



Ultrasound Contrast Agents

Recent Safety Studies,
Quality Assurance Documents
& Consensus Documents

March 27, 2009

FDA Revised Product Labeling

May 2008

- ☀ "Boxed Warning" remains for Definity and Optison highlighting the risk of "serious cardiopulmonary reactions" within 30 minutes of administration

- ☀ October 2007 "Contraindications" changed to "Warnings"
 - worsening or clinically unstable heart failure
 - acute myocardial infarction or acute coronary syndrome
 - serious ventricular arrhythmia or high risk for arrhythmias due to QT prolongation
 - respiratory failure
 - severe emphysema, pulmonary emboli, or other conditions that cause pulmonary hypertension

- ☀ Mandated 30 minute monitoring period following contrast administration only in patients with pulmonary hypertension or critically ill

FDA Cardio-Renal Advisory Panel

June 24, 2008

Conclusions:

- Sensitive and appropriate animal models should be used initially to identify signals and mechanism of possible risk
- There is a need for infrequent serious events to be studied in well-designed post-marketing studies, and for pre-market prospective studies in high-risk populations likely to receive the product.
- It may not be unrealistic to require adequate exposure under placebo controlled conditions to exclude a certain level of risk of cardiovascular events (upper end of the 95% CI, HR 1.5)
- The committee acknowledged certain features of each imaging agent as unique and noted that some features, but not all, are reasonable to define a "class". The specific features were not discussed in detail.

Summary minutes of the Cardiovascular and Renal Drugs Advisory Committee June 24th, 2008 available on the web at: <http://www.fda.gov/ohrms/dockets/ac/08/minutes/2008-4369m1-final.pdf> accessed September 13, 2008

Recent CEUS Safety Studies

N = 228,611 patients

References

Safety Studies (abridged list):

- Erb J, Shanewise J. JAmSocEchocardiogr 2001;14:595-600
- Herzog CA. JAMA 2008;299:2023-2025
- Dolan MS, Gala SS, Dodla S, et al. Safety and efficacy of commercially available ultrasound contrast agents for rest and stress echocardiography a multicenter experience. J Am Coll Cardiol 2009;53:32-8.
- Gabriel RS, Smyth YM, Menon V, et al. Safety of ultrasound contrast agents in stress echocardiography. Am J Cardiol 2008;102:1269-72.
- Kusnetzky LL, Khalid A, Khumri TM, Moe TG, Jones PG, Main ML. Acute mortality in hospitalized patients undergoing echocardiography with and without an ultrasound contrast agent: results in 18,671 consecutive studies. J Am Coll Cardiol 2008;51:1704-6.
- Main ML, Ryan AC, Davis TE, Albano MP, Kusnetzky LL, Hibberd M. Acute mortality in hospitalized patients undergoing echocardiography with and without an ultrasound contrast agent (multicenter registry results in 4,300,966 consecutive patients). Am J Cardiol 2008;102:1742-6.
- Wei K, Mulvagh SL, Carson L, et al. The safety of deFinity and Optison for ultrasound image enhancement: a retrospective analysis of 78,383 administered contrast doses. J Am Soc Echocardiogr 2008;21:1202-6. Kusnetzky LL. J Am Coll Cardiol 2008; 51:1704-5
- Main M, et al. J Am Coll Cardiol (abstract) 2009

Consensus Documents:

- Mulvagh SL, Rakowski H, Vannan MA, et al. American Society of Echocardiography Consensus Statement on the Clinical Applications of Ultrasonic Contrast Agents in Echocardiography. J Am Soc Echocardiogr 2008;21:1179-201
- Senior R, Becher H, Monaghan M, et al. Contrast echocardiography: evidence-based recommendations by European Association of Echocardiography. Eur J Echocardiogr 2009;10:194-212

Safety Studies

Intraoperative Contrast Echocardiography with Intravenous Optison Does Not Cause Hemodynamic Changes During Cardiac Surgery

Jochim M. Erb, MD, DEAA, and Jack S. Shanewise, MD, Berlin, Germany, and Atlanta, Georgia

Background: The echocardiographic contrast agent Optison may be useful in patients undergoing cardiac surgery. This study investigates its effects on hemodynamics, cardiac performance, and oxygenation in this group of patients.

Methods: Parameters of hemodynamic stability, cardiac performance, and oxygenation were measured in 57 patients by transesophageal echocardiography, electrocardiography, invasive arterial blood pressure and central venous pressure monitoring, capnography, pulse oximetry, and pulmonary artery catheter before and 5 and 10 minutes after an intravenous bolus of 0.3 ml of Optison.

Results: No statistically significant differences in ST-

segment changes, heart rate, arterial and central venous pressure, peripheral oxygen saturation, cardiac index, left ventricular ejection fraction, and regional wall motion were seen 5 and 10 minutes after injection of Optison compared with baseline parameters.

Conclusions: Optison did not cause clinically important changes in parameters of hemodynamic stability, cardiac performance, and oxygenation in our patients. The intraoperative use of intravenous Optison appears to be safe in patients undergoing cardiac surgery, including in the use of cardiopulmonary bypass. (J Am Soc Echocardiogr 2001;14:595-600.)

INTRODUCTION

Although the first reported use of an echocardiographic contrast agent dates back to 1968, when Gamiak and Shah¹ observed an ultrasound contrast effect after injection of hand-agitated indocyanine green during coronary arteriography, contrast echocardiography was confined to the research laboratories for many years. A more widespread use of contrast echocardiography as a diagnostic tool in daily clinical practice became possible with the introduc-

tion of a method of sonication² in 1984 and the availability of commercially produced contrast agents. The first available FDA-approved echocardiographic contrast agent in the United States was a suspension of air filled albumin microspheres (Albutex, Mallinckrodt Inc, St Louis, Mo). Since 1998, a second-generation echocardiographic contrast agent consisting of a suspension of octafluoropropane-filled albumin microspheres (Optison, Mallinckrodt Inc, St Louis, Mo) has been available and approved by the FDA to improve endocardial border delineation with 2-dimensional echocardiography after intravenous injection. Optison has an average microsphere size of 2.0 to 4.5 μm and a concentration of 5 to 8 $\times 10^8$ microspheres/mL. Compared with Albutex, the smaller size and greater stability of the microspheres allow for improved transpulmonary passage with less decrease of the microsphere concentration caused by destruction or filtering in the pulmonary capillary bed.

