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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061, HFA - 305
Rockville, MD 20852

CITIZEN PETITION – International Contrast Ultrasound Society

I. Introduction

On behalf of the International Contrast Ultrasound Society (“ICUS”), the undersigned respectfully submit this Citizen Petition under §§ 502 and 505 of the Federal Food, Drug & Cosmetic Act (21 U.S.C. §§ 352 and 355; “FDCA”) to request that the Commissioner of Food and Drugs (the “Commissioner”) remove the boxed warnings from ultrasound contrast agent product labels in order to bring the labeling into line with the current body of scientific research, which now clearly demonstrates the favorable safety profile and clinical benefits of these radiation-free diagnostic imaging products.

ICUS is a not-for-profit medical society that is dedicated to advancing the safe and appropriate use of contrast enhanced ultrasound (“CEUS”) diagnostic imaging to improve patient care and save lives. ICUS members include physicians, nurses, sonographers, scientists, medical payors and members of the general public. Physician members represent a broad range of medical specialties including cardiology (echocardiography), radiology (body imaging including liver and kidney), pediatrics, vascular imaging, internal medicine, gastro-intestinal medicine, emergency medicine, intensive care, OB-GYN and others.

CEUS is an enhanced form of diagnostic ultrasound imaging that utilizes ultrasound contrast agents (UCAs), sometimes also known as ultrasound enhancement agents, to improve the clarity and reliability of ultrasound scans, thereby helping physicians more accurately diagnose medical conditions and monitor therapy. UCAs are routinely used by physicians throughout the world.

The FDA first required boxed warnings on UCA labels in 2007 following spontaneous reports of a small number of serious adverse events (“SAEs”) that occurred after UCA administration; however, the SAEs were not contemporaneously adjudicated and some were later attributed to underlying medical conditions and/or other medication. Since 2007, peer-reviewed publications have consistently shown that UCAs are exceedingly safe, efficacious and save lives. Indeed, the most current safety data convincingly show that UCAs are among the safest diagnostic imaging products available. [2-20]

ICUS supports appropriate safety warnings for UCAs and appreciates the FDA’s actions in response to the growing body of data demonstrating the strong safety profile and clinical efficacy of UCAs. These actions have narrowed UCA boxed warnings and contraindications, approved a new UCA, and approved the use of CEUS for new indications and new patient populations including children under
appropriate circumstances. However, ICUS believes that with the compelling evidence of safety and efficacy accumulated since the last narrowing of the boxed warning, it is now time for the Commissioner to remove the boxed warning from UCA product labels.

Boxed warnings are appropriate only as an indicator of the very highest level risk associated with FDA-approved products. [1] This extreme level of risk is simply not presented by the use of UCAs, and ICUS is deeply concerned that the current boxed warnings unduly deter the use of UCAs when medically indicated -- to the detriment of our patients. This result is fundamentally inconsistent with the FDA's statutory responsibility to protect and promote public health.

For a comprehensive review of these issues, please see the recent paper by Muskula and Main. [25]

II. Actions Requested

ICUS respectfully requests the Commissioner to remove the boxed warning from UCA product labels. In support of this request, ICUS will demonstrate that:

   a) Since 2007, the risk-benefit ratio for UCA use has dramatically changed. Scientific data now consistently show that UCAs are extremely safe, and expanded indications in larger patient populations have extended the benefits of UCAs. [21-24]

   b) Boxed warnings on UCAs deter patient access to safe, real time diagnostic information and therefore have serious deleterious implications on the health of the American public.

   c) The UCA boxed warnings do not meet the requirements of the FDA's own internal guidance -- which authorizes the use of boxed warnings in limited circumstances, e.g., as where the risks of a product are not in proportion to the potential benefit.

   d) The black box warning for UCAs disregards the FDA's policy of encouraging innovation and cost savings.

As discussed below, ICUS recommends the inclusion of appropriate warnings in the “warnings and precautions” section of UCA labels, without a “black box.”

