Perflutren-based ultrasound contrast agents have been in clinical use in the United States for >10 years. Since their approval by the US Food and Drug Administration (FDA) (Optison in 1995, Definity in 2001), >2 million doses have been used for left ventricular (LV) opacification and endocardial border definition in technically difficult patients and for other off-label uses (detailed in Table 1). Despite the widespread use of contrast echocardiography, recent concerns have prompted an FDA box warning and the convening of an advisory panel. A box warning (or black box warning) is a method used by the FDA to highlight adverse reactions so serious in proportion to the potential benefit from the drug that it is essential that they be considered by the prescriber. Contraindications, warnings, or precautions can be included.

Within the matter of a year, regulations on ultrasound contrast agents underwent several changes. Initially, a new box warning was required (October 2007) in response to isolated reports of serious adverse events. Then, in May 2008, after review of additional safety reports on larger cohorts of patients, the box warning was modified. At approximately the same time as the black box modification, an FDA advisory panel was organized and convened to provide guidance for the agency to delineate what further actions are necessary to further evaluate the safety of ultrasound contrast agents. This review summarizes the proceedings of the FDA advisory panel meeting, which took place on June 24, 2008, in which all of these issues were addressed.

The Concern About Safety and FDA Box Warning
On October 10, 2007, after reviewing spontaneously reported serious adverse events, the FDA issued a box warning for the use of intravenous perflutren-based microbubble contrast agents in echocardiography. The requirement for the warning was based primarily on the report of 4 cases of death after administration of such agents. All 4 patients had underlying illnesses. One death occurred in a patient with coronary disease during an exercise stress test; 1 occurred in the setting of an acute myocardial infarction with severe LV dysfunction; and 2 deaths were due to pulmonary embolism. Of these 2 pulmonary embolism patients, 1 had a history of deep vein thrombosis and coronary artery bypass surgery, and 1 was in the intensive care unit with cardiomyopathy and severe pneumonia requiring mechanical ventilation and vasopressors. Clearly, all 4 patients had underlying diseases that could account for their demise, and event reporting does not allow determination of cause and effect. Event reporting also is subject to selection bias by the reporting physician. However, deaths temporarily related to the administration of a contrast agent to improve an ultrasound image (noninvasive diagnostic test with no known adverse effects) were very alarming. As a result of concern raised from these cases, new contraindications for the use of contrast were added that included decompensated heart failure, acute coronary syndromes, risk for serious ventricular arrhythmias, hypoxemia, hypercarbia, and any cause of pulmonary hypertension, including emphysema and pulmonary embolism. New recommendations for patients receiving contrast included monitoring patients during and for 30 minutes after administration of the drug, including vital sign measurements and ECG in all patients and cutaneous oxygen saturation in patients at risk for hypoxemia.

The impact of the FDA box warning in clinical practice was feared by some to be major. Many cardiologists have been using contrast for years without complication, so some questioned the clinical relevance of 4 rare cases. The greatest fear was that contrast would not be used when clinically indicated. If contrast was inappropriately not used, there could be a significant increase in nondiagnostic ultrasound tests in critically ill patients. Critically ill patients are the ones targeted with the new contraindications, as well as the population in whom contrast is most helpful for improving test accuracy, which guides patient management. Likewise, the inconvenience of having to monitor healthy outpatients for 30 minutes after the infusion could so severely affect the dynamics of an echocardiography laboratory that contrast would not be used in technically difficult outpatient tests. Again, this could lead to further unnecessary testing. As reported at the advisory meeting, these concerns proved to be valid, and the use of contrast agents declined sharply in subsequent months. The cardiovascular community reacted during the
subsequent months with several editorials criticizing the box warning.3–6

In one of these editorials, Main and colleagues3 reviewed the 4 cases in which patients died after receiving perflutren lipid microsphere (Definity) and found support for pseudocomplications, adverse events that were not due to cause and effect from the contrast but were just coincidental to the timing that contrast was administered, ie, an epiphenomenon. Given the clinical scenarios of the 4 cases and the severity of underlying disease in these patients, death would not be unexpected in any of these patients. Thus, Main et al suggested that attributing the death to the contrast is not appropriate.