Because this development improves the practical application of echocardiographic contrast agents, their intraoperative use in patients undergoing cardiac surgery may become more frequent. Studies have shown that Optison can improve the quality of

- 57 patients mean age 63 years
- CABG or valve surgery
- Bolus Optison (0.3 ml) administered in wall motion (n=35) and perfusion (n=22) studies
- Hemodynamic assessments at 0, 5 and 10 minutes
- No clinically significant change from baseline in:
 - ST segment
 - Heart Rate
 - Blood pressure
 - Central venous pressure
 - Pulmonary artery pressure
 - End tidal carbon dioxide
 - Oxygen saturation
 - Cardiac Index
 - Left Ventricular Ejection Fraction

- **Conclusion: No hemodynamic effects of Optison when administered in clinically relevant doses in patients undergoing cardiac surgery**

From the Department of Anesthesiology (J.M.E.), German Heart Institute Berlin; and the Department of Anesthesiology (J.S.S.), Division of Cardiothoracic Anesthesiology, Emory University School of Medicine, Atlanta, Ga.

Echocardiography equipment was provided by the Department of Anesthesiology, Emory University. The contrast agent Optison was provided by Mallinckrodt Inc, St Louis, Mo.

Presented at the Society of Cardiovascular Anesthesiologists (SCA) 1999 Annual Meeting, April 24-28, 1999, Chicago, Ill.

Reprint requests: Jochim M. Erb, MD, DEAA, Staff Anesthesiologist in Cardiothoracic Anesthesia, Department of Anesthesiology, German Heart Institute Berlin, Augustenburger Platz 1, D-13353 Berlin, Germany (E-mail: erb@ghfai.de).

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0894-7317/2001/\$35.00 + 0 27/1/111856

doi:10.1067/mjc.2001.111856

Safety Studies

- 35 heart surgery patients (CABG, ASA class IV*), received 97 total injections of 0.3ml bolus doses of Optison delivered via a central venous catheter
- No statistically significant differences in ST-segment changes, HR, arterial and central venous pressure, peripheral O₂ saturation, cardiac index, LVEF and regional wall motion were seen 5 and 10 min after Optison in all patients undergoing concurrent use of anesthetics, high oxygen content and positive end expiratory pressure (PEEP).

Sub-groups	Time of measurements	PAs mmHg	PAd mmHg	CO ₂	comments
97 injections (n=35 patients, ASA class IV*)	5 min vs baseline	1.3 ± 2.4	0.6 ± 2.4	0.2 ± 2.3	NS
	10 min vs baseline	0.7 ± 5.0	0.9 ± 3.0	-0.5 ± 2.0	NS

Erb JM, Shanewise JS. Intraoperative contrast echocardiography with intravenous optison does not cause hemodynamic changes during cardiac surgery and is a constant threat to life. *ASA* 600.

Safety Studies

JAMA[®]

Incidence of Adverse Events Associated With Use of Perflutren Contrast Agents for Echocardiography

Charles A. Herzog

Online article and related content
current as of May 7, 2008.

JAMA. 2008;299(17):2023-2025 (doi:10.1001/jama.299.17.2023)

<http://jama.ama-assn.org/cgi/content/full/299/17/2023>

Hennepin County MC Registry

- ★ 16,025 patients received an ultrasound contrast agent
 - Optison=3051
 - Definity=12,974
- ★ Overall adverse event rate=0.12
 - Optison=0%
 - Definity=0.15%
- ★ Serious Adverse Event rate=0.03%
- ★ Patients experiencing adverse events had high (65%) history of allergy

- ★ **Conclusions: Adverse event rate with perflutren containing compounds similar to low-osmolar iodinated radiocontrast media**

Herzog CA. Incidence of Adverse Event Associated with Use of Perflutren Containing Contrast Agents for Echocardiography. *JAMA* 2008;299:2023-2025.

Safety Studies

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doi:10.1016/j.jacc.2008.03.006

EXPEDITED PUBLICATION

Short Original Research Paper

Acute Mortality in Hospitalized Patients Undergoing Echocardiography With and Without an Ultrasound Contrast Agent

Results in 18,671 Consecutive Studies

Lisa L. Kusnetzky, BA, Adnan Khalid, MD, Taiyeb M. Khumri, MD, Tabitha G. Moe, MD, Philip G. Jones, MS, Michael L. Main, MD, FACC

Kansas City, Missouri

Objectives	We sought to define acute mortality in hospitalized patients undergoing clinically indicated echocardiography with and without use of an ultrasound contrast agent.
Background	The U.S. Food and Drug Administration recently issued a boxed warning and new contraindications for the perflutren-containing ultrasound contrast agents following post-marketing reports of 4 patient deaths that were temporally related to Definity (Bristol-Myers Squibb Medical Imaging, Billerica, Massachusetts) administration. To appreciate the incremental risk of any medical procedure, the ambient risk of untoward outcome in the population in question must first be defined. There are no published data on short-term major adverse cardiac events in hospitalized patients undergoing echocardiography, either with or without administration of an ultrasound contrast agent.
Methods	A retrospective analysis of hospitalized patients undergoing clinically indicated echocardiography between January 2005 and October 2007, within Saint Luke's Health System, Kansas City, Missouri, was performed. Studies were separated into 2 groups, those performed without contrast enhancement (n = 12,475) and those performed with Definity (n = 6,196). Vital status within 24 h of the echocardiographic study was available for all patients using a combination of the Social Security Death Master File and Saint Luke's Health System medical records. Incidence of death within 24 h was compared by chi-square test between Definity and unenhanced procedures.
Results	Of the 18,671 patient events, 72 patients died within 24 h. Of those that underwent unenhanced echocardiography, 46 died within 24 h (0.37%). Of patients receiving Definity during the echocardiogram, 26 died within 24 h (0.42%). There was no statistical difference between these 2 groups (p = 0.60). No patient died within 1 h of the echocardiographic study. In a random sampling from the unenhanced (n = 201) and Definity groups (n = 202), patients who underwent Definity-enhanced echocardiography exhibited higher clinical acuity, and more significant comorbidities.
Conclusions	Approximately 0.4% of hospitalized patients die within 24 h of echocardiography. There is no increased mortality risk associated with Definity-enhanced examinations, despite evidence for higher clinical acuity and more comorbid conditions in patients undergoing contrast studies. (J Am Coll Cardiol 2008;51:1704-6) © 2008 by the American College of Cardiology Foundation

