Joint Meeting of the Cardiovascular and Renal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee

DEFINITY®

May 2, 2011

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Presenters

- **Dana Washburn, MD**
  VP, Clinical Development & Medical Affairs
  Lantheus Medical Imaging
- **Mark Hibberd, MD, PhD**
  Senior Medical Director,
  Global Medical Affairs & Pharmacovigilance
  Lantheus Medical Imaging
- **Michael Main, MD**
  Medical Director, Echocardiography Laboratory
  Saint Luke's Mid-America Heart Institute
  Professor of Medicine, University of Missouri-Kansas City

Overview

- **Introduction**
- **Pharmacovigilance Safety Data**
- **Post-Marketing Studies**
- **Benefit-Risk Assessment**
- **Labeling Recommendation**

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Introduction

- **DEFINITY® microsphere**
  - Perflutren gas and outer lipid shell
- **Indication**
  - Patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border
- **Pharmacokinetics**
  - Circulation $t_{1/2}$ 1.3 minutes
  - Perflutren not detectable after 10 minutes in blood or expired air

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DEFINITY® Pharmacovigilance

Mark Hibberd, MD, PhD
Senior Medical Director,
Global Medical Affairs & Pharmacovigilance

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Lantheus Safety Reporting System

- **Pro-active Pharmacovigilance System**
  - –Spontaneous AE case reporting
    - From HCPs via toll free number or website link
    - From employees, contractors, and distributors in AE reporting worldwide
    - Via weekly literature review for AEs
  - –Risk Management Plan (EU)
  - –Independent Data Monitoring Committee

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Pharmacovigilance Summary Since Last Advisory Committee Meeting

- **No new adverse safety signals**
- **Adverse event rates are stable**
- **SAEs typically occurred in patients with confounding factors**
  - –Significant underlying disease
  - –Concomitant medications
  - –Physiologic/Pharmacologic stress

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Spontaneous SAE Reports

- **Since the last Advisory Committee Meeting 12/28/2007 through 12/27/2010**

	Cases (N)	Rate
All Serious	169	Less than 1 in 6,000
Cardiopulmonary	45	Less than 1 in 24,000
Anaphylaxis	23	Less than 1 in 47,000

No meaningful change in type or frequency of reported events

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AEs with Fatal Outcomes

- **Since the last Advisory Committee Meeting 12/28/2007 through 12/27/2010**
- **Cases with fatal outcomes, N=10 (less than 1 in 110,000)**
  - **Time to onset ≤ 30 minutes, N=6**
    - **Cardiac arrest with dobutamine co-administration, N=2**
    - **Anaphylactic reaction plausible, N=2**
    - **Acutely progressive underlying disease, N=2**

Fatal case rates unchanged since 2008

Risk of Diagnostic Testing

Procedure	Event Rate[2]
Coronary Angiography	1:1,000
Exercise Treadmill Testing	1:2,500
SPECT Imaging	1:1,000 to 1:10,000
TEE	1:10,000
Contrast TTE	1:100,000

[2] Main et al. J Am Coll Cardiol 2007;50:2434–7

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Post-Marketing Studies

Michael Main, MD
Medical Director, Echocardiography Laboratory
Saint Luke's Mid-America Heart Institute
Professor of Medicine, University of Missouri-Kansas City

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Post-Marketing Safety Studies

- **Retrospective ICU Study**
  - –Mortality Assessment in Critically Ill Patients (DMP 115-418)
- **Pulmonary Hemodynamic Study**
  - –Prospective Study, in Patients with Elevated Pulmonary Artery Systolic Pressure (DMP 115-416)
- **Registry Study**
  - –Prospective Registry Study, Routine Clinical Practice (DMP 115-415)

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Retrospective ICU Study – Methods

- **Premier Perspective™ database (1 Jan 2002-15 Jun 2008)**
  - Largest U.S. hospital inpatient clinical database
  - Date-stamped log of all billed items for individual patients
- **1,008,206 ICU patients identified**
  - TTE (ICD-9 codes) on the same day as ICU stay
  - **991,983** non-contrast (from 536 facilities)
  - **16,223** DEFINITY® (from 199 facilities)

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Retrospective ICU Study – Methods

- Propensity Score Matching was performed and used to construct contrast and non-contrast control cohorts that have similar distributions of:
  - Demographics - age group, gender, race, hospital bed size, geographic region, urban/rural population, teaching hospital, admission type, severity of illness, risk of mortality, discharge status, attending physician specialty
  - Comorbid conditions - Myocardial Infarction, Congestive Heart Failure, Acute coronary syndromes, Ventricular arrhythmias, Pulmonary Hypertension, Hypertension, Intra-aortic balloon pump, Cardiogenic shock, Renal Failure, Venous catheterization for renal dialysis, Hemodiafiltration, Peritoneal dialysis, Diabetes, Chronic Obstructive Lung Disease, Pneumonia, Mechanical ventilation, Continuous positive airway pressure, Stroke, Sepsis, Septic shock, Anaphylatic shock, Gastrointestinal hemorrhage, Transfusion procedure

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Retrospective ICU Study – Methods

- **"Greedy Match"**
  - Trade off between strength of match (# of decimal places) vs. patients included (% matched)
- **Matched Dataset (5-decimal) 31,596 patients**
  - **15,798** non-contrast (from 480 facilities)
  - **15,798** DEFINITY® (from 199 facilities)

Decimal Place	Number of Pts	% Matched
9	12,922	39.8%
8	14,570	44.9%
7	22,026	67.9%
6	28,728	88.5%
5	**31,596**	**97.4%**
4	32,316	99.6%
3	32,382	99.8%

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Primary Endpoint: 48-hour post echocardiogram all-cause mortality

	Matched Dataset				
	N	Died (n)	% died	Odds ratio[a]	95% CI
Non-Contrast Group	**15,798**	**488**	**3.09%**	**0.683**	**(0.591, 0.789)**
DEFINITY® Group	**15,798**	**338**	**2.14%**		

[a] Full model logistic regression adjusted odds ratio
Note: Cochran-Mantel-Haenszel odds ratio for matched dataset = 0.686 with 95% CI = (0.596, 0.789)

In the matched data DEFINITY® administration was associated with a 32% lower mortality.