III. Background

A. CEUS and UCAs, Generally

CEUS is a radiation-free diagnostic imaging tool that uses UCAs to improve the clarity and reliability of an ultrasound image. [2] UCAs are comprised of liquid suspensions of gas-filled microbubbles that may be injected into a patient’s arm vein during a diagnostic ultrasound scan. UCAs are biocompatible, do not contain radioactive dye or material and are not known to damage the kidney. They are metabolized and expelled from the body, primarily through the lungs, within minutes. [26-28]

Conventional ultrasound scans are often used as front-line diagnostic tools. Unlike CT, PET and MRI, ultrasound utilizes portable and relatively inexpensive equipment and can be offered in a variety of settings - including the intensive care unit and outpatient clinics - to make an initial diagnosis or to monitor therapy. In addition, ultrasound scans provide immediate real-time information. However, in the general population, a conservative estimate is that 10%-15% of standard cardiac ultrasound scans may be suboptimal or uninterpretable due to inadequate resolution -- exposing patients to the risk of misdiagnosis.
or missed diagnosis. Non-diagnostic ultrasound scans may be even more prevalent in particular patient populations - e.g., obese patients, patients with breast cancer or lung disease, patients with left ventricular assist devices (LVADs), etc. [29-33]

UCAs allow physicians to salvage non-diagnostic ultrasound scans and identify abnormalities that otherwise might go undetected. This often avoids the need for additional redundant downstream tests which can expose patients and health care workers to ionizing radiation, require invasive catheterization, utilize other forms of contrast that may increase a patient’s risk of kidney damage or brain deposits, require sedation or anesthesia, prolong hospitalization, increase health care costs, and delay access to appropriate therapy.

Studies demonstrate that UCAs can save lives, improve patient care in expanding clinical circumstances, reduce overall health care costs, speed up time to diagnosis and reduce the length of hospital stays, and improve the efficiency of health care delivery. These studies will be described in more detail below.

B. Regulatory Background

Pursuant to the Commissioner’s authority under 21 C.F.R. §§ 10.30 and 201.57©(1), a boxed warning is currently included on the labels of the three UCAs that are commercially available in the United States: Optison, Definity, and Lumason. [23, 34, 35] Each of these products is approved for use in patients with suboptimal echocardiograms to opacify the left ventricle and to improve the delineation of the left ventricular endocardial borders. In addition, Lumason is approved for use in ultrasonography of the liver in adult and pediatric patients, and in ultrasonography of the urinary tract in pediatric patients. The boxed warning for each product advises that “serious cardiopulmonary reactions” may occur during or following the injection of UCAs.

As noted above, the FDA initially required boxed warnings on UCAs in October 2007. This action was largely based on reports of four patient deaths and approximately 190 other serious cardiopulmonary reactions that were temporally related, but not clearly caused by, UCAs. At the time, Optison and Definity were the only two FDA-approved UCAs. [2]

Since 2007, ICUS and other stakeholders have advocated for modifications of the UCA labels. In response to the FDA’s 2007 action, 160 cardiologists and radiologists from around the world sent a letter to the FDA stating that the boxed warnings do not reflect the established record of safety and efficacy for UCAs, or potential risks of alternative diagnostic procedures and inaccurate non-diagnostic ultrasound scans. Following a December 2007 meeting with physicians and clinicians, in the spring of 2008 the FDA modified and reversed certain contraindications and warnings, stating that “the benefits from the diagnostic information … may outweigh the risk for serious cardiopulmonary reactions, even among some patients at particularly high risk for these reactions.”

Following the publication of additional favorable safety data, ICUS in 2011 filed a citizen petition with the FDA requesting the removal of boxed warnings and modification of warnings on UCAs. In October 2011, the FDA announced a revision of the product labeling for UCAs, including deletion of a previously-mandated 30-minute monitoring period after UCA administration in patients with certain cardiac conditions. [36]

In September 2012, ICUS presented a professional society briefing for the FDA’s Center for Drug Evaluation and Research (“CDER”) and Center for Devices and Radiological Health (“CDRH”). The ICUS presentation addressed, among other topics, the importance of CEUS in pediatric imaging and in patients...
with known or suspected cardiac shunts. ICUS followed up with the preparation and publication of two peer reviewed scientific papers regarding both topics. [21, 22]

In 2016, the FDA approved a third UCA, Lumason, for use in liver and pediatric imaging, and removed the cardiac shunt contraindication from all UCA labels. In May 2017, ICUS presented an additional professional society briefing for the FDA Division of Medical Imaging Products, highlighting new safety data and the use of CEUS to image other organs “off-label.”