The Need for Contrast Echocardiography in Clinical Practice

The use of perflutren-based contrast agents has been approved for LV opacification in patients with suboptimal endocardial border delineation. In 1995, the US FDA approved Optison; in 2001, Definity was approved. Multiple studies have reported that these agents improve the accuracy in determining LV volumes, ejection fraction (EF), and regional wall motion abnormalities (Table 2).2,7–9 In a recent meta-analysis, the correlation coefficient compared with a variety of established standard methods improves with contrast from 0.84 to 0.93.5 Reproducibility of echocardiography is significantly better when contrast is added to contemporary harmonic imaging. Nayyar et al10 reported a significantly lower interobserver variation in reporting both estimated and calculated LV EF. This finding was consistent when analyzing patients with technically limited or adequate baseline ultrasound images. Similar interobserver and intraobserver findings were reported by Malm et al.8 Hoffman et al7 reported an improved reproducibility for contrast-enhanced echocardiography compared with cardiac magnetic resonance imaging (MRI; interobserver correlation coefficient, 0.91 versus 0.86), cine-ventriculography (0.80), and unenhanced echocardiography (0.79).

The use of contrast echocardiography has also been proved to be cost-effective. Because a nondiagnostic echocardiogram needs to be followed by another imaging modality (transesophageal echocardiogram, nuclear stress test, cardiac MRI, catheterization, etc), the cost is significantly higher if no contrast is used.11–13 Additional imaging modalities add substantial expensive and carry a higher risk than the injection of contrast.

Although contrast agents have been approved for just LV opacification, other potential applications such as myocardial perfusion, tumor detection, and vascular imaging are at advanced stages of investigation. The description of such uses has been reviewed recently in detail.14 Technical aspects of ultrasound contrast agent administration, applications, and

![Table 1. Common Uses of Contrast Agents in Echocardiography](https://www.ahajournals.org/)

<table>
<thead>
<tr>
<th>Labeled use of contrast agents</th>
<th>Off-label use of contrast agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients with suboptimal echocardiograms to opacify the LV chamber and to improve delineation of the LV endocardial border (LV function)</td>
<td>Myocardial perfusion imaging</td>
</tr>
<tr>
<td>Identification of LV thrombus and cardiac masses</td>
<td>Diagnosis of LV noncompaction and LV apical hypertrophy</td>
</tr>
<tr>
<td>Diagnosis of LV aneurysm and pseudoaneurysm</td>
<td>Selection of LAD septal perforators to be embolized during percutaneous ablation in HOCM</td>
</tr>
<tr>
<td>Improvement of Doppler signal in suboptimal echocardiograms</td>
<td>LAD indicates left anterior descending artery; HOCM, hypertrophic obstructive cardiomyopathy.</td>
</tr>
</tbody>
</table>

Table 2. Efficacy of Contrast-Enhanced Echocardiography (LV Opacification) for Assessment of LV EF and Wall Motion Abnormalities Compared With Noncontrast Echocardiography

<table>
<thead>
<tr>
<th>Population, n</th>
<th>Gold Standard</th>
<th>EF Contrast/Noncontrast</th>
<th>Other Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>55</td>
<td>MRI</td>
<td>ICC, 0.77/0.60</td>
<td>&lt;0.05 Interobserver agreement was superior for contrast echocardiography vs MRI, ventriculography, and noncontrast echocardiography</td>
</tr>
<tr>
<td>120</td>
<td>Cine-ventriculography</td>
<td>ICC, 0.83/0.72</td>
<td>&lt;0.05 Similar findings in good or poor baseline image quality</td>
</tr>
<tr>
<td>110</td>
<td>MRI</td>
<td>LoA (mean differences) vs MRI, −7.7%–4.1%–18.1%–8.3%</td>
<td>...</td>
</tr>
<tr>
<td>70 ICU patients</td>
<td>Comparison of echocardiography methods, no gold standard</td>
<td>Nonevaluable EF, 0%/13%</td>
<td>&lt;0.0001 5.4 segments/patient were uninterpretable without contrast vs 1.1 with contrast</td>
</tr>
<tr>
<td>50</td>
<td>Radionuclide</td>
<td>0.95/0.84; 0.91/0.7</td>
<td>... Higher agreement with gold standard both for EF and wall motion abnormalities</td>
</tr>
<tr>
<td>1018</td>
<td>Meta-analysis</td>
<td>Mean correlation coefficient, 0.84 (95% CI, 0.82–0.85)/0.93 (95% CI, 0.90–0.96)</td>
<td>...</td>
</tr>
</tbody>
</table>