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Secondary Endpoint: In-hospital all-cause mortality

	Matched Dataset				
	N	Died (n)	% died	Odds Ratio[a]	95% CI
Non-Contrast Group	**15,798**	**2,616**	**16.56%**	**0.834**	**(0.779, 0.892)**
DEFINITY® Group	**15,798**	**2,321**	**14.69%**		

[a] Full model logistic regression adjusted odds ratio

Note: Cochran-Mantel-Haenszel odd's ratio for Matched Dataset = 0.868, 95% CI (0.817, 0.922)

In the matched data DEFINITY® administration was associated with a 17% lower mortality throughout hospital stay.

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48-hour Mortality by Comorbidity

	Non-Contrast Group N=15,798			DEFINITY® Group N=15,798			p-value
Co-morbid Condition	N	Deaths (n)	%	N	Deaths (n)	%	
Congestive heart failure	7,410	196	2.7%	7,340	146	2.0%	0.008
Myocardial infarction	5,841	204	3.5%	5,758	135	2.3%	<0.001
Acute coronary syndromes	696	7	1.0%	712	4	0.6%	0.156
Pulmonary hypertension	1,566	54	3.5%	1,592	34	2.1%	0.025
Cardiogenic shock	1,134	106	9.4%	1,052	66	6.3%	0.008
Mechanical ventilation	5,647	336	6.0%	5,675	235	4.1%	<0.001

Across a range of co-morbidities, the survival advantage in the DEFINITY® group was maintained.

Pulmonary Hemodynamic Study – Design & Objectives

- **32 patients at 7 sites**
  - –16 patients with PASP >35 mmHg at baseline
  - –16 patients with PASP <=35 mmHg at baseline

- **Primary Objective**
  - –Pulmonary artery hemodynamics in patients undergoing right heart catheterization
- **Secondary Objectives**
  - –Safety and potential immunologic effects of DEFINITY® administration

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Pulmonary Hemodynamic Study – Procedures

- **Right heart catheterization**
- **Safety monitoring**
  - Vital signs, clinical labs, pulmonary hemodynamic monitoring, immune response
- **DEFINITY® administration**
- **30-minute pulmonary hemodynamic monitoring**
- **60-minute safety monitoring**
  - Vital signs, clinical & immune response labs, 12-lead ECG
- **Adverse event follow-up 24±8 hours**
- **Serious adverse event follow-up 4±3 days**

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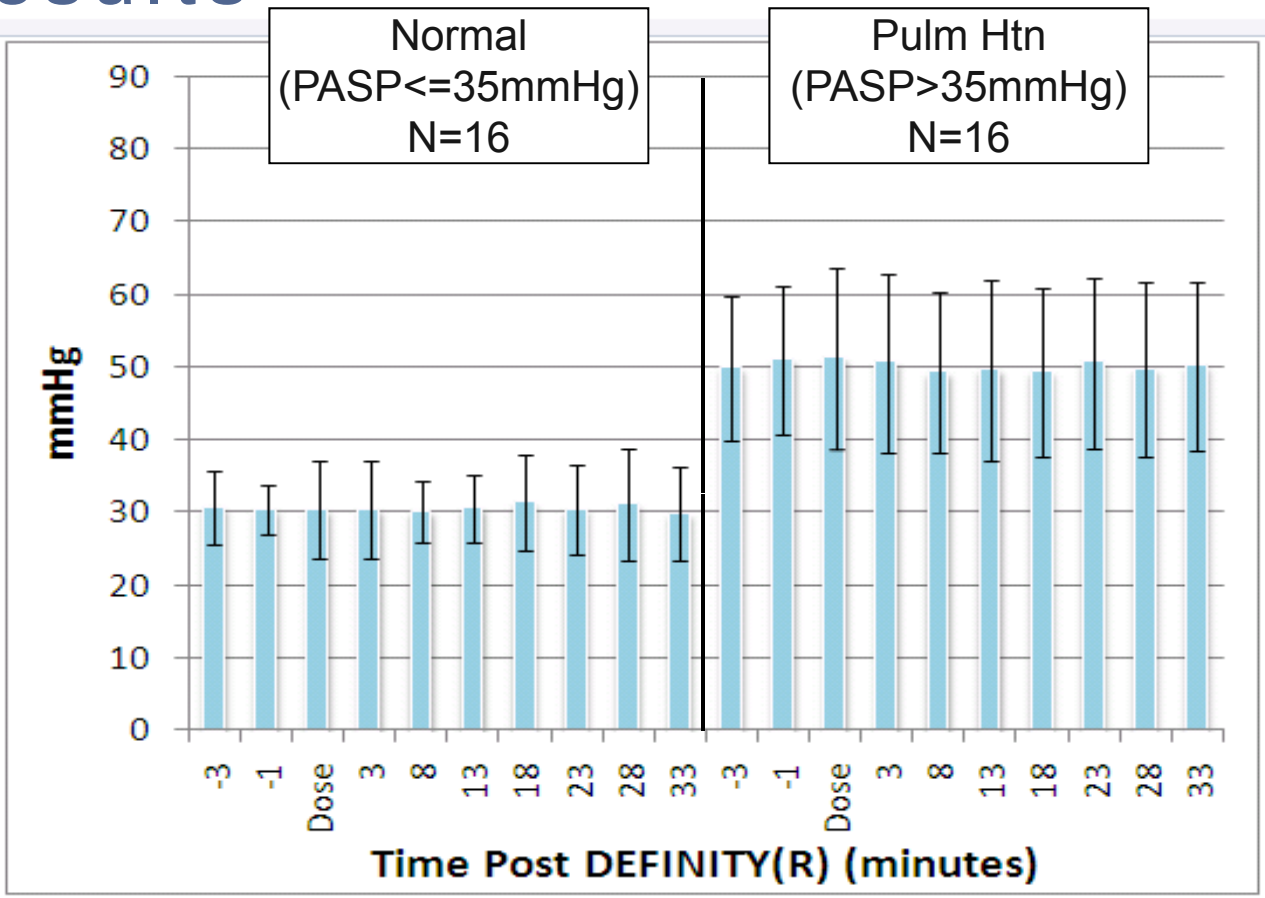
Pulmonary Hemodynamic Study – Results