With the development of additional safety data from 2007 to 2016, the boxed warnings have been reduced to the following:

For **DEFINITY**
**WARNING: SERIOUS CARDIOPULMONARY REACTIONS**
Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly during or following perflutren-containing microsphere administration [see WARNINGS AND PRECAUTIONS (5.1)]. Most serious reactions occur within 30 minutes of administration.

- Assess all patients for the presence of any condition that precludes DEFINITY® administration [see CONTRAINDICATIONS (4)].
- Always have resuscitation equipment and trained personnel readily available.

For **OPTISON**
**WARNING: SERIOUS CARDIOPULMONARY REACTIONS:**
Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly during or following perflutren-containing microsphere administration. Most serious reactions occur within 30 minutes of administration [see WARNINGS and PRECAUTIONS].

- Assess all patients for the presence of any condition that precludes Optison administration [see CONTRAINDICATIONS].
- Always have resuscitation equipment and trained personnel readily available [see WARNINGS and PRECAUTIONS].

For **LUMASON** - indicated for cardiac and liver
**WARNING: SERIOUS CARDIOPULMONARY REACTIONS**
Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly during or following the injection of ultrasound contrast agents, including sulfur hexafluoride lipid microspheres (5.1). Most serious reactions occur within 30 minutes of administration (5.1).

- Assess all patients for the presence of any condition that precludes administration (4).
- Always have resuscitation equipment and trained personnel readily available.
For the reasons detailed in Section IV below, we believe now is the time for the FDA to eliminate the boxed warning. A safety statement addressing potential for a cardiopulmonary reaction currently exists in the “warnings and precautions” section of the UCA labels as noted above.

IV. Statement of Grounds

A. Scientific Data Now Show That a “Black Box” on UCAs is Not Warranted

UCA “black box warnings” do not reflect the strength of current safety data and the favorable risk-benefit ratio of UCAs. [25] A growing body of scientific research now provides compelling support for the conclusion that UCAs are exceedingly safe. In addition, scientific studies along with new UCA clinical indications demonstrate the important and expanding clinical benefits of UCAs. These compelling data and clinical experiences demonstrate a new understanding of both the numerator and denominator of the risk-benefit ratio, making it clear that the benefits of UCAs far outweigh any risk of a SAE.

I. The Numerator of the Risk-Benefit Ratio: New, Positive Safety Data

Since 2007, six studies, designed collaboratively between the FDA and UCA manufacturers, resulted in no deaths or SAEs, and the FDA subsequently made certain revisions to UCA product labeling. [37, 38] Since that time, data from an additional 18 large studies, including more than 260,000 patients, confirmed that UCAs have an excellent safety profile. [2-20] Subsequent additional studies now demonstrate the safety and efficacy of CEUS in expanding clinical circumstances. For example:

- Multiple studies have examined the risk of adverse effects occurring after the administration of UCAs, including the risk of idiosyncratic anaphylactoid reactions, and concluded that these risks may occur in one in ten thousand patients. [25] In a meta-analysis evaluating the use of UCAs in 110,500 patients, the incidence of serious allergic or anaphylactoid reactions immediately after administration of the UCA was estimated at only 0.009% (for serious allergic reactions) and 0.004% (for anaphylactoid reactions). [39]

- One recent study evaluated 32,434 critically ill hospitalized patients who underwent echocardiography, and compared outcomes among patients who received a UCA and those who did not. This retrospective observational outcome study demonstrated a 28% lower mortality rate in the critically ill patients who underwent CEUS compared to propensity-matched patients that underwent an echocardiogram without a UCA. [19]

- Although in rare circumstances UCAs may elicit complement activation related pseudo allergy, or CARPA reactions, these reactions tend to be mild and may occur with a wide variety of other drugs and agents, including nonsteroidal anti-inflammatory drugs and analgesics that are commonly prescribed and are not subject to a boxed warning. [40]

- Kurt et al. demonstrated that CEUS, when used as a front-line diagnostic imaging tool, changes outcomes and reduces the need for redundant downstream diagnostic imaging -- which may expose patients to added, unnecessary risk. [29] CEUS does not utilize any ionizing radiation, and UCAs do not contain radioactive dye or present a risk of brain deposits.