ICC indicates correlation coefficient; LoA, limits of agreement; and ICU, intensive care unit.
Table 3. Postmarketing Safety Data

<table>
<thead>
<tr>
<th>Population, n</th>
<th>Postinfusion Follow-Up</th>
<th>Mortality, %</th>
<th>Other Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herzog (^{16})</td>
<td>16 025 (3051 Optison, 12 974 Definity)</td>
<td>30 min</td>
<td>0</td>
</tr>
<tr>
<td>Kusnetsky et al (^{17})</td>
<td>18 671 inpatients (6196 received Definity)</td>
<td>24 h</td>
<td>0.37 without contrast; 0.42 with contrast ((P=0.6))</td>
</tr>
<tr>
<td>Main et al (^{18})</td>
<td>4 300 966 (58 254 received Definity)</td>
<td>24 h</td>
<td>1.08 without contrast; 1.06 with contrast ((P=0.6))</td>
</tr>
<tr>
<td>Wei et al (^{19})</td>
<td>78 383 (12 219 Optison, 66 164 Definity)</td>
<td>(\ldots)</td>
<td>0</td>
</tr>
</tbody>
</table>

These reports, published after the FDA box warning in October 2007, emphasize the low mortality and high safety of Definity.

Recent Postmarketing Safety Data

Retrospective analysis of large databases followed the box warning from the FDA, aiming to evaluate the safety of perflutren-based contrast agents (Table 3). Although limited by their retrospective nature with no (or imperfect) controls, they were the first attempts to better understand the potential safety issues of contrast agents. Herzog \(^{16}\) reviewed the data on a single-center experience since 1998 in which 16 025 doses of perflutren were used. Within 30 minutes of administration of the agent, no fatalities were reported. The incidence of serious adverse events (back pain, pruritus, presyncope, seizure, dyspnea, bronchospasm, chest pain) was 0.031%.

Kusnetsky et al \(^{17}\) reviewed 18 671 consecutive hospitalized patients undergoing clinically indicated echocardiograms since 2005. Mortality within 24 hours of an echocardiogram in patients receiving perflutren was compared with that of unmatched patients not receiving contrast. No difference was found in overall mortality (0.42% versus 0.37%; \(P=0.6\)). Evaluation of a small number of these patients suggested that those receiving contrast, however, had more comorbid diseases. They had lower EF and a higher incidence of coronary artery disease, chronic obstructive pulmonary disease, hypertension, and diabetes mellitus. This finding supports the contention that any adverse event temporally related after contrast administration is incidental and not the cause of death (pseudocomplications or epiphenomenon). Main et al \(^{18}\) recently reemphasized this concept. Data on >4 million inpatients undergoing an echocardiogram were extracted from the Premier Perspective Database. Mortality at 24 hours was similar in patients receiving Definity \((n=58254)\) and those who did not \((1.06% \text{ versus } 1.08\%; \ P=0.61)\). However, after adjustment for covariables such as age, comorbidities, and level of illness, the 24-hour mortality was significantly lower in the Definity group \((\text{odds ratio, } 0.76; 95\% \text{ CI, } 0.70 \text{ to } 0.82)\). Although this observation does not imply a therapeutic role of the use of contrast agents, it reflects the importance of the additional diagnostic information gained from its use. In a multicenter, retrospective safety analysis of the largest number of doses of contrast agents to date \((n=78383)\), Wei et al \(^{19}\) recently reported no deaths and only 8 serious adverse events \((0.01\%)\), including anaphylactoid and vasovagal reactions, urticaria, and hypoxemia.