No significant change post-dose in either group

Pulmonary Hemodynamic Study

- **No change in PASP associated with DEFINITY®**
- **No deaths or SAEs**
- **Similar AE profiles in both groups**
- **No change in immunological parameters (C3a, C5a, tryptase, IL-6)**

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Registry Study – Design & Objectives

- **1053 patients at 15 sites**
- **DEFINITY® Dosing (rest, stress, or both)**
- **30-minute safety monitoring**
  - Pre-dose, 5 min, 15 min, and 30 min assessments
  - Vital signs, ECG abnormality, O_2 saturation by pulse oximetry
- **Adverse event follow-up to 24±4 hours**

- **Primary Objective**
  - Life-threatening cardiopulmonary events within 30 minutes
- **Secondary Objective**
  - All adverse events within 24 hours

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Registry Study – Population

- **Population had significant cardiac conditions:**
  - –Previous MI: 20.7%
  - –PCI/CABG: 30.9%
  - –Cardiomyopathy: 19.8%
  - –Congestive Heart Failure: 21.3%
  - –Acute Coronary Syndrome: 10.3%
  - –Hypertension: 65.3%
  - –Other Cardiac Conditions: 80.1%
  - –4 or more Cardiac Medications: 49.9%

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Registry Study – Safety Results

- **No deaths or life-threatening cardiopulmonary events occurring within 30 minutes**
- **No SAEs within 24 hours of DEFINITY® dosing**
- **Non-serious AE profile**
  - –Patients with at least 1 adverse event: 10.8%
  - –Adverse Events seen at ≥0.5%
    - Tremor 1.4%, Headache 1.2%, Nausea 0.9%, Back Pain 0.7%
  - –Adverse Events attributable to study drug: 3.5%
  - –Adverse Events attributable to stress test: 15.4%

No new safety findings

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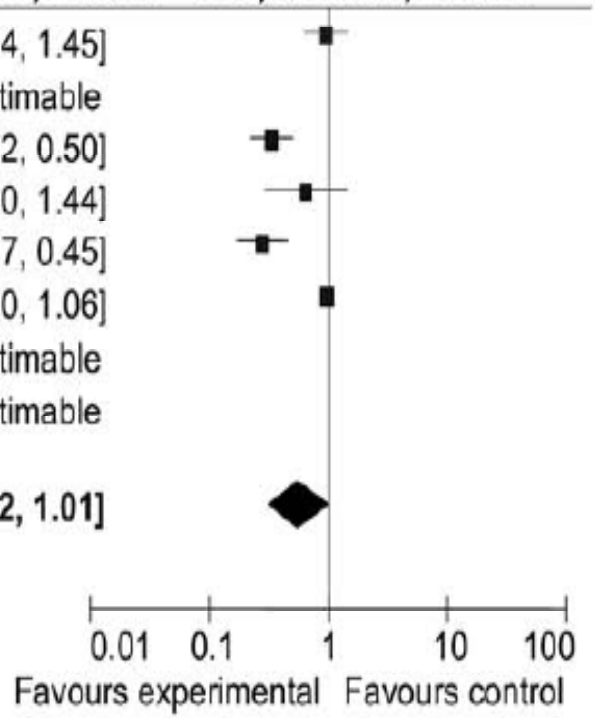
Meta-Analysis of Cardiovascular Events

Study or Subgroup	Contrast Events	Contrast Total	No Contrast Events	No Contrast Total	Weight	Odds Ratio M-H, Random, 95% CI
Abdelmoneim	37	10792	57	15982	20.6%	0.96 [0.64, 1.45]
Anantharam	0	1150	0	2554		Not estimable
Dolan	37	42408	62	23812	20.7%	0.33 [0.22, 0.50]
Gabriel	10	4786	16	5012	16.0%	0.65 [0.30, 1.44]
Kusnetzky	26	12475	46	6196	19.8%	0.28 [0.17, 0.45]
Main	616	58254	45789	4242712	23.0%	0.98 [0.90, 1.06]
Shaikh	0	2914	0	2155		Not estimable
Wei	0	78383	0	780243		Not estimable
Total (95% CI)		**211162**		**5078666**	**100.0%**	**0.57 [0.32, 1.01]**
Total events	726		45970			

Heterogeneity: $Tau^2 = 0.36$; $Chi^2 = 50.27$, df = 4 ($P < 0.00001$); $I^2 = 92\%$

Test for overall effect: $Z = 1.93$ ($P = 0.05$)



Khawaja et al. Am J Cardiol 2010;106:742-747

Summary of Allergic Events

Incidence of allergic/anaphylactic reactions with echocardiography contrast agents

Studies	Patients Receiving Contrast Agent (n)	Allergic Reactions (n)	Anaphylactic Reactions (n)
Abdelmoneim et al[10]	10,792	2	1
Gabriel et al[13]	4,786	0	0
Dolan et al[12]	42,408	NA	NA
Shaikh et al[15]	2,914	1	0
Main et al[16]	58,254	NA	NA
Wei et al[17]	78,383	6	4
Kusnetzky et al[14]	12,475	0	0
Anantharam et al[11]	1,150	2	0
Total	110,500 (excluding NA studies)	11 (0.009%)	5 (0.004%)

NA = not applicable.