- Safety studies of pediatric CEUS now demonstrate very few adverse events and very rarely SAEs. In addition, pediatric patients are also at greater risk when exposed to certain downstream tests. Since children are more sensitive to ionizing radiation than adults, and
since the cancer risk associated with exposure to ionizing radiation is cumulative over a patient’s lifetime, it may be especially important to avoid pediatric CT scans, which are the single largest contributor to medical radiation exposure in the United States. [41] In pediatric patients, CEUS may reduce or replace the need for fluoroscopic exams and CT exams. [21]

• In addition, MRI often requires the use of MRI contrast agents - with yet unknown long-term consequences of their deposition in various organs, particularly the brain. For example, in December 2017 the FDA announced that it is requiring a new class warning and other safety measures for all gadolinium-based contrast agents (GBCAs) for MRI concerning possible links to adverse health effects from gadolinium retention in patients’ bodies, including the brain, months to years after receiving these drugs. (50) This is of particular concern in children, whose brains are still developing.

• CEUS is a patient-friendly, non-intimidating imaging technique that does not require sedation or anesthesia, which entail their own adverse events. [41] This, too, can be particularly significant when imaging children.

• In addition, recent studies addressed the use of CEUS in patients with left ventricular assist devices (“LVADs”). Normal echocardiographic imaging is difficult in some LVAD patients because of the positioning of the device. The use of CEUS improved image interpretation in 83% of these patients, and no adverse events or known side effects were reported during or after the CEUS. In addition, LVAD function was not affected during or after the CEUS. Ultimately, the study concluded that CEUS was feasible, safe and improved image interpretation in a sample of LVAD patients undergoing clinically indicated echocardiography. [42, 43]

II. The Denominator of the Risk-Benefit Ratio: New Efficacy Data and Indications

ICUS believes that the denominator of the “risk-benefit ratio” has changed and now independently supports the conclusion that any risk associated with UCAs is far outweighed by the benefits of their use in an expanding range of clinical settings. Expanded evidence of UCA benefits is supported by expanded clinical indications, reduced contraindications and new and positive efficacy data, some of which overlaps with the safety literature discussed above. For example:

• UCAs are now used in the United States to image the liver and characterize focal liver lesions, and for certain pediatric indications. [44] Further, UCAs are no longer contraindicated in patients with known or suspected cardiac shunts.

• CEUS can be used in difficult to image patients, including those who are obese, have breast cancer or severe lung disease, or who have other physical impediments that make alternative imaging (including conventional ultrasound) challenging. [29]

• CEUS has been shown to save the lives of critically ill patients in the intensive care unit. [19]

• CEUS offers multiple advantages over alternative forms of imaging [21] and reduces fluoroscopic exams, CT exams [21] and MRI. In fact, one recent study showed an almost 50% reduction of downstream CT and/or MRI examinations in pediatric patients after the introduction of CEUS. [47]

• CEUS offers a patient-friendly, non-intimidating imaging experience that does not require sedation or anesthesia; this can be especially important for pediatric patients. [41, 45-47]
• By utilizing portable and widely available ultrasound equipment and by providing real-time diagnostic information, CEUS expands access to diagnostic imaging, speeds the introduction of appropriate therapy, reduces hospitalization time, and improves the efficiency of health care delivery. [24]

• By reducing the need for downstream testing, CEUS reduces overall health care costs and improves outcomes without exposing patients to ionizing radiation or increasing the risk for nephrotoxicity.