- ★ 18,671 patients
 - ★ 12,475 unenhanced
 - ★ 6,196 Definity
- ★ In-patient echocardiography between January 2005 and October 2007
- ★ Vital status at 24 hours available for all patients

Kusnetzky LL, Khalid A, Khumri TM, Moe TG, Jones PG, Main ML. Acute mortality in hospitalized patients undergoing echocardiography with and without an ultrasound contrast agent: results in 18,671 consecutive studies. J Am Coll Cardiol 2008;51:1704-6

Results

Table 1

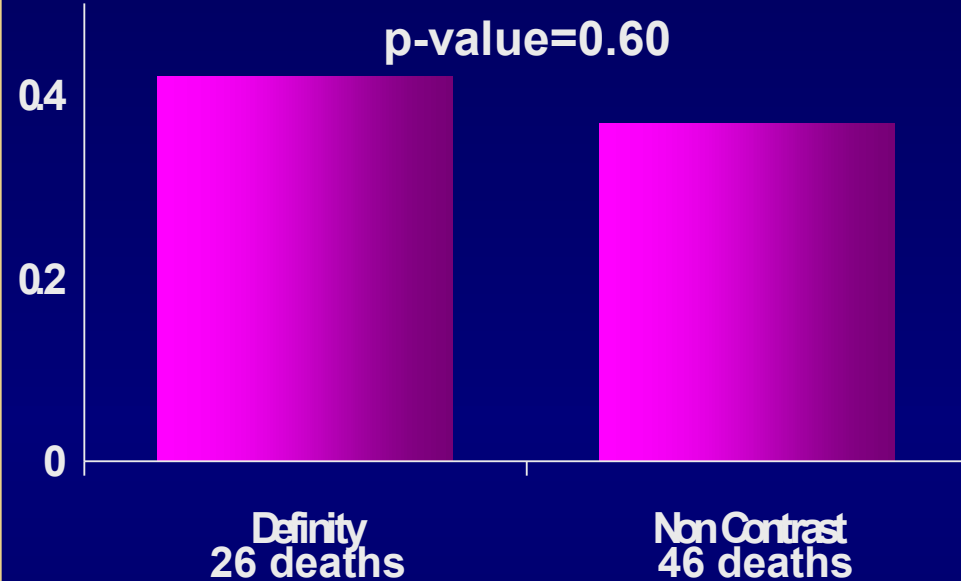
Characteristics of Patients Undergoing Echocardiography With and Without Contrast Enhancement

	Echocardiography With Contrast (n = 202)	Unenhanced Echocardiography (n = 201)	p Value
Age (yrs)	66.1 ± 15.0	64.2 ± 18.3	0.254
Gender			<0.001
Female	72 (35.6%)	117 (58.2%)	
Male	130 (64.4%)	84 (41.8%)	
Hospital length of stay			0.181
Mean ± SD	9.6 ± 25.7	7.1 ± 8.9	
Median (IQR)	5.0 (3.0–8.0)	4.0 (2.0–9.0)	
ICU (days)			0.007
Mean ± SD	2.9 ± 9.5	1.0 ± 2.4	
Median (IQR)	0.0 (0.0–3.0)	0.0 (0.0–1.0)	
Diabetes mellitus	73 (36.3%)	37 (18.4%)	<0.001
Hypertension	173 (86.1%)	118 (58.7%)	<0.001
Serum creatinine			0.107
Mean ± SD	1.6 ± 1.3	1.4 ± 1.2	
Median (IQR)	1.2 (0.9–1.6)	1.1 (0.9–1.4)	
Chronic obstructive lung disease	48 (23.9%)	22 (10.9%)	<0.001
Coronary artery disease	143 (71.1%)	64 (31.8%)	<0.001
Stroke	37 (18.4%)	31 (15.4%)	0.425
Left ventricular ejection fraction	48.3 ± 15.8	58.9 ± 12.1	<0.001

Continuous variables are reported as mean ± SD and/or median and IQR as appropriate, and were compared using t tests. Categorical variables are reported as frequency and percent and were compared using chi-square tests.

ICU = intensive care unit; IQR = interquartile range.

Percent Mortality at 24 hours



Conclusion:

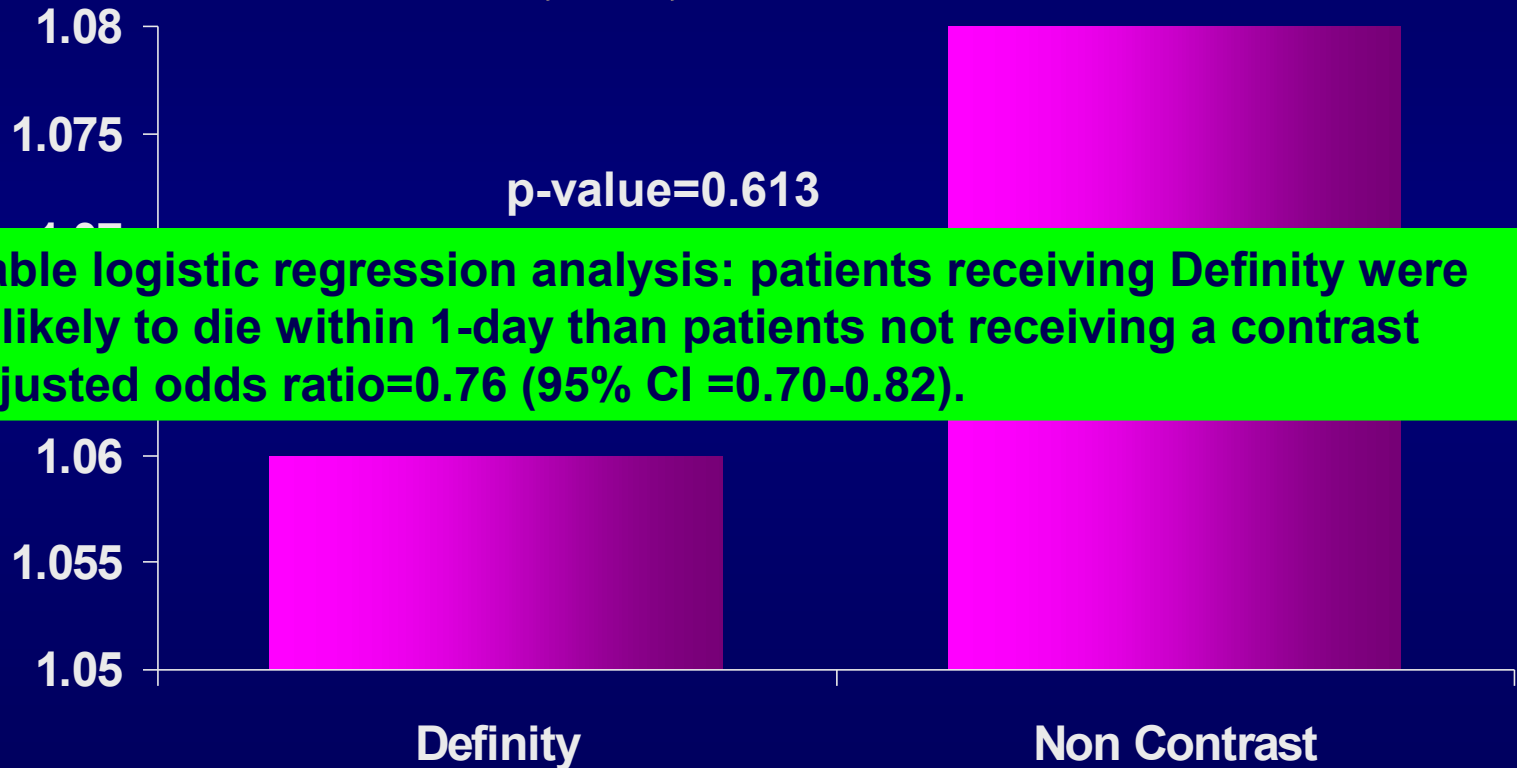
★ **No difference in 24 hour mortality in hospitalized patients undergoing echocardiography with or without contrast administration**

Safety Studies

Acute Mortality in Hospitalized Patients Undergoing Echocardiography with and without an Ultrasound Contrast Agent:

Contrast Agent:

Multicenter Results in 4,300,966 Consecutive Patients



Multivariable logistic regression analysis: patients receiving Definity were 24% less likely to die within 1-day than patients not receiving a contrast agent (adjusted odds ratio=0.76 (95% CI =0.70-0.82)).

Main ML, Ryan AC, Davis TE, Albano MP, Kusnetzky LL, Hibberd M. Acute mortality in hospitalized patients undergoing echocardiography with and without an ultrasound contrast agent (multicenter registry results in 4,300,966 consecutive patients). Am J Cardiol 2008;102:1742-6.

Safety Studies

Acute Mortality in Hospitalized Patients Undergoing Echocardiography with and without an

Table 3 Frequency of Unstable Cardiopulmonary Conditions (as defined by the FDA in October, 2007)

	Non Contrast Echocardiograms		Definity-enhanced Echocardiograms		P-value
	4,242,712		58,254		
1. Worsening or clinically unstable congestive heart failure	1,341,263	31.61%	25,040	42.98%	<0.0001
2. Acute myocardial infarction or acute coronary syndrome	592,128	13.96%	13,871	23.81%	<0.0001
3. Serious ventricular arrhythmias or high risk for arrhythmia due to prolongation of the QT interval	200,923	4.74%	4,742	8.14%	<0.0001
4. Respiratory failure, as manifest by signs and symptoms of hypoxemia	606,615	14.30%	12,480	21.42%	<0.0001
5. Severe emphysema, pulmonary emboli or other conditions that may cause pulmonary hypertension	54,803	1.29%	765	1.31%	0.6478
6. Pulmonary hypertension	244,475	5.76%	4,380	7.52%	<0.0001

Main ML, Ryan AC, Davis TE, Albano MP, Kusnetzky LL, Hibberd M. Acute mortality in hospitalized patients undergoing echocardiography with and without an ultrasound contrast agent (multicenter registry results in 4,300,966 consecutive patients). Am J Cardiol 2008;102:1742-6.

Safety Studies

American Society of Echocardiography Multicenter Registry 2008

- ✱ Retrospective, 13 sites (January 1, 2001-September 30, 2007)
- ✱ 66,164 doses of Definity and 12,219 doses of Optison (5% of transthoracic/28% stress)
- ✱ Severe adverse reactions in 8 patients (0.01%)
- ✱ Anaphylactoid reactions in 4 patients (0.006%)
- ✱ No deaths
- ✱ No SAE in hospitalized patients

Conclusions: The incidence of severe adverse reactions to ultrasound contrast agents is lower than, or similar to, that reported for contrast agents commonly used in other cardiac imaging tests.

