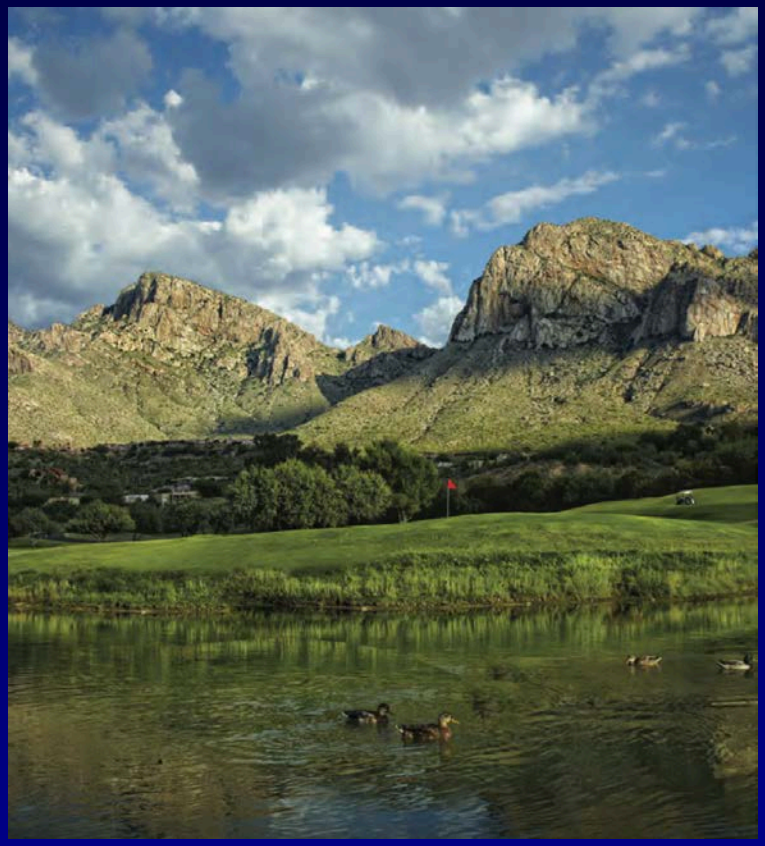


I Hear Contrast is Not Safe, Is That True?

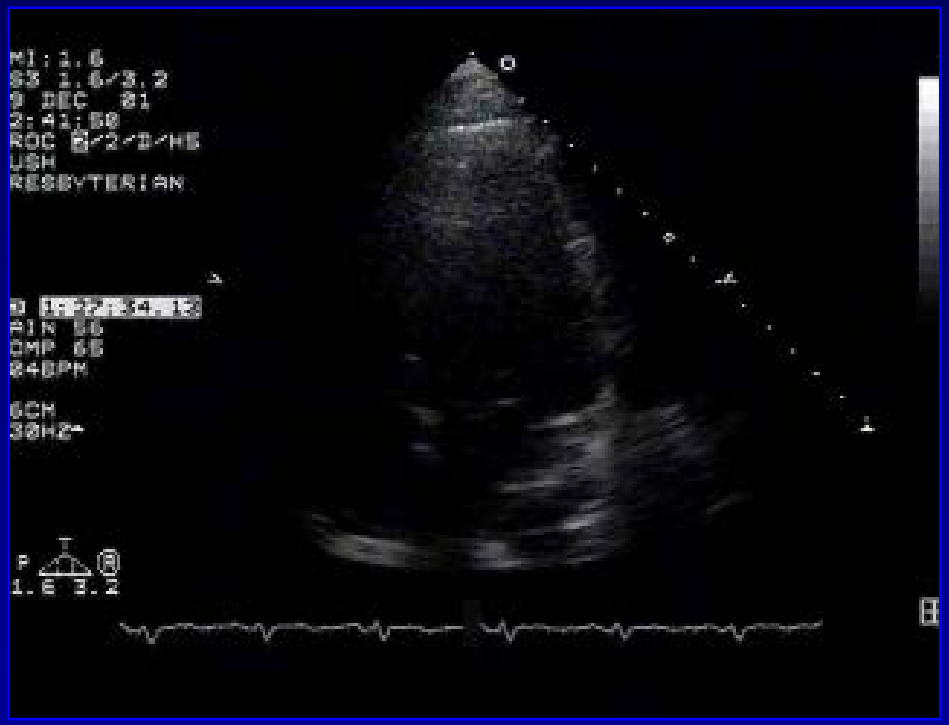
State-of-the-Art ECHOCARDIOGRAPHY: ECHO SOUTHWEST 29th ANNUA