Khawaja et al. Am J Cardiol 2010;106:742-747

Safety Summary

- **Pharmacovigilance data show no change in the DEFINITY® adverse event profile**
- **Two prospective studies had no deaths or SAEs within 24 hours of DEFINITY®**
- **Pulmonary hemodynamic study showed DEFINITY® had no effect on PASP in patients with normal or elevated PASP**
- **Retrospective ICU study showed DEFINITY® was associated with a lower mortality**
- **Literature findings are consistent**

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Impact of Contrast Echocardiography

"Impact of Contrast Echocardiography on Evaluation of Ventricular Function and Clinical Management in a Large Prospective Cohort", Kurt et al. (JACC 2009)

- 632 consecutive patients with rest contrast TTE
- DEFINITY® contrast used according to ASE consensus recommendations
- Evaluated clinical utility and cost effectiveness of contrast
- Patients acted as their own control

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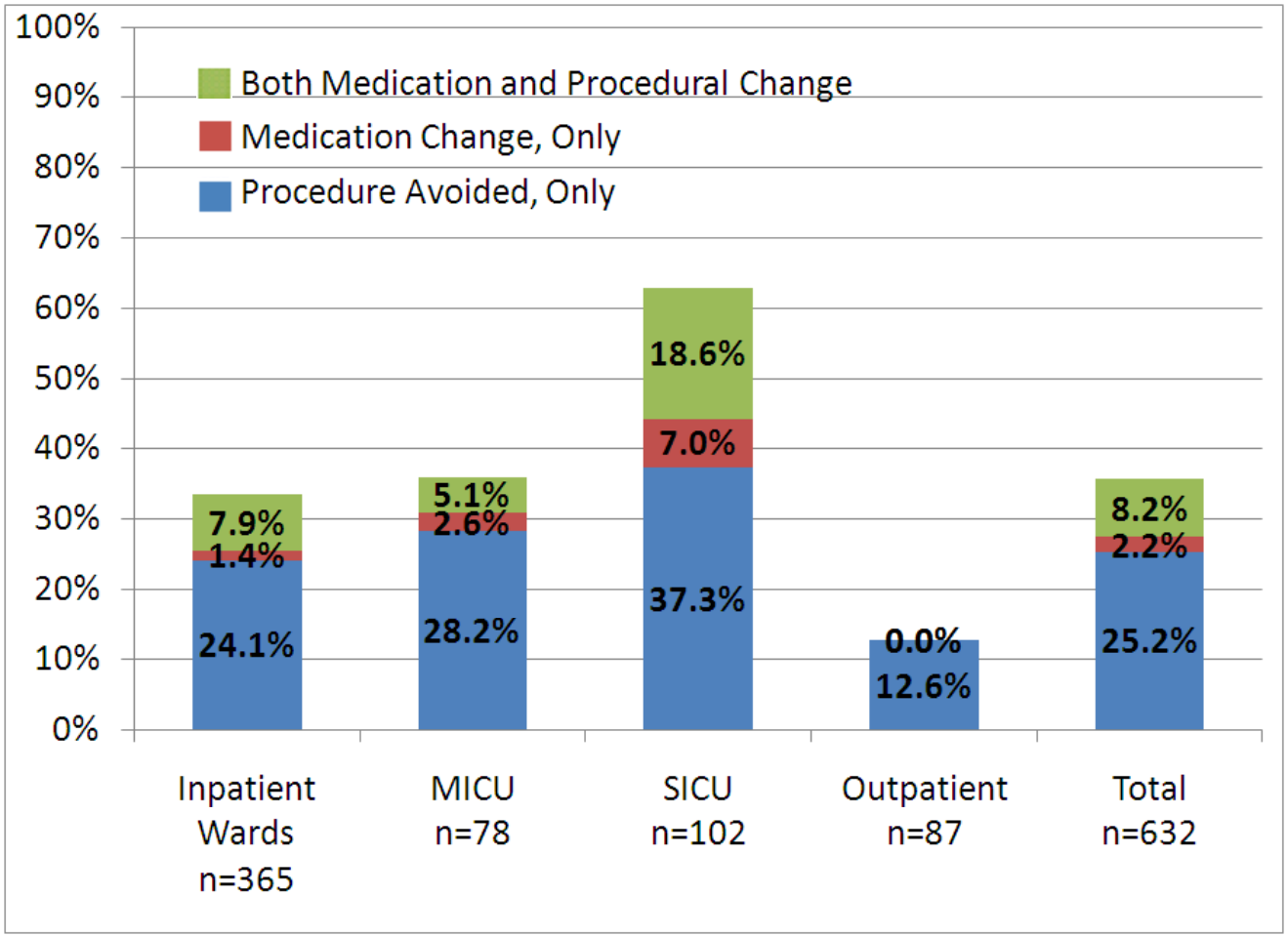
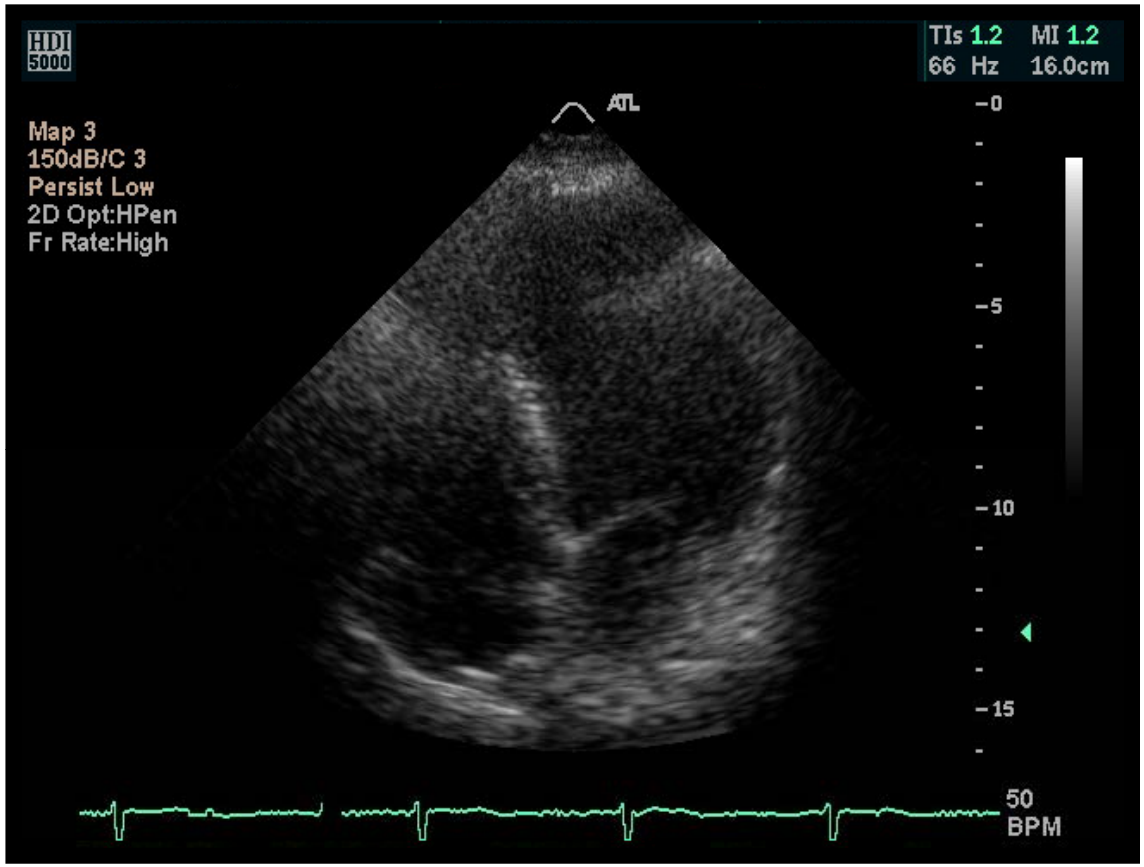
Impact of Contrast TTE on Patient Management Decisions