FDA Modifies Box Warning

In May 2008, the FDA modified the labeling for Definity and Optison. Most previous contraindications were labeled as warnings, not as contraindications. \(^1\) Specifically, the contraindications that were removed include worsening or clinically unstable congestive heart failure, acute myocardial infarction or acute coronary syndromes, serious ventricular arrhythmias or high risk of arrhythmias as a result of prolongation of the QT interval, respiratory failure, severe emphysema, and pulmonary emboli or other conditions that cause pulmonary hypertension. These changes were made after the FDA determined that the benefits that could be obtained through the use of perflutren-based ultrasound contrast may outweigh the risk for serious cardiopulmonary reactions, even among patients at particularly high risk for these reactions.

The FDA Advisory Committee

On June 24, 2008, the FDA convened a panel of experts to review the preclinical safety evaluation of the contrast agents, potential clinical trial designs to establish clinical safety and efficacy, and potential “class” effects that relate safety and risks of ultrasound contrast agents. Industry representatives for 3 contrast agents \((\text{SonoVue, Bracco, Princeton, NJ; Definity, Lantheus, North Billerica, Mass; and Optison, General Electric, Waukesha, Wis}))) presented data on safety and clinical benefit of using contrast agents. Their presentations included data on a diversity of animal models for preclinical safety evaluation. Overall, the preclinical safety profile for all contrast agents was very good, and the findings were discussed by the panel after all presentations were concluded (see below).

Sanjiv Kaul, MD, professor and chief of cardiology at the University of Oregon, was invited to present an overview of the use of contrast agents in clinical practice. He reviewed the literature, described the routine use of contrast for LV...
opacification, and focused on off-label uses in which the addition of contrast leads to a diagnosis that would otherwise not be recognized. Examples included detection of an LV aneurysm and pseudoaneurysm, LV apical hypertrophy, ventricular noncompaction, and intracavitary thrombi and masses. The potential use of contrast for myocardial perfusion during stress testing and in the emergency department was also discussed.\(^{20}\) Contrast echocardiography as the initial evaluation of suspected cardiac chest pain has been extensively studied by Rinkevich and colleagues\(^ {20}\) and was discussed during his presentation. In a cohort of 1017 patients, evaluation of regional LV function with contrast was better than usual emergency department clinical evaluation in predicting adverse cardiovascular outcomes (cardiac death, acute coronary syndromes, heart failure, and need for revascularization) at 48 hours and at a 7-month follow-up. Adding myocardial perfusion imaging with contrast echocardiography further improved the prognostic value (\(P<0.001\)). Risk stratification in this setting also was improved during emergency department admission, allowing identification of high-risk coronary syndromes even before cardiac biomarkers were available.\(^ {21}\) According to a cost-efficiency analysis, such a strategy would reduce the number of admissions from the emergency department by 22%, reduce the emergency department stay, and therefore decrease the cost by approximately \$900 per patient.\(^ {22}\)

Barry Goldberg, MD, professor of radiology at Thomas Jefferson University, represented the American College of Radiology. He presented a variety of noncardiac uses of contrast and compared the safety of contrast ultrasound and alternative modalities that may be needed if contrast is not used. When LV EF or wall motion abnormalities cannot be determined, a variety of different tests may be needed to obtain this information. Mortality rates for cardiac catheterization have been reported to be \(\approx 1\) in 1000;\(^ {23}\) for treadmill stress test, 1 in 2500;\(^ {24}\) and for transesophageal echocardiography, 1 in 10,000.\(^ {25}\) Mortality related to newer imaging modalities such as cardiac computed tomography or cardiac MR has not yet been analyzed in a systematic way in large cohorts of patients. From the overall postmarketing experience with Definity, \(\approx 1\) in 10,000 experience some serious adverse events, and mortality is roughly 1 in 100,000. As detailed before, these numbers may be higher if only inpatients are considered.\(^ {17,18}\)

William Zoghbi, MD, chair of cardiovascular imaging at the Methodist DeBakey Heart Center and president of the American Society of Echocardiography, objected to the box warning from October 2007 and its amendment in May 2008. The use of contrast echocardiography was strongly supported by its cost-effectiveness and clinical utility in patients with limited ultrasound windows. On behalf of the American Society of Echocardiography, however, he emphasized the importance of continued surveillance for side effects and encouraged the medical community and pharmaceutical companies to continue research. There is growing concern that institutions do not use contrast when it is clinically indicated, thus leading to an increased percentage of nondiagnostic studies. This will ultimately lead to other tests with higher morbidity and side effects such as catheterizations, stress tests, and nuclear studies.