THE UNIVERSITY OF CHICAGO
CARDIAC IMAGING CENTER

Roberto M. Lang, MD

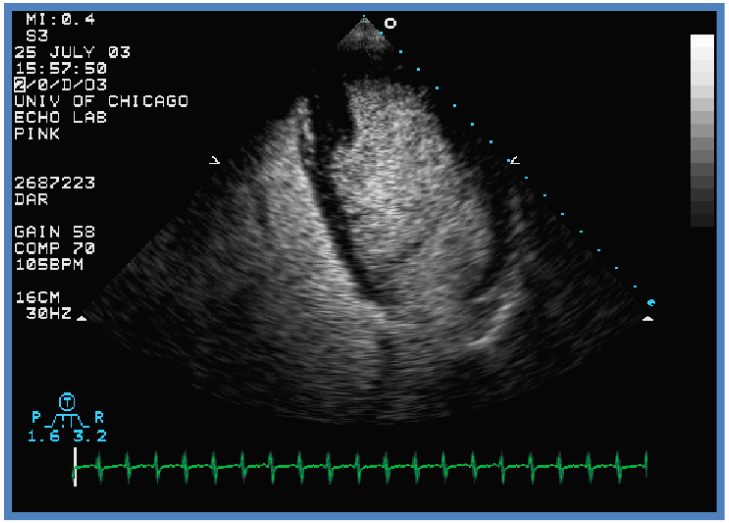
Suboptimal Images: Consequences

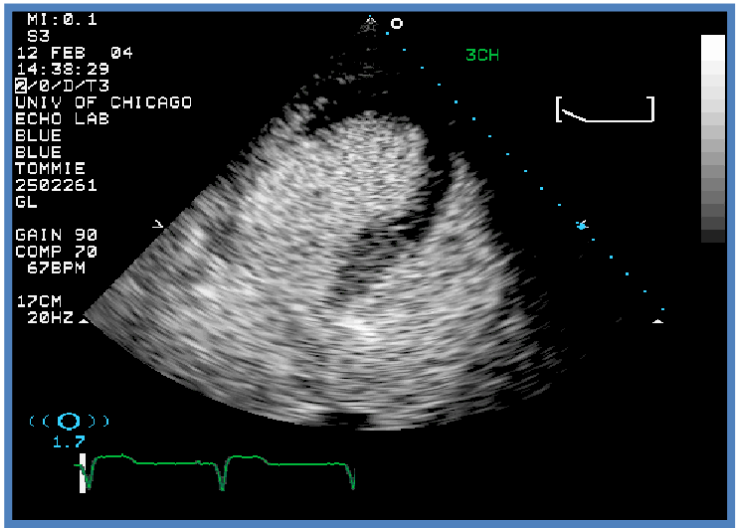
- Misdiagnosis
- Low diagnostic confidence
- Need for additional testing procedures
- Interobserver variability



Ikonomidis et al. *Coronary Artery Dis*. 1998;9:567.
Zotz et al. *J Am Soc Echocardiogr*. 1996;9:1.

FDA Approved Contrast Agents



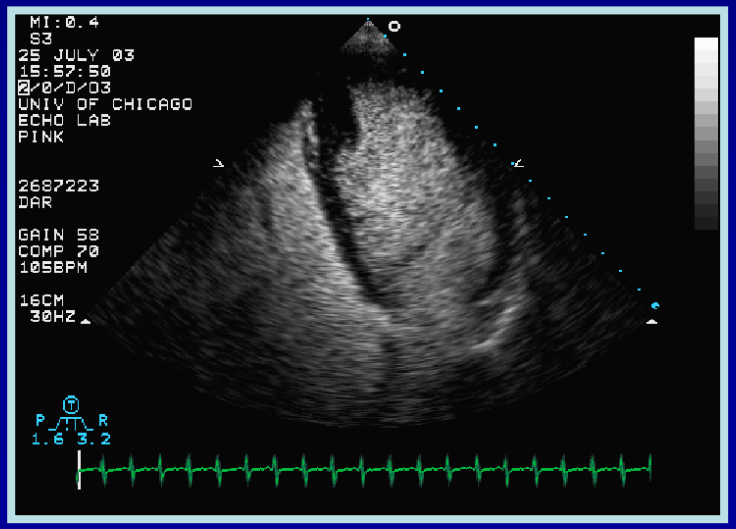


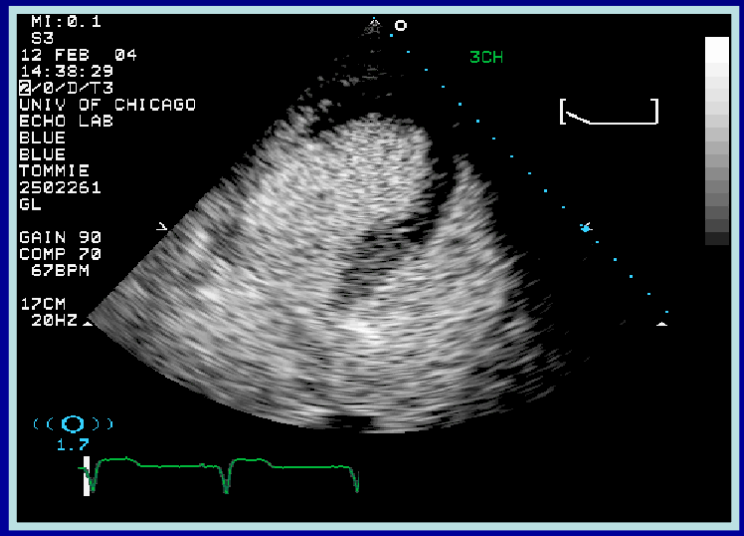
Agent	Size (µm)	Gas	Shell	Indication
Optison	3.0-4.5	Perflutren	Albumin	LVO/EBD
Definity	1.3-3.3	Perflutren	Phospholipid	LVO/EBD
Lumason (Sonovue)	1.5-2.5	Sulfur hexafloride	Phospholipid	LVO/EBD