Wei K, Mulvagh SL, Carson L, et al. The safety of deFinity and Optison for ultrasound image enhancement: a retrospective analysis of 78,383 administered contrast doses. J Am Soc Echocardiogr 2008;21:1202-6. Kusnetzky LL. J Am Coll Cardiol 2008; 51:1704-5

Safety Studies

Saint Louis University, University of Nebraska, Mayo Clinic Multicenter Retrospective Study (1999-2007)

- 42,408 consecutive patients with poor endocardial border delineation received contrast
- 18,749 stress echo with contrast
- 6513 DSE contrast patients compared with 6249 DSE unenhanced patients
- 4275 patients exercise contrast patients compared with 9740 exercise unenhanced patients

Results:

- **No events within 30 minutes**
- **One death and 5 non-fatal MI within 24 hours (none believed associated with contrast agent)**
- **Thirty day stress contrast mortality=0.34% vs 0.39% non-contrast (p=NS)**
- **Thirty day stress contrast myocardial infarction=0.63% vs. 0.46% non-contrast stress (p=NS)**

Dolan MS, Gala SS, Dodla S, et al. Safety and efficacy of commercially available ultrasound contrast agents for rest and stress echocardiography a multicenter experience. J Am Coll Cardiol 2009;53:32-8.

Safety Studies

Cleveland Clinic Safety Audit

Retrospective safety audit for serious adverse events (1998-2007)

5,550 patients underwent with contrast at the Cleveland Clinic.

Definity 2001-2007

Optison 1998-2005

SAE rate in TTE:

- 24 hour mortality n=8 (0.15%)
- Cardiopulmonary arrest n=0
- Serious ventricular arrhythmias n=0
- Anaphylaxis n=0

SAE rate in stress echo:

- 24 hour mortality n=0
- Cardiopulmonary arrest n=2 (0.04%) (p=NS compared to non-contrast)
- Anaphylaxis n=0
- Severe hypoxia n=1 (0.02%) (p=NS compared to non-contrast)
- sustained VT n=6 (0.2%) (p=NS compared to non-contrast)

Conclusions:

- SAE, arrhythmias and symptoms are rare in patients undergoing TTE with contrast
- No difference in SAE rates and arrhythmia in patients undergoing stress echo with and without contrast

Gabriel RS, Smyth YM, Menon V, et al. Safety of ultrasound contrast agents in stress echocardiography. Am J Cardiol 2008;102:1269-72.

Safety Studies

**Optison™ does not increase mortality in critically ill patients:
A retrospective matched case-control study***

- ★ Retrospective analysis: n=2,588,722 and 22,499 with Optison™ (Premier Perspective™, Charlotte, NC) January 2003 and October 2005 compared to 11,600 case-matched controls (no CEUS)
- ★ Controls were matched by level of care (intensive care unit, cardiac care unit), and mechanical ventilation status. Adjustments were made for demographic factors, hospital-specific factors and co-morbidities using a conditional logistic regression model.

* Michael L Main, Alex Exuzides, Chris Colby, Steven Feinstein, Jonathan Goldman, Anne Waaler, Paul Grayburn. To be presented March 2009, American College of Cardiology

Safety Studies

**Optison™ does not increase mortality in critically ill patients:
A retrospective matched case-control study***

- * Optison™ was not associated with a statistically significant increase in same-day mortality (odds ratio=1.22, P=0.29) in critically ill patients.**
- * This lack of increase was despite a greater Deyo-modified Charlson comorbidity index (P<0.0001) and coronary artery disease (P<0.0001) in Optison™ patients.**
- * The lack of mortality effect is reassuring given that Optison™ patients have increased co-morbidity, including coronary disease.**

* Michael L Main, Alex Exuzides, Chris Colby, Steven Feinstein, Jonathan Goldman, Anne Waaler, Paul Grayburn. To be presented March 2009, American College of Cardiology

Prospective Analysis

Impact of Contrast Echocardiography on Evaluation of Ventricular Function and Clinical Management in a Large Prospective Cohort

Mustafa Kurt, MD, Kamran A. Shaikh, MD, Leif Peterson, PhD, Karla M. Kurrelmeyer, MD, FACC, Gopi Shah, MD, FACC, Sherif F. Nagueh, MD, FACC, Robert Fromm, MD, Miguel A. Quinones, MD, FACC and William A. Zoghbi, MD, FACC*
Department of Cardiology, The Methodist Hospital



J Am Coll Cardiol, 2009; 53:802-810, doi:10.1016/j.jacc.2009.01.005
(Published online 11 February 2009).

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PUBLICATION

Clinical Outcomes with CEUS: Impact of Contrast Echocardiography on Evaluation of Ventricular Function and Clinical Management in a Large Prospective Cohort