Paul Grayburn, MD, from Baylor University Medical Center in Dallas, reviewed the concept of pseudocomplications (or epiphenomenon). Although some patients died in the hours after contrast agent injections, all of these patients were severely ill; therefore, it would be inappropriate to attribute these deaths to the contrast agent, as discussed above.

In the FDA panel discussion that followed, the stated goal was to seek guidance in 3 different areas of interest: (1) preclinical safety evaluation, (2) clinical trial design to establish clinical safety and efficacy, and (3) potential class effect that relates to safety. The panel’s recommendations are summarized in Table 4.

### Preclinical Safety Evaluation

Although no severe adverse events for these contrast agents were described in the animal models, several hemodynamic findings may be related to the adverse events now described in patients with acute cardiac and lung disease. These include pulmonary hypertension (secondary to vasoconstriction), acute respiratory failure, and pulmonary macrophage infiltration, which were mostly described in pigs, dogs, rats, and primates at doses 15 to 150 times higher than clinical doses. Cardiovascular events described included transient hypotension (in the setting of pulmonary vasoconstriction), ST depression, and QT prolongation. The panel recognized that there is no perfect animal model as a surrogate for human metabolism and experience. Indeed, these cardiopulmonary events have not been documented in humans. Therefore, although the animal findings were probably not representative of humans, they should raise awareness of potential problems. The panel mentioned that animal data may apply to a healthy population but may not apply to ill patients such as those case fatalities.

### Clinical Trial Design to Establish Clinical Safety and Efficacy

Contrast agents were approved on an anatomic basis; the outcomes evaluated were “prettier pictures” or more accurate assessment of endocardial borders and EF. However, the FDA panel expressed concerns about the clinical benefit of getting prettier pictures. Although it is logical to assume that a more accurate image is beneficial, there are no data supporting the direct link between the accuracy of the image
and clinical benefit. The FDA is now more interested in clinical outcomes, i.e., the clinical impact of such improved accuracy. The change in the FDA approach on this matter may be related to the recent serious postmarketing cardiovascular events involving highly used and popular drugs. In short, there needs to be a strongly favorable risk-benefit balance for any drug or injectable agent.

How to obtain postmarketing safety data was discussed. The panel recognized the limitations of spontaneous reporting of adverse events because this methodology introduces significant selection biases, including the potential for pseudocomplications discussed. Although spontaneous reports may be informative, they would not clarify cause and effect because the risk of an event may be strongly linked to the underlying diseases rather than to the contrast agent. Therefore, a control group is needed. Furthermore, spontaneous reports do not give the opportunity to estimate the incidence of a side effect and do not provide a systematic evaluation of the cases reported that would help researchers understand the mechanisms responsible for the adverse events. The panel reinforced the advantages of large blinded randomized trials in overcoming these limitations but stated that large observational studies would be acceptable. The panel suggested postmarketing surveillance of side effects by creating prospective registries/databases with control groups included for comparison.

**Determining Class Effects That Relate to the Safety of Ultrasound Contrast**

Safety risks for 1 member of a class of drugs may represent risks for all members of the drug class, given similarities among the products. The panel highlighted the importance of characteristics that contrast agents have in common such as the physical and chemical nature of microbubbles, their mechanisms of diagnostic action (echogenicity), and the similar effects in animal models (even in different species). These were considered important in determining class safety risks, including serious but rare risks that are not likely detectable in the premarketing clinical studies.

**Conclusions**

The safety data on echocardiography contrast agents recently published and presented during this meeting are reassuring. The FDA modification of the box warning to reduce the contraindication to a warning lends further reinforcement to the use of contrast when clinically appropriate. Although this meeting did not have as an objective changing the box warning and contraindications/recommendations for the labeling of perflutren-based ultrasound contrast agents, the FDA advisory committee outlined some guidelines and recommendations for future steps in the evaluation of the safety of these drugs. The committee called for the evaluation of clinical outcomes and the development of large randomized controlled trials or postmarketing registries to evaluate potential rare serious adverse events.

**Acknowledgment**

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**References**


**KEY WORDS:** contrast media, echocardiography, imaging
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