B. The “Black Box” Deters Use of UCAs and Impacts Public

ICUS believes that boxed warnings deter the use of UCAs. Indeed, that is exactly what boxed warnings are designed to do. [1]

After the addition of the boxed warning to UCA product labels in 2007, CEUS precipitously declined as a percentage of total echocardiography studies. [49] And, despite recent increases in CEUS, it remains an underutilized imaging modality as evidenced by the discrepancy between the estimated number of non-diagnostic ultrasound scans (conservatively between 10%-15 and in practice potentially closer to 30%) and the actual use of CEUS (5.5% of 32 million ultrasound scans). [49] Removal of the boxed warnings would lift a significant impediment to the appropriate use of safe, reliable, and potentially life-saving CEUS imaging technology.

C. The “Black Box” is Inconsistent With the FDA's Internal Guidance

Boxed warnings are only appropriate in limited circumstances which do not include UCAs. According to the FDA’s 2011 Guidance, boxed warnings are used to highlight certain risks, including the possibility of “an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is “essential” that it be considered in assessing the risks and benefits of using the drug.” [1] Boxed warnings are not to be applied for rare, idiosyncratic reactions, which have no dose-response relationship.

Based on the safety data now available, it is clear that the boxed warnings on UCAs fail to meet the test established by the FDA. The risk of idiosyncratic anaphylactoid reactions associated with UCAs is rare and occurs in only one in ten thousand patients. [25] A meta-analysis of UCA use in 110,500 patients showed that the incidence of serious allergic or anaphylactoid reactions immediately after UCA administration was only 0.009% (for serious allergic reactions) and 0.004% (for anaphylactoid reactions). [39] Any CARPA reactions tend to be mild and may occur with other drugs and agents, including nonsteroidal anti-inflammatory drugs and analgesics that are commonly prescribed and are not subject to a boxed warning. [25]

The evidence more clearly supports a warning in the “warnings and precautions” section, as the potential adverse reactions (namely, a serious allergic or anaphylactoid reaction or CARPA reaction) do not occur frequently enough to rise to the boxed warning standard. This section “is intended to identify and describe a discrete set of adverse reactions and other potential safety hazards that are serious or are otherwise clinically significant because they have implications for prescribing decisions or for patient management.” [1]

Since 2007, the FDA has steadily responded to the mounting evidence of CEUS safety and efficacy by downgrading package insert contraindications three times and removing a 30-minute monitoring requirement after UCA administration in patients with pulmonary hypertension or unstable cardiopulmonary conditions. More recently, the FDA approved CEUS for use in additional populations and for additional indications. Now, with even more research and clinical experience demonstrating the
safety and efficacy of UCAs, together with expanded UCA indications and patient populations for whom CEUS is clinically appropriate, it is time to remove the "black box" entirely.

D. The “Black Box” Disregards the FDA’s Move Toward Encouraging Innovation and Cost-Saving

In its 2018 strategic policy roadmap, the FDA expressed a commitment to leveraging innovation to improve health care, broaden access, and advance public health; these goals were identified as a key priority of the agency.[48] Indeed, the FDA’s core mission is to protect public health, which includes ensuring that products are properly labeled.

Unfortunately, although CEUS is a reliable and accurate diagnostic tool, the current boxed warning deters appropriate use and should be removed. Removing the boxed warning for UCAs would encourage more widespread adoption of this innovative technique that can save lives and healthcare costs.

V. Conclusion

Product labels can and should be updated and evolve as new information modifies our understanding of product safety and efficacy. Since 2007, new research and new clinical applications of UCAs have incrementally demonstrated the exceedingly favorable safety profile and utility of UCAs, and the FDA has appropriately responded by downgrading warnings and contra-indications, and approving new indications for expanded population groups. Now, with even more evidence of the favorable “risk-benefit” ratio of UCAs, it is time to remove the "black box" from these innovative, life-saving diagnostic tools. Doing so will help patients across America access safer, more reliable and more cost-effective diagnostic imaging -- while speeding up the introduction of appropriate therapy and saving lives. The public interest -- as well as the FDA's own standards -- demand nothing less.

VI. Environmental Impact

Pursuant to 40 C.F.R. § 1508.4 and 21 C.F.R. § 25.30(h), the requested action falls within the categorical exclusion for environmental impact statements.