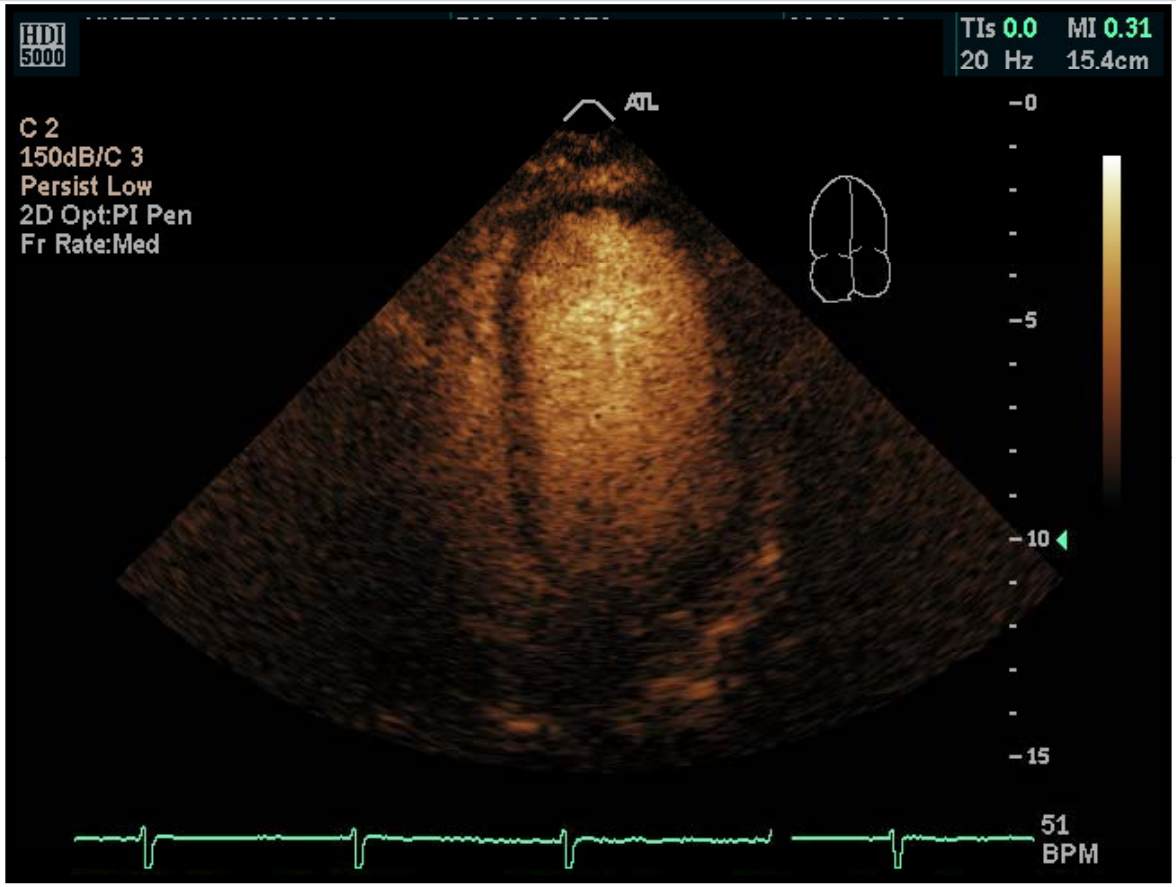
Kurt et al. J Am Coll Cardiol 2009;53

82 year-old man presents with left arm pain and nausea



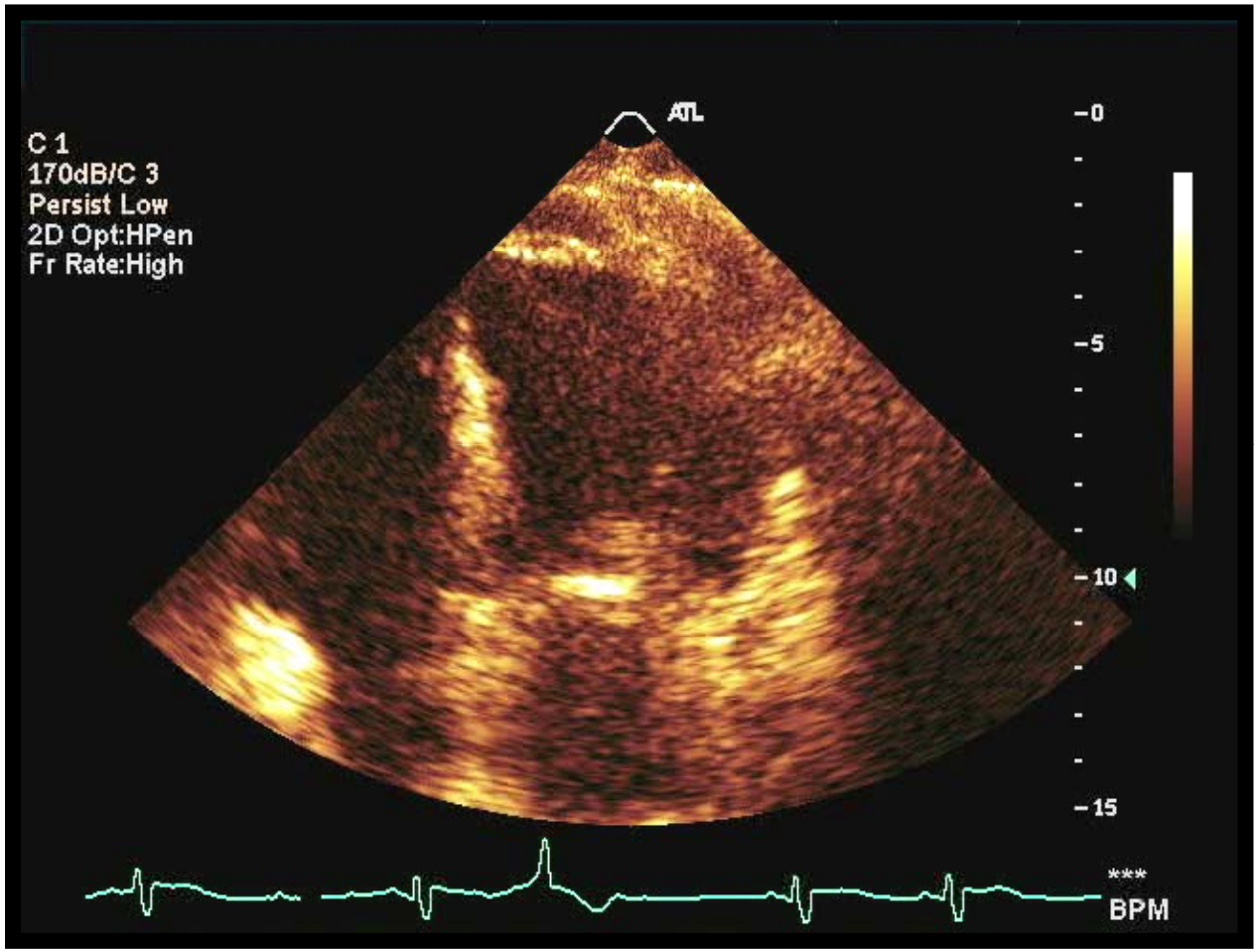
Apical 4-chamber

Contrast Enhanced Image Reveals A Large Zone of Apical Dyskinesis

