbody>
</table>

*Temporary pass-through payment, bill in addition to APC for contrast procedure


### 5. References

1. Definitions for Informed Consent

Informed consent is the legal embodiment of the concept that each individual has the right to make decisions affecting their health. Generally, the law protects the patient’s right to informed consent by requiring medical personnel to disclose all pertinent information about risks and benefits of a procedure to the patient.1

There are three main types of medical informed consent;2 these are stratified according to the respective potential risks of the procedure to be performed:

1) **Implied consent**: Implied consent refers to when a patient passively cooperates in a process or procedure without formal consent. This process generally is associated with procedures that are deemed less than minimal risk, such as transthoracic echocardiography. The principles of good communication apply in these circumstances and health professionals need to provide the patient with enough information to understand the procedure and why it is being done. Implied consent does not need to be documented in the clinical record.

2) **Verbal consent**: A verbal consent occurs when a patient states their consent to a procedure verbally but does not sign any written form. This process is considered to be appropriate for routine treatments or procedures that involve minimal risk or greater but with low likelihood of significant risk. Documentation of verbal consent must appear in the patient’s medical record.

3) **Written consent**: A written consent is necessary in situations where significant risk may be entailed, such as use of anesthesia or conscious sedation, invasive or surgical procedures, and administration of medications with high likelihood for potential adverse events.

- There are 3 types of consents, the selection of which is determined according to level of risk of the process or procedure to be performed.
- Documentation of verbal and written consent must be made in the patient’s medical record.

2. Informed Consent for Ultrasound Enhancing Agents (UEAs)

Transthoracic Echocardiography (TTE) is a minimal risk procedure that is almost universally performed with implied consent. As outlined in the Safety section of this document, UEAs are characterized by an excellent safety profile, and are generally considered the safest of all contrast agents given during non-invasive and invasive imaging studies. Because there is a small risk of side effects, including rare incidence of severe hypersensitivity reactions (approximately 1 in 10,000), the ASE recommends the process of verbal consent before administration of UEAs. Most institutions have not required written consent for the clinical administration of UEAs. However, if an institution chooses to utilize written consent, there are required items that must be included within such a document.

- Due to the documented safety of administration of the available UEAs, verbal consent is considered adequate, and written consent is not required.
- Patients should be informed that the risk of severe hypersensitivity reaction is minimal (1:10,000).
- If giving a UEA that contains albumin, history of allergy to blood products should be reviewed and if present, or patient expresses personal objections to receiving a blood-based product, an alternate UEA should be utilized.
- If giving a UEA that is lipid-based and contains polyethylene glycol (PEG), a known hypersensitivity to this agent should be reviewed and if present, an alternate non-lipid-based UEA should be utilized.
3. Obtaining Informed Consent for UEA administration

Informed consent can be obtained by any member of the ultrasound imaging team (sonographer, nurse, or physician) as long as the personnel are trained in the safety, knowledge, and indications for use of UEAs; and are working within their recognized scope of practice. Key skills include the ability to communicate with the patient in a manner that is appropriate to the patient's ability to understand. Items that should be explained to the patient include the following:

- Why UEAs are being administered or are indicated in each individual case
- Need for insertion of an IV if not already present
- Rare possibility of a hypersensitivity reaction (1:10,000, less than other imaging modalities)

The decision to administer UEA is primarily empowered to the sonographer through standing orders approved by the supervising physician. Any qualified member of the ultrasound imaging team (as defined above) may obtain the verbal consent; this is usually done by the sonographer or nurse; however, the supervising physician should be available to assist as needed or to confirm eligibility or appropriateness of UEA administration, if there is uncertainty on part of the sonographer. Careful consideration in clarity of wording choice should be made while obtaining verbal consent for UEA use. Terms such as “ultrasound enhancing agent” to “enhance your ultrasound images” or “improve quality of your images” are preferred over “contrast” as these words are easily understood and distinct from the term “contrast agent” which traditionally implies radiographic or gadolinium agents that are used in CT, angiography, and MRI respectively, and that are associated with higher rates of adverse reactions, particularly involving renal dysfunction.