Contrast Applications

- **Left Ventricular Opacification (LVO)**
  - **Contrast agent used as marker for blood pool**
  - **Better endocardial border visualization, i.e. Wall Motion**

- **Myocardial Contrast Enhancement (MCE)**
  - Contrast agent used as marker for blood flow in capillary beds, microcirculation
  - Optimized to see low concentrations of agent in myocardium





Contrast Echo: Weaknesses Underutilization

- Lack of awareness of indications?
- Technology too complicated
- IV initiation?
- Cost/reimbursement? Acceptance of mediocrity
- Inertia?
- Lingering concerns about safety?

FDA Post Marketing Survey

- Temporally related, but not clearly causally attributable to Definity
  - (4 patients deaths and approx 190 “serious cardiopulmonary reactions”)
- October 12, 2007
  - FDA Black BOX Warning
- May 12, 2008:
  - Revision of Black Box Warning

http://www.fda.gov

FDA Black Box Warning on 10/12/07

- **Precluded the use of Perflutren-containing ultrasound contrast agents in the following**
  - **Worsening or clinically unstable CHF**
  - **Acute MI or ACS**
  - **Serious ventricular arrhythmias**
  - **Respiratory failure**
  - **Severe emphysema**
  - **Pulmonary embolus**
  - **Conditions that cause pulmonary hypertension**
  - **Right-to-left, bidirectional, or transient right-to-left cardiac shunts**
  - **Hypersensitivity to Perflutren**
  - **Intra-arterial injection**

http://www.fda.gov

All Patients: 30 minutes observation period with vital signs, ECG, o2 sat monitoring