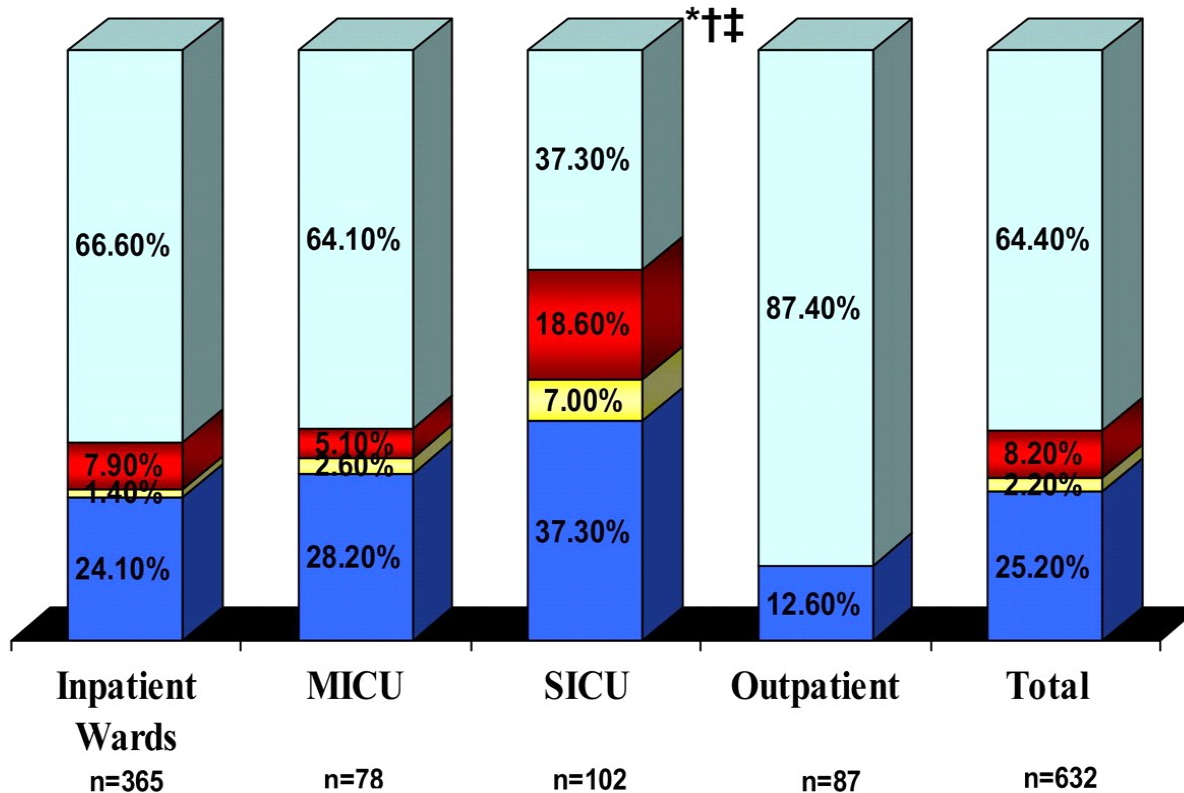
- ★ The authors concluded that the appropriate use of contrast ultrasound resulted in improved endocardial visualization, which positively affected diagnostic efficiency, resource utilization, and, critically, resulted in changes in patient management (632 consecutive patients).**

Clinical Outcomes with CEUS: Impact of Contrast Echocardiography on Evaluation of Ventricular Function and Clinical Management in a Large Prospective Cohort

- ★ Uninterpretable studies decreased from 11.7% to 0.3%**
- ★ Technically difficult studies decreased from 86.7% to 9.8% (p = 0.0001)**
- ★ LV thrombus was suspected in 35 patients and was considered definite in 3 patients before contrast echocardiography and after utilizing contrast, only 1 patient had a suspected thrombus, and 5 (new) additional patients with thrombus were identified (p = 0.0001)**

Total Impact of Contrast on Patient Management

- Procedure Avoided, only
- Medication Change, only
- Both Medication and Procedural Change
- Unchanged



Kurt, M. et al. J Am Coll Cardiol 2009;53:802-810

Safety Study Abstracts – ACC 3/09

A254 ABSTRACTS - Imaging and Diagnostic Testing

3:30 p.m.

1027-271 Optison™ Does Not Increase Mortality in Critically Ill Patients: Preliminary Results From a Retrospective Matched Case-Control Study

Michael L. Main, Alex Ekuzides, Chris Colby, Steven B. Feinstein, Jonathan H. Goldman, Anne Waaler, Paul A. Grayburn, Saint Luke's Mid America Heart Institute, Kansas City, MO, ICON Medical Imaging, Warrington, PA

Background: Due to serious cardiopulmonary reactions reported immediately following administration of perflutren containing contrast agents, the United States Food and Drug Administration (FDA) required a Black Box Safety warning for this class of agents including Optison™ (Perflutren Protein-Type A Microspheres Injectable Suspension, USP). FDA has requested a database analysis to compare in-hospital mortality in critically ill patients undergoing echocardiography with and without Optison. This study provides preliminary results of the retrospective analysis.

Methods: The study utilized the largest available hospital service-level database in the U.S. (Premier Perspective™, Charlotte, NC). Patients were characterized by diagnoses, dates of treatments, and outcomes. All adult patients undergoing inpatient echocardiography between Jan. 2003 and Oct. 2005 were identified (n=2,586,722 of which 22,499 received Optison). Of those administered Optison, 2,900 had diagnoses meeting defined criteria for critical illness (heart failure, acute myocardial infarction, arrhythmia, respiratory failure, pulmonary embolism, emphysema, and pulmonary hypertension). Outcomes for these patients were compared to 11,600 case-matched controls who received echocardiography without contrast. Controls were matched by level of care (e.g., intensive care unit or cardiac care unit), and mechanical ventilation status. Adjustments were made for demographic factors, hospital-specific factors, and co-morbidities using a conditional logistic regression model.

Results: Optison was not associated with an increase in same-day mortality (odds ratio=1.22, P=0.29) in critically ill patients. This was in spite of a higher Deyo-modified Charlson comorbidity index (P<0.0001) and incidence of coronary artery disease (P<0.0001) in Optison patients.

Conclusions: There is no increase in mortality in critically ill patients undergoing echocardiography with Optison compared to case-matched controls, despite the fact that Optison patients demonstrated greater comorbidity, including coronary artery disease.

3:30 p.m.

1027-272

Safety of Ultrasound Contrast Agents During Echocardiography in Patients With Pulmonary Hypertension

Buyin S. Gabbai, Yvonne M. Smyth, Richard A. Grimm, James D. Thomas, Venu Menon, Allan L. Klein, Ellen Mayer Sabik, Cleveland Clinic, Cleveland, OH

Background:

Despite the revision of the "Black Box" warning by the Federal Drug Administration (FDA) on the safety of ultrasound contrast agents in echocardiography, there remains concern the risk of serious cardiopulmonary reactions are increased in patients with pulmonary hypertension. This audit reviews the rate of adverse events in patients with underlying pulmonary hypertension receiving ultrasound contrast agents at the Cleveland Clinic.

Methods: All patients undergoing transthoracic (TTE) or exercise (ESE) or dobutamine (DSE) stress echocardiography who received perflutren based contrast agents at the Cleveland Clinic between 1998 and 2007 were included. Pulmonary hypertension was estimated from continuous wave Doppler interrogation of the tricuspid regurgitant jet. Mild-moderate pulmonary hypertension was defined as a right ventricular systolic pressure (RVSP) of 30-50 mmHg and severe pulmonary hypertension as an RVSP of greater than 50 mmHg. Serious adverse events were defined as: death within 24 hours of contrast administration and cardiac arrest, anaphylaxis and sustained ventricular arrhythmias within 30 minutes of contrast administration.