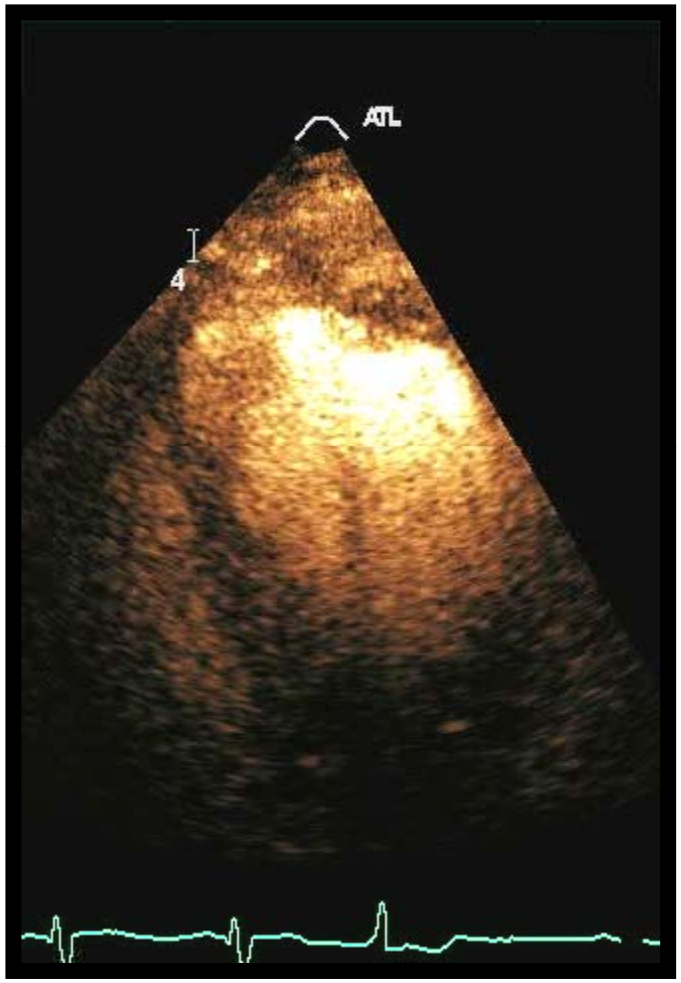


Apical 4-chamber

History of Remote Myocardial Infarction



Contrast Enhanced Study Reveals Apical Pseudoaneurysm



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Impact on LV Thrombus Detection