4. Miscellaneous Issues Related to Informed Consent

The main indication for UEA use is for image enhancement when two or more contiguous segments cannot be visualized or when there is “poor quality endocardial visualization.” However, there are other situations that, without UEAs, a study can or will be rendered uninterpretable resulting in inadequate medical care. This is the statement of purpose and benefits for the procedure, and forms the basis for patient selection as described in further detail in the 2018 guideline document. When performing verbal consent, there should be description of any foreseeable risks such as those stated in the 2014 ASE Guidelines on UEA use. Prior to administration of UEAs, all known allergies in the medical record should be reviewed for contraindications as noted in the 2014 Guidelines. ASE also endorses policies where allergic or other reactions to UEAs are noted not only in the medical record, but also on the echocardiogram report. Any specific diagnostic, treatment, or prognostic questions are directed to the appropriate physician or healthcare provider.

5. References

1. Safety Considerations

Contrast echocardiography is performed through the acoustic detection of stable FDA-approved microbubble ultrasound enhancing agents (UEAs). The main considerations regarding safety of any microbubble agent are: (1) the potential for hypersensitivity reactions to microbubble component; (2) the potential of microbubbles to “lodge” in the microcirculation, and (3) the possibility of producing tissue bioeffects during ultrasound cavitation (ringing and collapse) of the microbubbles. With these issues in mind, the following facts are known regarding the UEAs and their application within FDA-approved dosing:

- **UEAs are manufactured using shell constituents known to be biocompatible (lipids, albumin) in order to minimize any allergic reactions.**
- **Microbubbles are designed to be small enough to pass freely through the smallest vessels of the body. These microbubbles behave identically to red blood cells in the circulation without systemic microvascular lodging or aggregation.**
- **Hypersensitivity reactions to UEAs can occur in about 1 in 10,000 administrations, and can be classified as either classical type-I IgE-mediated allergy from antibodies formed against components of the UEA, or as non-IgE mediated reactions that occur secondary to activation of complement (complement activation-related pseudoallergy, or CARPA) which is involved in the body’s ability to maintain surveillance for the membranes of foreign pathogens.**
- **CARPA reactions are more likely to occur with lipid microbubbles, are minimized by the presence of polyethylene glycol in their shell, and occur extremely rarely. Clinically, it is not possible to distinguish between IgE and non-IgE-mediated reactions.**
- **Hypersensitivity reactions to polyethylene glycol (PEG) have been described in patients with known hypersensitivity to PEG, and if reported, should be avoided.**

2. Safety Studies

A partial list of the major safety studies is provided in the Table on the following page. A more comprehensive list of safety studies can be found in an extensive review by Muskula, et al. A summary of key points of these and other studies are:

- **UEAs are among the safest of any diagnostic imaging contrast agent that have been applied in humans, with serious reactions occurring only in 1 in 10,000 administrations.**
- **The use of UEAs in in-patients with clinical indications is not associated with increased mortality, but actually is associated with decreased mortality, suggesting clinical impact.**
- **There are no safety concerns with the use of UEAs in tenuous populations (critically ill patients or those with pulmonary hypertension) or during stress echocardiography.**
- **The presence of an intracardiac shunt is not a contra-indication to the use of UEAs and does not need to be excluded prior to their use.**
- **Safety of UEAs in the pediatric population has been demonstrated (although not all agents have FDA-approval for pediatric patients).**
- **Flank, back, or muscle pain is infrequently associated with the use of UEAs, and is likely to also be complement-mediated.**
- **Despite the demonstrated safety of UEAs, the FDA has not removed the “Black Box” warning issued in 2007 in response to several adverse events from millions of post-marketing surveillance administrations, most of which could not be directly linked to UEAs.
### Partial List of Safety Studies on the Use of UEAs