Contrast Echocardiography as % of echos in USA

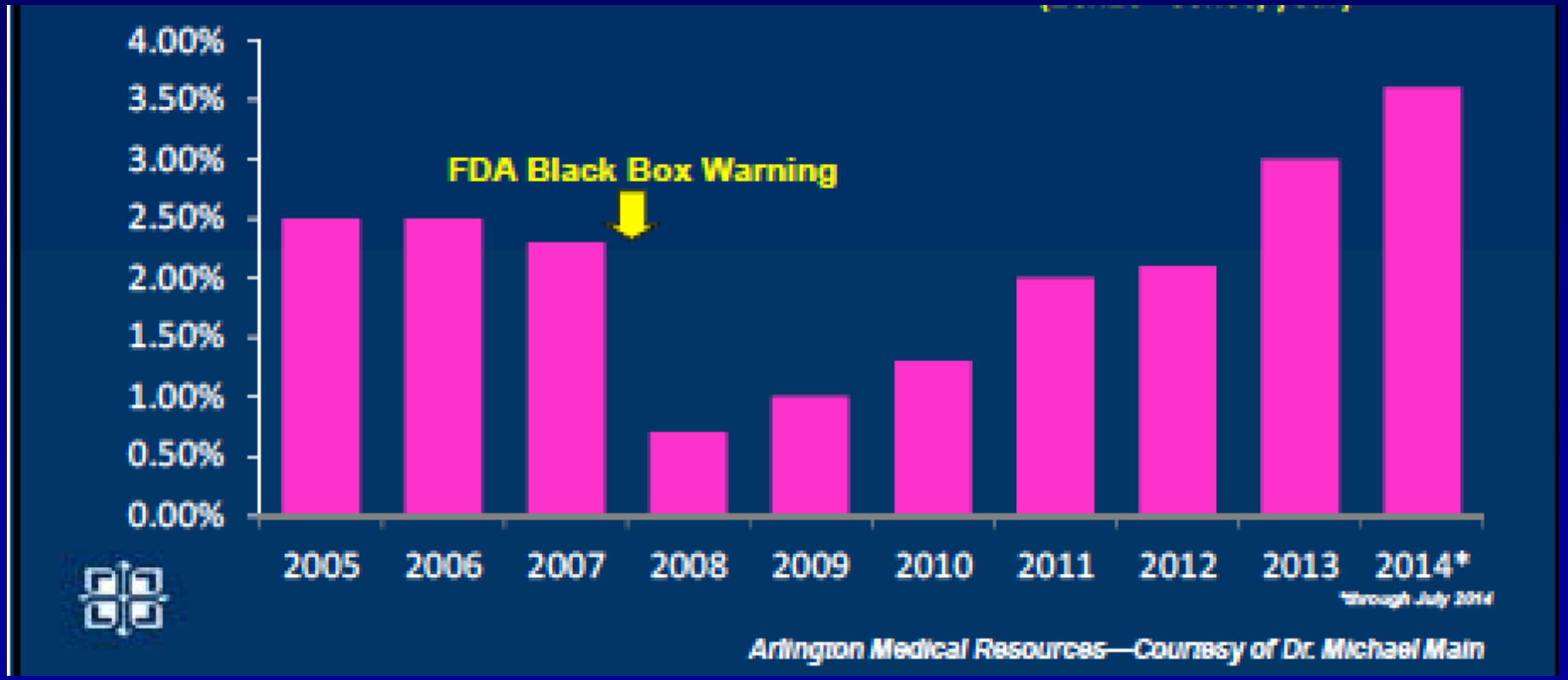


Table 5. Previous Reports on the Safety of Ultrasound Contrast Agents in 2008

	Kusnetzky et al., 2008 (16)	Herzog, 2008 (15)	Wei et al., 2008 (14)	Gabriel et al., 2008 (17)	Main et al., 2008 (18)	Shaikh et al., 2008 (19)	Dolan et al., 2009 (20)	Aggeli et al., 2008 (21)
Site(s)	1*							
Number of patients	18							
Population included	Ho							
Type of echo study	Re							
Number of patients: contrast vs. noncontrast	6,1							0
Outcome of interest	De							ents after f contrast CTCAE
Event rate (%)	Co							requiring 2 (0.04%) equiring 10 (0.18%) ctions in equiring

*Saint Luke's Health System, Kansas City, Missouri. †Hennepin County Medical Center, Minneapolis, Minnesota. ‡From the Oregon Health and Science University, Portland, Oregon; Mayo Clinic, Rochester, Minnesota; Baptist Memphis Department of Echocardiography, Memphis, Tennessee; Boston Medical Center, Boston, Massachusetts; Cleveland Clinic, Cleveland, Ohio; Foothills Medical Centre, Calgary, Alberta, Canada; Hennepin Heart Center at Hennepin County Medical Center, University of Minnesota, Minneapolis, Minnesota; Methodist DeBakey Heart and Vascular Center, Houston, Texas; North Kansas City Hospital, North Kansas City, Missouri; St. Luke's-Roosevelt Hospital Center, Columbia University College of Physicians & Surgeons, New York, NY; University of Nebraska Medical Center, Omaha, Nebraska; Vanderbilt Heart and Vascular Institute, Nashville, Tennessee; and the University of Chicago, Chicago, Illinois. §Cleveland Clinic, Cleveland, Ohio. ||Premier Perspective Database is the largest United States hospital-based database and contains information from approximately 5.5 million patient discharges per year from not-for-profit, nongovernmental, community and teaching hospitals, and health systems. ¶The Methodist Hospital and the Methodist DeBakey Heart and Vascular Center Imaging Institute, Houston, Texas. #Saint Louis University Hospital, St. Louis, Missouri; University of Nebraska Medical Center, Omaha, Nebraska; and the Mayo Clinic, Rochester, Minnesota. **University of Athens, First Cardiology department, Hippokration Hospital, Athens, Greece.

CI = confidence interval; CTCAE = Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events version 3.0; ICU = intensive care unit; TTE = transthoracic echocardiography; VF = ventricular fibrillation; VT = ventricular tachycardia; other abbreviations as in Table 1.

>200000 cardiac patients world-wide, carefully documented, have received echo contrast without evidence of increased death or serious cardiac event

Abdelmoneim SS, Mulvagh SL, J Am Coll Cardiol Img 2009; 2:1048-56

Safety Studies

CLINICAL INVESTIGATIONS
CONTRAST ECHOCARDIOGRAPHY

The Safety of Definity and Optison for Ultrasound Image Enhancement: A Retrospective Analysis of 78,383 Administered Contrast Doses

Kevin Wei, MD, Sharon L. Mulvagh, MD, Lisa Carson, MSc, Ravin Davidoff, MD, Ruvin Gabriel, MB, ChB, Richard A. Grimm, DO, Stephanie Wilson, MD, Lorrie Fane, RDCS, Charles A. Herzog, MD, William A. Zoghbi, MD, FASE, Rhonda Taylor, AS, RDCS, Michael Farrar, MD, Farooq A. Chaudhry, MD, Thomas R. Porter, MD, Waleed Irani, MD, FASE, and Roberto M. Lang, MD, FASE,
Portland, Oregon; Rochester, Minnesota; Memphis, Tennessee; Boston, Massachusetts; Cleveland, Ohio; Alberta, Canada; Minneapolis, Minnesota; Houston, Texas; Kansas City, Missouri; New York City, New York; Omaha, Nebraska; Nashville, Tennessee; and Chicago, Illinois

This multicenter, retrospective analysis includes the largest number of doses of ultrasound contrast agents **ever published with a large number of patients evaluated in a wide variety of settings, including the critically ill.**