Clinical Assessment	Before Contrast	After Contrast	p-value
Suspected Thrombus	35	1	<0.0001
Definite Thrombus	3	0	n/a
In addition, 5 previously undetected thrombi noted with contrast			

- 37/38 incorrectly assessed

Profound implications for patient safety

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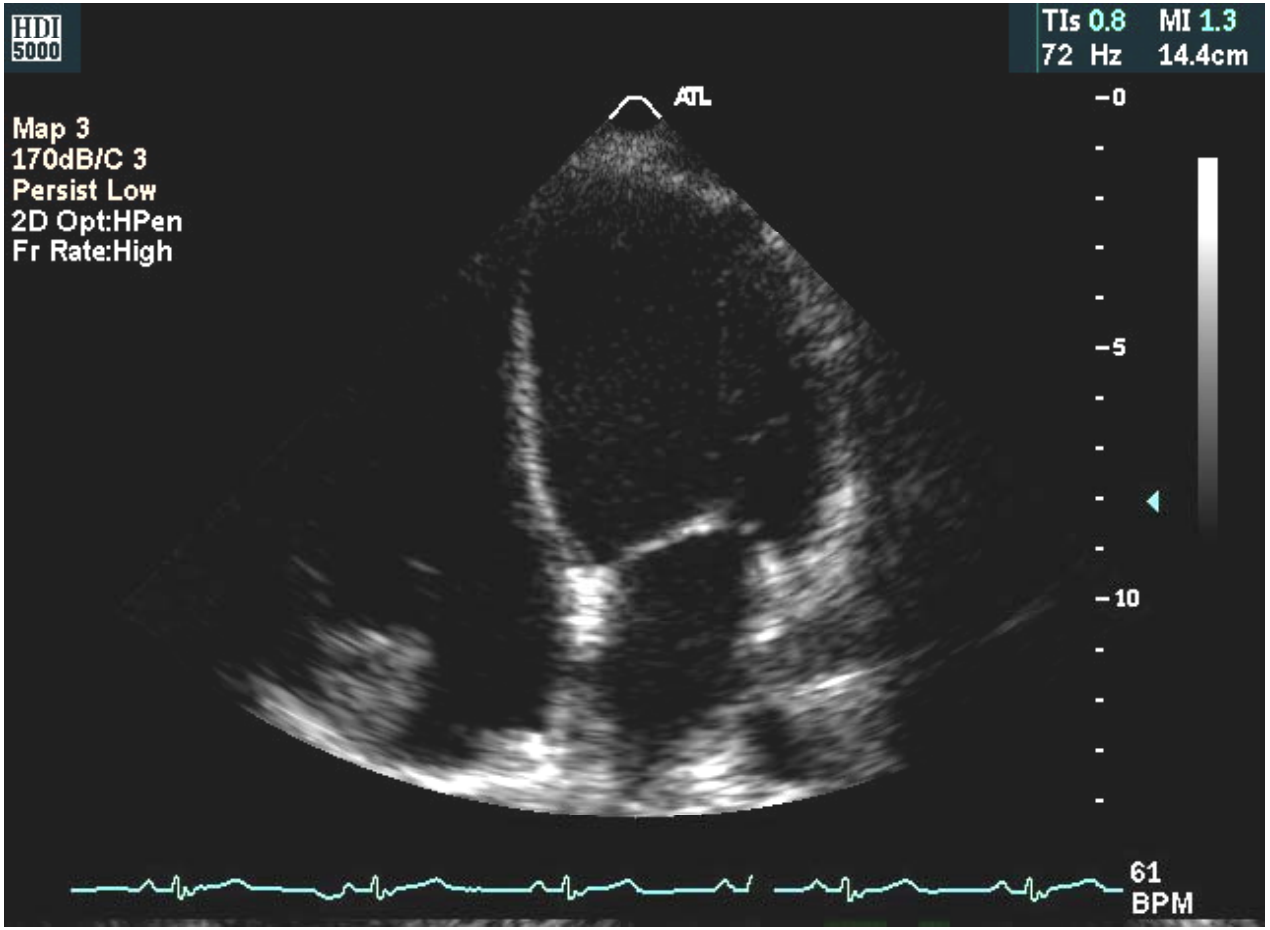
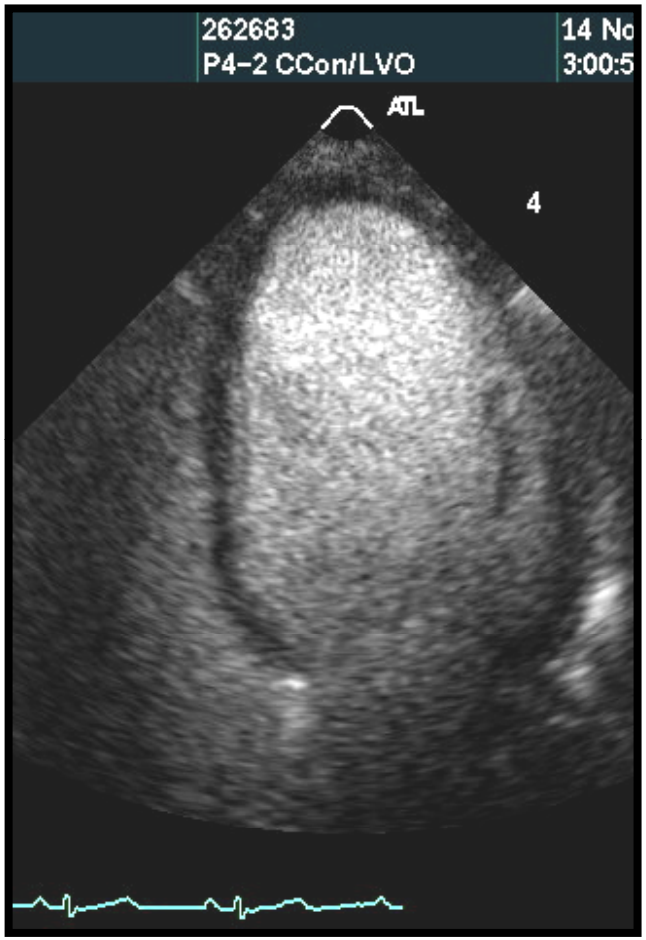
Kurt et al. J Am Coll Cardiol 2009;53