VII. Economic Impact

The requested action is not likely to impact the cost of ultrasound contrast agents to industry, government, or consumers. Furthermore, there is no reason to believe the removal of the boxed warning will affect: (1) productivity of wage earners, businesses, or government; (2) competition; (3) suppliers of important materials, products or services; (4) employment; or (5) energy supply or demand.
VIII. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this Citizen Petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petitioner.

Respectfully submitted,

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Table 1. Echocardiographic Contrast Agents Approved by the Food and Drug Administration

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>FDA Approval</th>
<th>Composition</th>
<th>Bubble Size and Distribution</th>
<th>FDA-Approved Indications</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optium™</td>
<td>1985</td>
<td>Perfluoropropane/human albumin</td>
<td>3.5-4.5 μm (95% &lt; 10 μm), maximum 32 μm</td>
<td>LV0/LVID</td>
<td>GE Healthcare</td>
</tr>
<tr>
<td>Definity™</td>
<td>2001</td>
<td>Perfluoropropane/phospholipid</td>
<td>1.1-3.3 μm (95% &lt; 10 μm), maximum 20 μm</td>
<td>LV0/FVID</td>
<td>Lanthaus Medical Imaging</td>
</tr>
<tr>
<td>Lumason™</td>
<td>2014</td>
<td>Sodium hexafluoride/phospholipid</td>
<td>1.5-2.5 μm (95% &lt; 10 μm), maximum 20 μm</td>
<td>LV0/FVID</td>
<td>Bracco</td>
</tr>
</tbody>
</table>

FDA indicates Food and Drug Administration; EVID, endocardial border delineation; and LVID, left ventricular opacification.

Table 2. Large Studies (>1000 Patients) Published Since 2008 That Evaluated Echocardiographic Contrast Agent Safety