(J Am Soc Echocardiogr 2008;21:1202-1206)

Safety of Definity and Optison

- Contrast agents: 5% of TTE and in 28% of stress studies
- Severe reactions probably related to contrast agents developed in 8 patients (0.01%)
- 4 were anaphylactoid reactions (CARPA)
- Incidence of adverse reactions is lower than that reported for contrast agents commonly used in other cardiac imaging tests
  - Urticaria 0.5%
  - Sudden hypotension 0.3%
  - Cardiac arrest 0.2%

(J Am Soc Echocardiogr 2008;21:1202-1206)

Retrospective analysis of a large database of hospitalized patients undergoing echocardiography compared the acute effects of Definity-enhanced echocardiograms (n=58,254) with un-enhanced studies (n=4,242,712).

While the one-day mortality rates were similar for un-enhanced and contrast studies (1.08 vs. 1.06%), on multivariate logistic regression analysis, those receiving Definity were 24% less likely to die within one day than those not receiving contrast.

Main ML, Ryan AC, Davis TE et al. 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 and efficacy of contrast for stress echo was retrospectively analyzed in 42,408 patients from three centers.

The risks of both non-fatal myocardial infarction and death were very low (1 death and 5 nonfatal infarctions within 24 hours) and no different than a matched cohort of 18,749 patients who underwent stress echo without contrast.

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.

Comparative Mortality in Selected Cardiac Procedures

Procedures	Mortality
Contrast Echo	1:45,000 (SonoVue) 1: 500,000 (Definity)
Myocardial Scintigraphy	1:10,000
Exercise EKG	1:2500 (or AMI)
Coronary arteriography	1:1000

European Journal of Echocardiography (2009) 10, 194–212

Contrast Ultrasound Anaphylactoid Reactions

CARPA
Complement Activation Related Pseudo Allergy

- Ig-E mediated Type 1 reaction
- Angioedema, bronchospasm, hypoxemia, hypotension, LBP, and urticaria
- Reaction arises at first TX, milder or absent with repeated exposures

Contrast Ultrasound Anaphylactoid Reactions Complement Activation Related Pseudo Allergy CARPA

C Activation-related Related Pseudo-allergy and not via Ig-E mediated Type 1

1. Angioedema, bronchospasm, chest pain, lumbar pain, wheezing
2. Reaction arises at first treatment
3. Reaction is milder or absent upon repeated exposures
4. Spontaneous resolution
5. Reaction rate is high

Szebeni J. Toxicology 2005; 216:106-21

FDA Black Box Warning

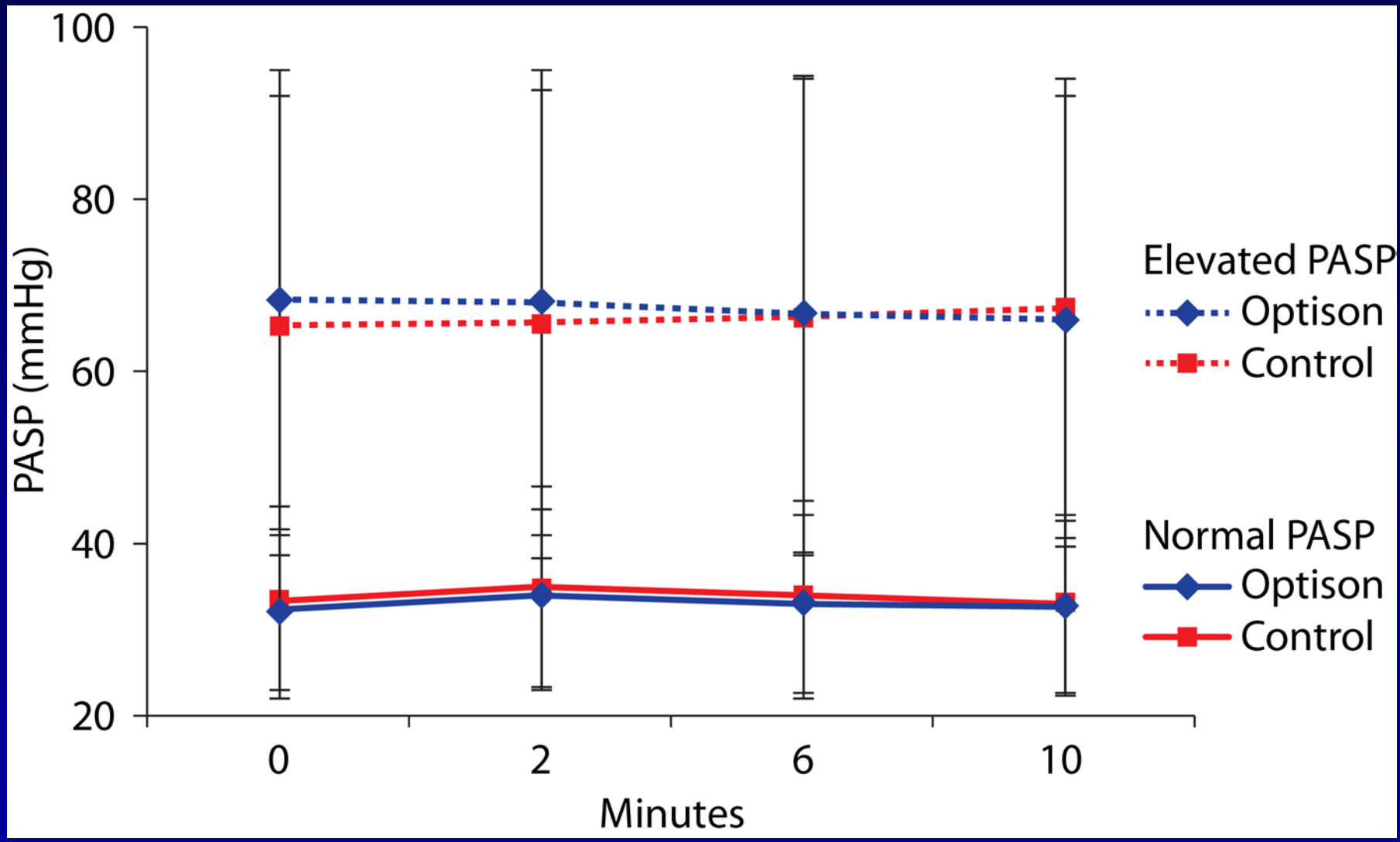
- Response from international physician community
- New contrast agent safety data published
- Special meeting of FDA Cardio-renal Panel, (May 12, 2008)
- Revision of Black Box warning (May 12, 2008
- FDA mandated that safety studies be performed in patients with pulmonary hypertension