Results: 10010 patients received intravenous ultrasound contrast during echocardiography at the Cleveland Clinic between 1998 and 2007. An accurate measurement of RVSP was obtained in 3479 (35%) of patients. Mild pulmonary hypertension was documented in 1921 (19%) patients and severe pulmonary hypertension in 346 patients (3%) patients. 60% of patients received Definity, 37% Optison and 3% were unknown. There were 1514 TTE, 399 ESE and 254 DSE performed with contrast in patients with pulmonary hypertension. There was no death within 24 hours of contrast administration, no cardiac arrest, no anaphylaxis and no sustained ventricular arrhythmias noted in patients with pulmonary hypertension.

Conclusions: No serious adverse events were noted in 2267 patients with documented pulmonary hypertension who received ultrasound contrast agents during echocardiography over a 10 year period at the Cleveland Clinic. These findings have major implications to the revised black box warning by the FDA.

3:30 p.m.

1027-268

Safety of Contrast Agents During Stress Echocardiography in Patients With High Right Ventricular Systolic Pressure: A Study of 16,434 Patients

Sahar S. Abdelmonem, Mathieu Bernier, Christopher G. Scott, Abhijeet Dhole, Stuart Moir, Robert B. McCully, Patricia A. Pellikka, Sharon L. Mulvagh, Mayo Clinic, Rochester, MN

Background: Microbubble safety concerns led to changes in product recommendations in patients (pts) with pulmonary hypertension. Pulmonary artery systolic pressure equals right ventricular systolic pressure (RVSP) in absence of pulmonary obstruction. We evaluated short and long-term safety in pts with increased RVSP undergoing clinical stress echo (SE) with and without contrast.

Methods: From 11/03 -12/07 we studied 26,774 SE pts. RVSP was measured in 16,434 pts: 10,270 (63%) had no contrast, 6,164 (38%) contrast (Optison or Definity). Short-term (<72 hrs. <30 days) & long-term (0.1 - 4.3 years) endpoints were death & myocardial infarction (MI). RVSP analysis at levels ≥ 35 , >50 & ≥ 60 mmHg was done. Cox regression models were used.

Results: Contrast-SE cohorts were older (67 ± 12 vs 64 ± 14 yrs, $P < 0.001$), male (53 vs 49%, $P < 0.001$) & with positive SE (35 vs 30%, $P < 0.001$) vs no contrast-SE, Table. Short-term events for contrast & no contrast-SE cohorts were comparable. For RVSP ≥ 50 mmHg, there was no significant difference in long-term events in contrast vs no contrast-SE cohorts [adjusted hazard ratio (HR 95% C.I): death = 1.1 (0.8, 1.5), $P = 0.56$; MI = 0.34 (0.11, 1.0), $P = 0.06$ and combined = 1.01 (0.75, 1.3), $P = 0.94$]. Similarly RVSP ≥ 35 & ≥ 60 mmHg showed no significant differences for all endpoints [HR=1.02 (C.85, 1.2), $P = 0.85$ and 0.94 (0.55, 1.6), $P = 0.82$] for combined events, respectively.

Conclusions: Microbubble use in SE is not associated with increased risk of death/MI in pts with increased resting RVSP up to 60mmHg.

Demographics & short-term events in 16,434 SE pts stratified by RVSP from Nov 2003-Dec 2007

Variable	RVSP > 50 mmHg (N=1,025)			RVSP < 50 mmHg (N=15,409)		
	Contrast (N=414)	No Contrast (N=611)	P-value	Contrast (N=575)	No Contrast (N=9658)	P-value
Docutamine	363(88%)	467 (76%)	<0.001	3410 (59%)	3595 (37%)	<0.001
Exercise	51 (12%)	144 (24%)	<0.001	2340(41%)	606(63%)	<0.001
Age, years	73.8 ± 10	73.3 ± 12	0.57	67 ± 12	64 ± 14	<0.001
Males	210(51%)	287(48%)	0.24	3081(54%)	4777(50%)	<0.001
BMI, kg/m ²	31 ± 7	27 ± 6	<0.001	31 ± 6	27 ± 5	<0.001
Diabetes	143(34%)	167 (28%)	0.04	1361(24%)	1266(14%)	<0.001
Hypertension	324(79%)	403(78%)	0.81	3680(69%)	5282(56%)	<0.001
Heart failure	290(70%)	350(59%)	<0.001	3037(60%)	5645(59%)	<0.001
Prior Myocardial infarction	89(22%)	106(18%)	0.14	763(13%)	854(9%)	<0.001
Prior Coronary Bypass	88(21%)	102(17%)	0.09	795(14%)	686(7%)	<0.001
Death ≤ 72 hrs after SE	0(0.0%)	0(0.0%)	-	0(0.0%)	2(0.0%)	0.28
Death ≤ 30 days of SE	8(2%)	10(2%)	0.72	18(3%)	28(3%)	0.80
MI ≤ 72 hrs after SE	0(0.0%)	2(0.3%)	0.24	4(0.7%)	3(0.0%)	0.28
MI ≤ 30 days of SE	1(0.2%)	2(0.3%)	0.80	9(0.2%)	12(0.1%)	0.80

Summary

- ✦ Multiple clinical safety studies were reported in 2008-9
- ✦ Consistent conclusions: No unexpected or unidentified “safety signal” in more than 228,611 patients
- ✦ Further reversal of the October 2007 label changes awaits completion of the FDA mandated risk management plans

Comparative Safety

**Contrast ultrasound
and
other imaging modalities**

CEUS vs. comparable imaging modalities: Event Rates for Cardiovascular Procedures

Procedure	Event Rate	Event
Coronary Angiography	1:1000	Death
Exercise Treadmill Testing	1:2500	MI or Death
SPECT Exam or Radionuclide Ventriculography	1:1000 to 1:10,000	Fatal Malignancy
Contrast Echocardiography	1:500,000	Death