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Design</th>
<th>UEA</th>
<th>n</th>
<th>Rest vs Stress</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabriel, 2008</td>
<td>Retrospective</td>
<td>Definity, Optison</td>
<td>9,798</td>
<td>Stress</td>
<td>Controlled trial without increased SAE or mortality at 24 hours</td>
</tr>
<tr>
<td>Herzog, 2008</td>
<td>Retrospective</td>
<td>Definity, Optison</td>
<td>16,025</td>
<td>Both</td>
<td>SAE rate of 0.03% without any mortality</td>
</tr>
<tr>
<td>Aggeli, 2008</td>
<td>Prospective</td>
<td>Sonovue (Lumason)</td>
<td>5,250</td>
<td>Stress</td>
<td>No major SAE reported at 24 hours</td>
</tr>
<tr>
<td>Kusnetzky, 2008</td>
<td>Retrospective</td>
<td>Definity</td>
<td>12,475</td>
<td>Rest</td>
<td>Controlled trial without associated mortality</td>
</tr>
<tr>
<td>Main, 2008</td>
<td>Retrospective</td>
<td>Definity</td>
<td>4,242,712</td>
<td>Rest</td>
<td>Registry, controlled trial in inpatients showing no associated mortality</td>
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<tr>
<td>Wei, 2008</td>
<td>Retrospective</td>
<td>Definity</td>
<td>78,383</td>
<td>Both</td>
<td>Severe reactions in 0.01% (one in 10,000)</td>
</tr>
<tr>
<td>Abdelmoneim, 2009</td>
<td>Retrospective</td>
<td>Definity, Optison</td>
<td>26,774</td>
<td>Stress</td>
<td>Controlled trial without increased short- or long-term mortality</td>
</tr>
<tr>
<td>Goldberg, 2012</td>
<td>Retrospective</td>
<td>Definity</td>
<td>96,705</td>
<td>Both</td>
<td>Controlled trial showing no increased mortality</td>
</tr>
<tr>
<td>Main, 2014</td>
<td>Retrospective</td>
<td>Definity</td>
<td>32,434</td>
<td>Rest</td>
<td>Propensity-matched trial showing lower mortality in those receiving UEAs</td>
</tr>
<tr>
<td>Wei, 2012</td>
<td>Prospective</td>
<td>Definity</td>
<td>32</td>
<td>Rest</td>
<td>No significant changes in pulmonary hemodynamics including in those with pulmonary hypertension</td>
</tr>
<tr>
<td>Main, 2013</td>
<td>Prospective</td>
<td>Optison</td>
<td>30</td>
<td>Rest</td>
<td>No significant changes in pulmonary hemodynamics including in those with PH</td>
</tr>
<tr>
<td>Kalra, 2013</td>
<td>Retrospective</td>
<td>Definity, Optison</td>
<td>39,020</td>
<td>Rest</td>
<td>No AEs or neurologic symptoms in those with intracardiac shunt</td>
</tr>
</tbody>
</table>

AE, adverse event; PH, pulmonary hypertension; SAE, serious adverse event
3. Safety recommendations for Laboratories

- UEAs are extremely safe with serious AEs in only 1 in 10,000; in propensity-matched studies the use of UEAs is associated with decreased mortality.
- Based on extremely low risk:benefit ratio and clinical impact of UEAs, the American Society of Echocardiography strongly recommends the incorporation of UEAs in standard practice.
- Intracardiac shunts do not need to be excluded before the use of UEAs.
- Those who administer UEAs should be trained in the recognition of adverse events and the basic concepts in treatment.
- Laboratories using UEAs must have safety policies in place and have ready access to equipment and medications (epinephrine, diphenhydramine, steroids, etc.) needed to treat rare hypersensitivity reactions or other types of reactions.
- UEAs have been demonstrated to be safe in pediatric populations; some agents are approved for use in children.
- Because safety has not been rigorously tested in pregnancy or lactation, consideration of the benefit of using of UEAs in this population must be made based on the clinical situation.
- Flank, back, or muscle pain is associated with UEAs; these symptoms are usually mild, do not require treatment, and resolve with cessation of UEA administration.
- Contraindications for the use of UEAs are:
  (a) hypersensitivity to a “same class” (lipid or albumin) UEA agent
  (b) known hypersensitivity to PEG (for the lipid-based agents that contain PEG either in the shell or in the excipient) (Definity, Lumason)
  (c) allergy to albumin or blood product for albumin-based agents (Optison).
- Before administration of any UEA, the EHR should be reviewed and patients should be asked about known allergy to the lipid-based UEAs or albumin-based UEAs (as appropriate). For lipid-based agents, the EHR should be reviewed for allergy to PEG, and the patient should be asked about allergy to PEG-based agents (bowel prep for colonoscopy or laxatives that are 100% PEG [macrogol, Miralax]). For albumin based agents, the EHR and patient should be interrogated for allergy to blood products.

4. References


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