FDA Revised Contrast Agents Labeling on May 12, 2008

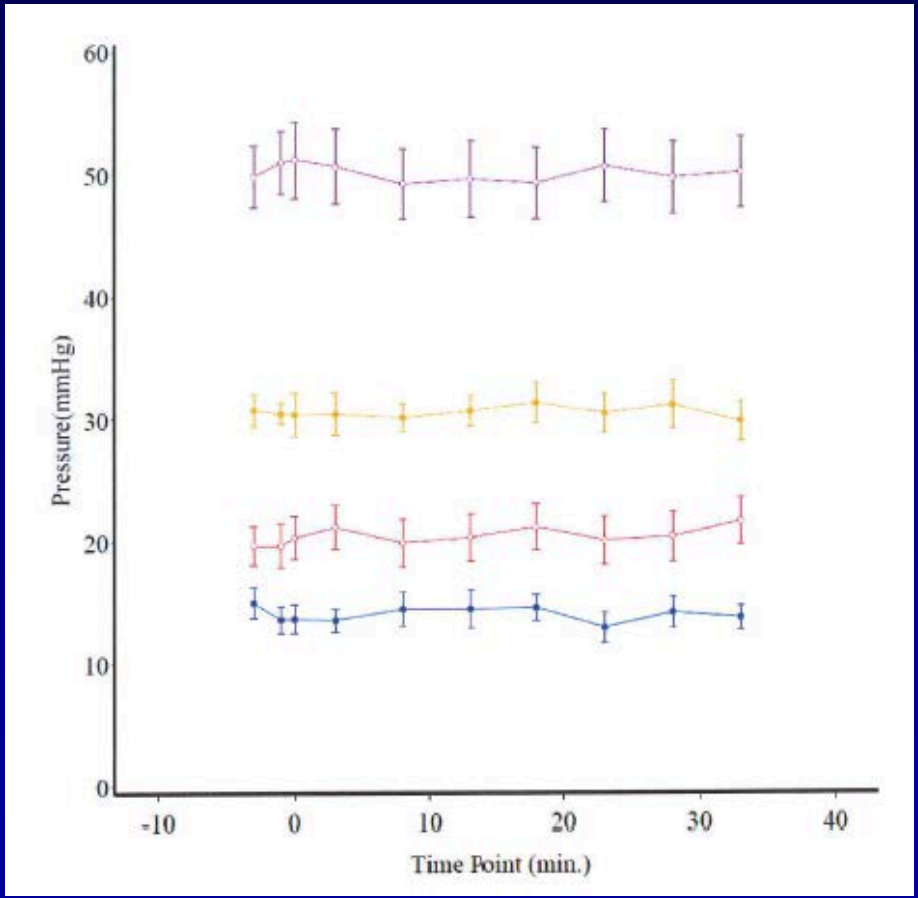
- Black Box remains, but contraindications to contrast agents restored to original labeling
- Right-to-left, bidirectional, or transient right-to-left cardiac shunts
- Hypersensitivity to Perflutren, to blood, to blood products, or albumin
- Intra arterial injection
- 30 min observational period (ECG, O2 sat after Contrast administration in pts with Pulmonary HTN and unstable cardiopulmonary conditions

http://www.fda.gov

The Effect of Optison on Systemic and Pulmonary Hemodynamics in Normal Subjects and Patients with Pulmonary Hypertension



The Effect of Definity on Systemic and Pulmonary Hemodynamics in Patients with Pulmonary Hypertension



Wei K, Main M, Lang RM, Klein A, Angeli S, Panetta C, Mikati, ,Lee L, Ahmad M

The Effect of Definity on Systemic and Pulmonary Hemodynamics

- Definity® at the approved dosage does not change pulmonary or systemic hemodynamics in control patients or those with mild to moderate pulmonary hypertension.
- No significant changes were noted clinical or laboratory safety assessments after Definity®.