CEUS vs. Nuclear Imaging

Ionizing Radiation in Cardiac Imaging

Science Advisory - American Heart Association Committee on Cardiac Imaging
of the Council on Clinical Cardiology and
Committee on Cardiovascular Imaging and Intervention
of the Council on Cardiovascular Radiology and Intervention

- ☀ *“Medical imaging is the largest controllable source of radiation exposure to the US population, and its most important determinant is the ordering healthcare provider.”*
- ☀ *“Considerations should include options for answering the clinical question at hand by means that do not use ionizing radiation or choosing the type of study that exposes the patient to the lowest amount of radiation.”*
- ☀ *“Therefore: Physician education should emphasize that cardiac imaging studies that expose patients to ionizing radiation should be ordered only after thoughtful consideration of the potential benefit to the patient and in keeping with established appropriateness criteria.”*

Ionizing Radiation in Cardiac Imaging

- Health care professionals are obligated to provide prudent advice that includes appropriate decisions regarding the implementation of high-yield, diagnostic imaging testing. Importantly, the associated, inherent risks must be considered when scheduling these imaging studies including the indiscriminate use of ionizing radiation.
- The intrinsic value of performing a high quality TTE with contrast if clinically indicated must be viewed in the context of performing alternative or consecutive and comparable imaging studies.
- If the TTE study is deemed inadequate for technical reasons, the patient is often referred for an additional test and includes additional risks which are as follows: (1) TEE has an associated risk of death of 1:10,000; (2) nuclear imaging test including Sestamibi = 9mSv or Thallium = 41 mSv imaging test; (3) CT-angiogram (mSv = 12-18), and (4) a coronary angiogram (2-16 mSv).

**Thomas C. Gerber, J. Jeffrey Carr, Andrew E. Arai, Robert L. Dixon, Victor A. et al.,
Circulation Online Feb 2, 2009: DOI10.1161/CIRCULATIONAHA.108.1916502009**

American Society of Echocardiography

Consensus Statement on the Clinical Applications of Ultrasonic Contrast Agents in Echocardiography

SUGGESTED APPLICATIONS:

- ✦ Difficult-to-image patients: rest echocardiography with reduced image quality resulting in improved endocardial visualization and assessment when 2 contiguous segments are not seen on non-contrast images
- ✦ All patients presenting for rest echocardiographic assessment of LV systolic function (not solely difficult-to image patients)
- ✦ Reduce variability and increase accuracy in LV volume and LV ejection fraction (LVEF) measurements by 2-dimensional (2D) echocardiography

Mulvagh SL, Rakowski H, Vannan MA, et al. American Society of Echocardiography Consensus Statement on the Clinical Applications of Ultrasonic Contrast Agents in Echocardiography. J Am Soc Echocardiogr 2008;21:1179-201

American Society of Echocardiography

Consensus Statement on the Clinical Applications of Ultrasonic Contrast Agents in Echocardiography

- ✱ Increase the confidence of the interpreting physician in LV functional, structure, and volume assessments for stress echocardiography with reduced image quality
- ✱ Obtain diagnostic assessment of segmental wall motion and thickening at rest and stress increasing diagnostic studies
- ✱ To increase reader confidence in interpretation

Mulvagh SL, Rakowski H, Vannan MA, et al. American Society of Echocardiography Consensus Statement on the Clinical Applications of Ultrasonic Contrast Agents in Echocardiography. J Am Soc Echocardiogr 2008;21:1179-201;

American Society of Echocardiography

Consensus Statement on the Clinical Applications of Ultrasonic Contrast Agents in Echocardiography

- To reduce variability in LV volume measurements through 2D echocardiography
- To increase the confidence of the interpreting physician in LV volume measurement
- To confirm or exclude the echocardiographic diagnosis of the following LV structural abnormalities, when nonenhanced images are suboptimal for definitive diagnosis
 - Apical variant of hypertrophic cardiomyopathy
 - Ventricular non-compaction
 - Apical thrombus
 - Complications of myocardial infarction, such as LV aneurysm, pseudoaneurysm, and myocardial rupture
- To assist in the detection and correct classification of intracardiac masses, including tumors and thrombi

Mulvagh SL, Rakowski H, Vannan MA, et al. American Society of Echocardiography Consensus Statement on the Clinical Applications of Ultrasonic Contrast Agents in Echocardiography. *J Am Soc Echocardiogr* 2008;21:1179-201

European Association of Echocardiography

Contrast echocardiography: Evidence-based Recommendations

March 2009

Indications for resting left ventricular opacification contrast echo in patients with suboptimal images:

- ✱ Improve endocardial visualization and assessment of LV structure and function when two or more contiguous segments are NOT seen on non-contrast images
- ✱ Provide accurate and precise measurements of LV volumes, and ejection fraction
- ✱ Confirm or exclude the echocardiographic diagnosis of the following LV structural abnormalities, when non-enhanced images are suboptimal for definitive diagnosis:
 - (a) apical hypertrophic cardiomyopathy
 - (b) ventricular non-compaction
 - (c) apical thrombus
 - (d) ventricular pseudoaneurysm

Senior R, Becher H, Monaghan M, et al. Contrast echocardiography: evidence-based recommendations by European Association of Echocardiography. Eur J Echocardiogr 2009;10:194-212

European Association of Echocardiography

Contrast echocardiography: Evidence-based Recommendations March 2009

Indications for contrast use in stress echocardiography:

- ★ When two or more endocardial border contiguous segments of LV are not well visualized in order to:
- ★ To obtain diagnostic assessment of segmental wall motion and thickening at rest and stress
- ★ To increase the proportion of diagnostic studies
- ★ To increase reader confidence in interpretation

Senior R, Becher H, Monaghan M, et al. Contrast echocardiography: evidence-based recommendations by European Association of Echocardiography. Eur J Echocardiogr 2009;10:194-212

I • C • U • S

**International Contrast
Ultrasound Society**