<table>
<thead>
<tr>
<th>Author and Publication Date</th>
<th>Study Design</th>
<th>ECA</th>
<th>Total Patients</th>
<th>ECA Patients</th>
<th>Control Patients</th>
<th>Impatient</th>
<th>Outpatient</th>
<th>Rest</th>
<th>Stress</th>
<th>Outcomes</th>
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</thead>
<tbody>
<tr>
<td>Aggarwal et al 2008</td>
<td>Retrospective</td>
<td>Definity or Optium</td>
<td>52910</td>
<td>4791</td>
<td>51012</td>
<td>Both</td>
<td>Both</td>
<td>Stress</td>
<td>No increase in rate of SAE or mortality at 24 h in ECA patients</td>
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<tr>
<td>Gharib et al 2008</td>
<td>Retrospective</td>
<td>Definity or Optium</td>
<td>9782</td>
<td>4791</td>
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<td>Both</td>
<td>Stress</td>
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<tr>
<td>Herzig 2008</td>
<td>Retrospective</td>
<td>Definity or Optium</td>
<td>10023</td>
<td>16025</td>
<td>NA</td>
<td>Both</td>
<td>Both</td>
<td>Stress</td>
<td>No increase in rate of SAE or mortality at 24 h in ECA patients</td>
<td></td>
</tr>
<tr>
<td>Kachrity et al 2008</td>
<td>Retrospective</td>
<td>Definity</td>
<td>18671</td>
<td>6198</td>
<td>12475</td>
<td>Impatient</td>
<td>Rest</td>
<td>Rest</td>
<td>No increase in mortality in ECA patients</td>
<td></td>
</tr>
<tr>
<td>Mann et al 2008</td>
<td>Retrospective</td>
<td>Definity</td>
<td>43009</td>
<td>58254</td>
<td>42427</td>
<td>12</td>
<td>Rest</td>
<td>Rest</td>
<td>No increase in mortality in ECA patients</td>
<td></td>
</tr>
<tr>
<td>Shibli et al 2008</td>
<td>Retrospective</td>
<td>Definity or Optium</td>
<td>5098</td>
<td>2114</td>
<td>2153</td>
<td>Both</td>
<td>Both</td>
<td>Stress</td>
<td>No increase in rate of SAE in ECA patients</td>
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<tr>
<td>Wei et al 2008</td>
<td>Retrospective</td>
<td>Definity or Optium</td>
<td>78332</td>
<td>78332</td>
<td>NA</td>
<td>Both</td>
<td>Both</td>
<td>Stress</td>
<td>Severe allergic reactions in 0.01% and anaphylactic reactions in 0.05%</td>
<td></td>
</tr>
<tr>
<td>Abdelmonem et al 2009</td>
<td>Retrospective</td>
<td>Definity or Optium</td>
<td>26771</td>
<td>10792</td>
<td>15902</td>
<td>NR</td>
<td>Stress</td>
<td>No increase in mortality in ECA patients</td>
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<td></td>
</tr>
<tr>
<td>Aranfam et al 2009</td>
<td>Retrospective</td>
<td>Definity or Lumason</td>
<td>3704</td>
<td>1190</td>
<td>2564</td>
<td>Both</td>
<td>Stress</td>
<td>No increase in adverse events in ECA patients</td>
<td></td>
<td></td>
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<tr>
<td>Udani et al 2009</td>
<td>Retrospective</td>
<td>Definity or Optium</td>
<td>66220</td>
<td>44208</td>
<td>23812</td>
<td>NR</td>
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<td>Stress</td>
<td>No increase in mortality in ECA patients</td>
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<td>Retrospective</td>
<td>Definity or Optium</td>
<td>16434</td>
<td>6164</td>
<td>10270</td>
<td>NR</td>
<td>Stress</td>
<td>No increase in risk of myocardial infarction or mortality in ECA patients with pulmonary hypertension</td>
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<td></td>
</tr>
<tr>
<td>Lousides et al 2010</td>
<td>Retrospective</td>
<td>Optium</td>
<td>14900</td>
<td>2390</td>
<td>11600</td>
<td>Impatient</td>
<td>Rest</td>
<td>Rest</td>
<td>No increase in mortality in ECA patients</td>
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<td>Goldberg et al 2012</td>
<td>Retrospective</td>
<td>Definity</td>
<td>95705</td>
<td>2519</td>
<td>94107</td>
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<td>Both</td>
<td>Stress</td>
<td>No increase in mortality in ECA patients</td>
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<td>Weber et al 2012</td>
<td>Retrospective</td>
<td>Definity</td>
<td>1053</td>
<td>1053</td>
<td>NA</td>
<td>NR</td>
<td>Both</td>
<td>Stress</td>
<td>No deaths or serious adverse events</td>
<td></td>
</tr>
<tr>
<td>Worr Pflum et al 2012</td>
<td>Retrospective</td>
<td>Definity</td>
<td>1513</td>
<td>1513</td>
<td>NA</td>
<td>Impatient</td>
<td>Both</td>
<td>Stress</td>
<td>No deaths or serious adverse events</td>
<td></td>
</tr>
<tr>
<td>Flott et al 2013</td>
<td>Retrospective</td>
<td>Definity</td>
<td>5956</td>
<td>5956</td>
<td>NA</td>
<td>Both</td>
<td>Both</td>
<td>Stress</td>
<td>No increase in mortality in ECA patients</td>
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<tr>
<td>Main et al 2014</td>
<td>Retrospective</td>
<td>Optium</td>
<td>32434</td>
<td>16222</td>
<td>16222</td>
<td>Impatient</td>
<td>Rest</td>
<td>Rest</td>
<td>Lower mortality in ECA patients</td>
<td></td>
</tr>
<tr>
<td>Wei et al 2014</td>
<td>Retrospective</td>
<td>Optium</td>
<td>10281</td>
<td>10281</td>
<td>NA</td>
<td>Outpatient</td>
<td>Both</td>
<td>Stress</td>
<td>No deaths or serious adverse events</td>
<td></td>
</tr>
</tbody>
</table>

Definity is marketed as Lumason in Europe; Lumason is marketed as Sonovue in Europe. ECA indicates echocardiography contrast agent; NA, not applicable; NR, not reported; and SAE, serious adverse events.
References