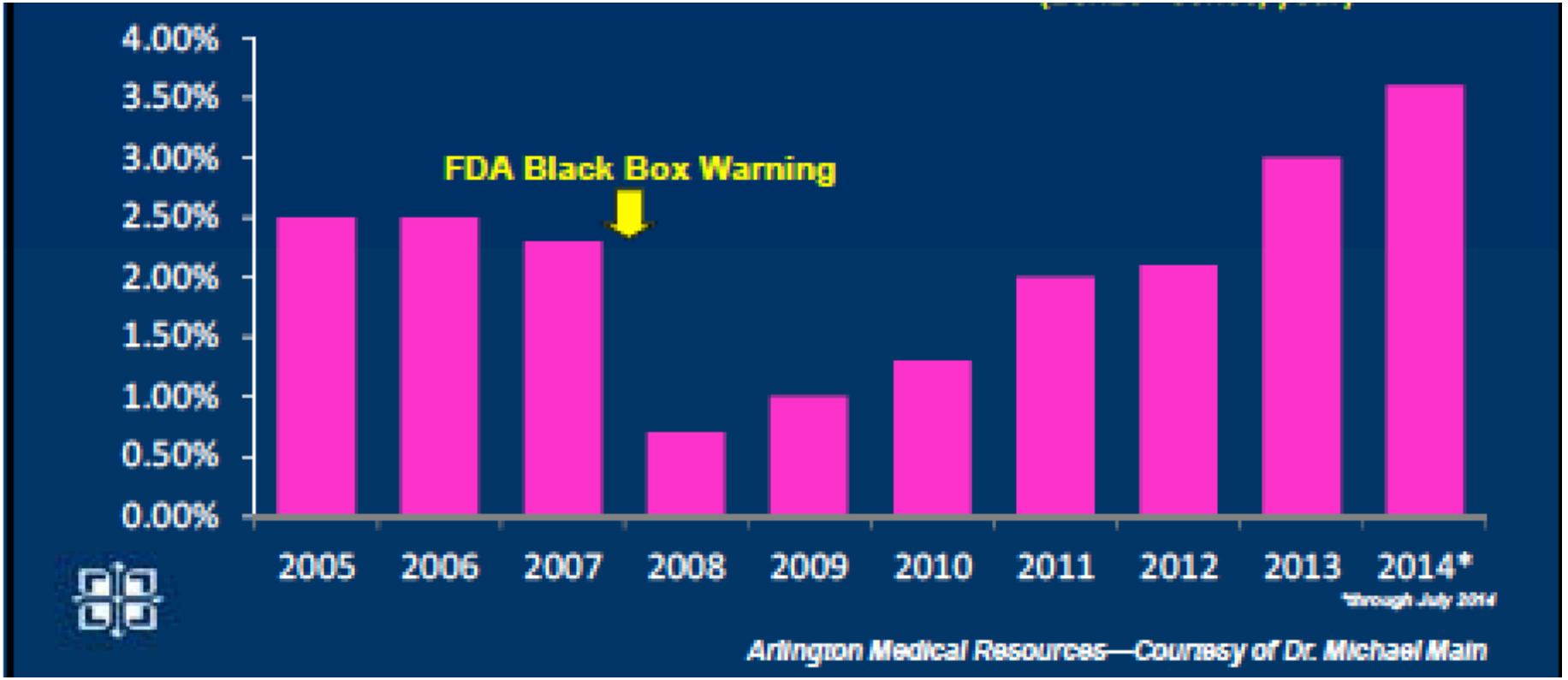
Wei K, Main M, Lang RM et al., 2011

Black Box

Do not administer Perflutren to patients with

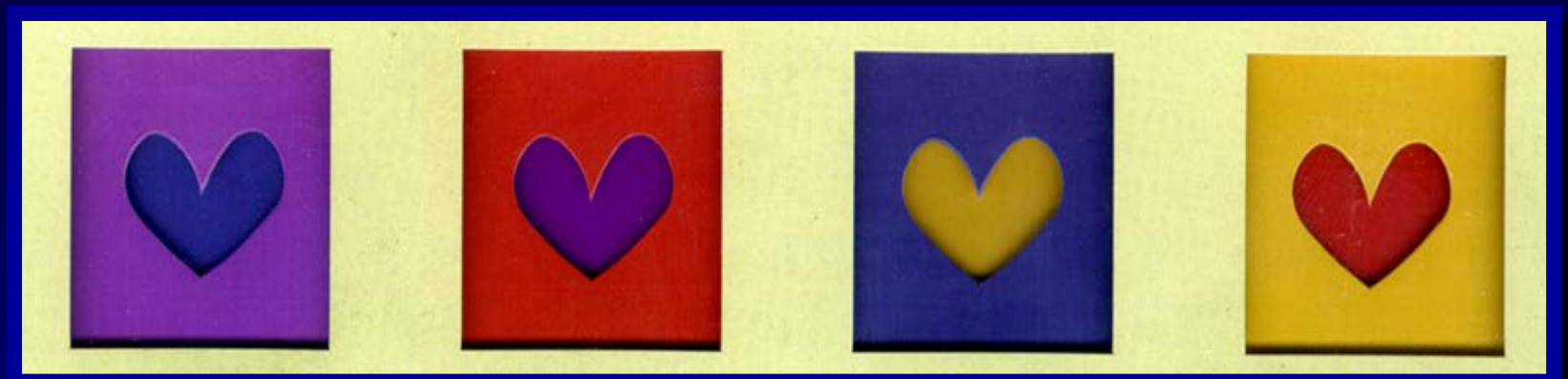
1) **Known or suspected right-to-left, bidirectional, or transient right-to-left cardiac shunts**
2) **Hypersensitivity to perflutren**
3) **Do not administer intra-arterial injection**
4) ***Monitoring only in patients with pulmonary hypertension or unstable cardiopulmonary conditions***

Contrast Echocardiography as % of echos in USA

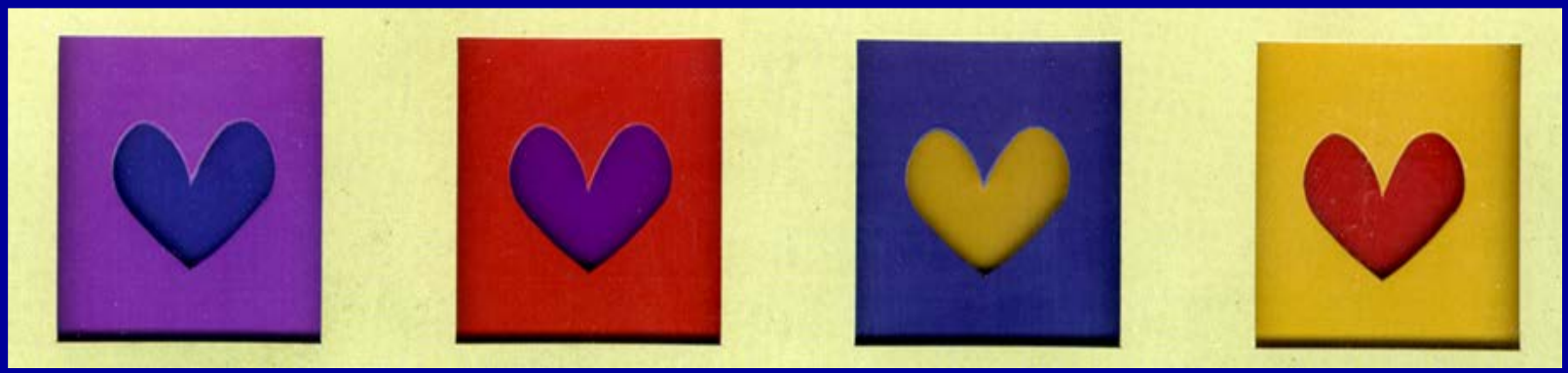


Safety of Ultrasound Contrast Agents

- Life threatening reactions are rare (<1:10,000)
  - Less than with contrast agents used in other imaging modalities
- Labs must have policies/procedures for early recognition/Rx of serious anaphylactic reactions
- Pulmonary hypertension does not preclude UCA use
- Patients with PFO are not at increased risk with UCA use
  - JACC Imaging 2014;7:206, J Am Soc Echocardiogr 2013; 112; 1039



Thanks for your attention



Side Effects

Most frequent side effect in clinical trials	Optison (GE)	Definity (Lantheus Medical Imaging)	Lumison (Bracco)
Most frequent side effect in clinical trials	Headache (5.4%) Nausea (4.3%) Flushing (3.6%) Dizziness 2.5%	Headache (2%) Flushing (1.0%) Back pain (0.9%) Urticaria, wheezing/anaphylaxis	Headache (2.1%) Nausea (1.3%) Taste perversion (0.9%) Hyperglycemia (0.6) Paresthesia (0.6%)

Summary Safety

- Ultrasound contrast safety is a complex issue; need to consider low risk of contrast agent side effect in sick patients, risk of misdiagnosis/missed diagnosis, and risks of alternative procedures
- No significant safety signal in >200,000 patient doses of contrast agents, low incidence of side effects (less current X-ray or MR contrast agents)
- Approximately 1/10,000 risk of an anaphylactoid reaction
- There is no increase in crude mortality in hospitalized patients undergoing MCE