Recent Anterior Myocardial Infarction and Possible Apical Thrombus



Contrast Enhanced Image



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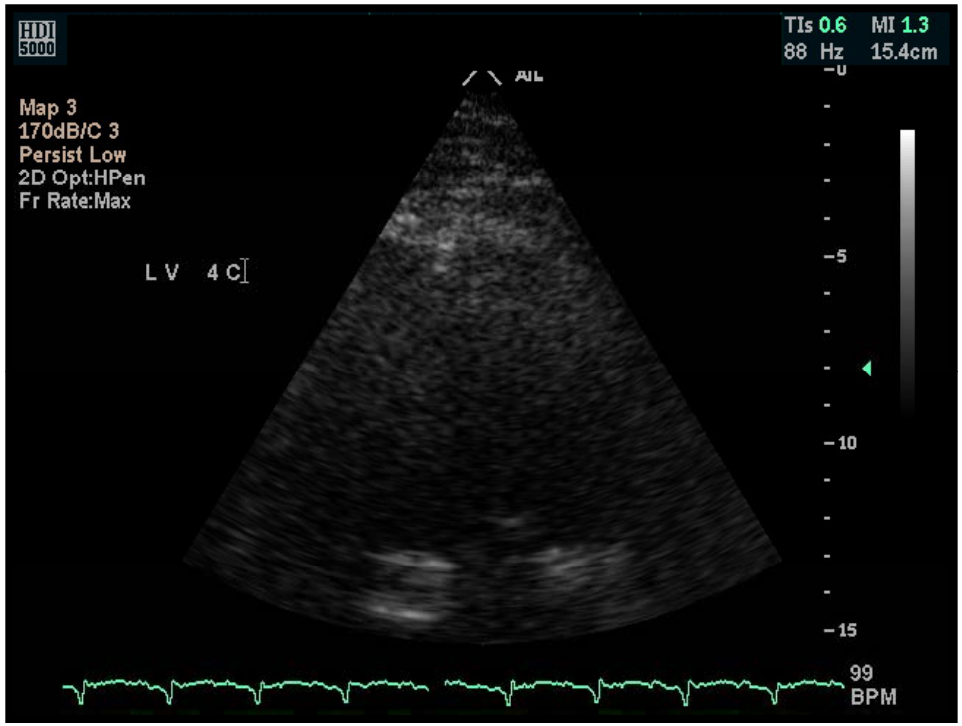
Apical mural thrombus or not?



Apical 4-chamber

- **45 year-old man with known coronary artery disease**
- **Percutaneous coronary intervention in 2003**

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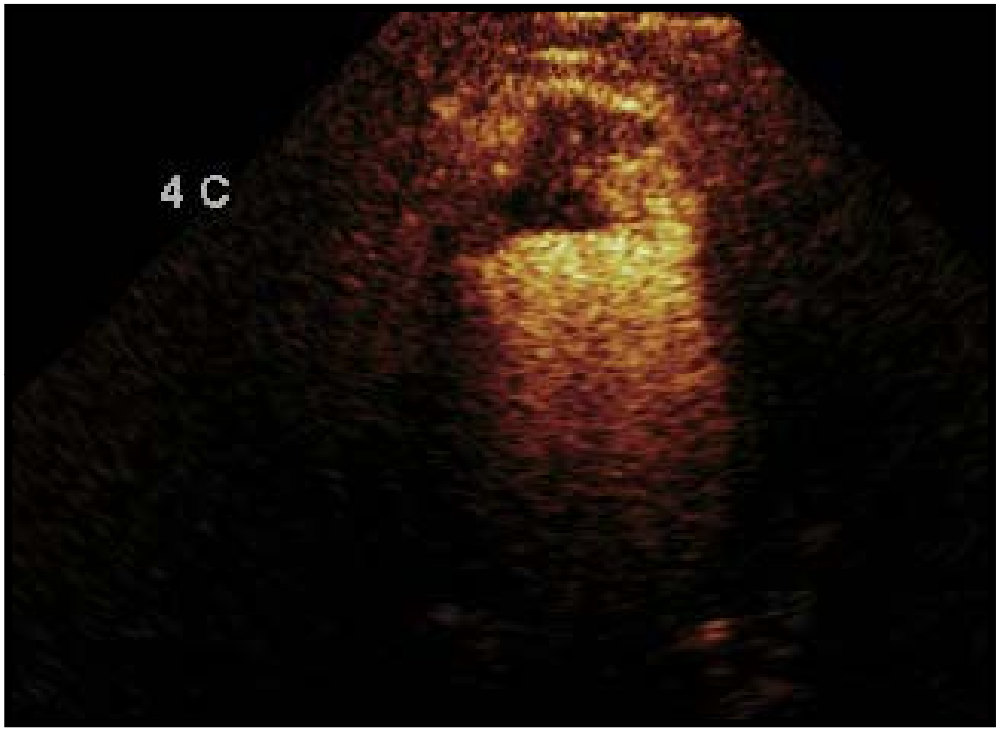
Contrast Enhanced Examination



Apical 4-chamber

Contrast enhanced image reveals a large left ventricular apical mural thrombus

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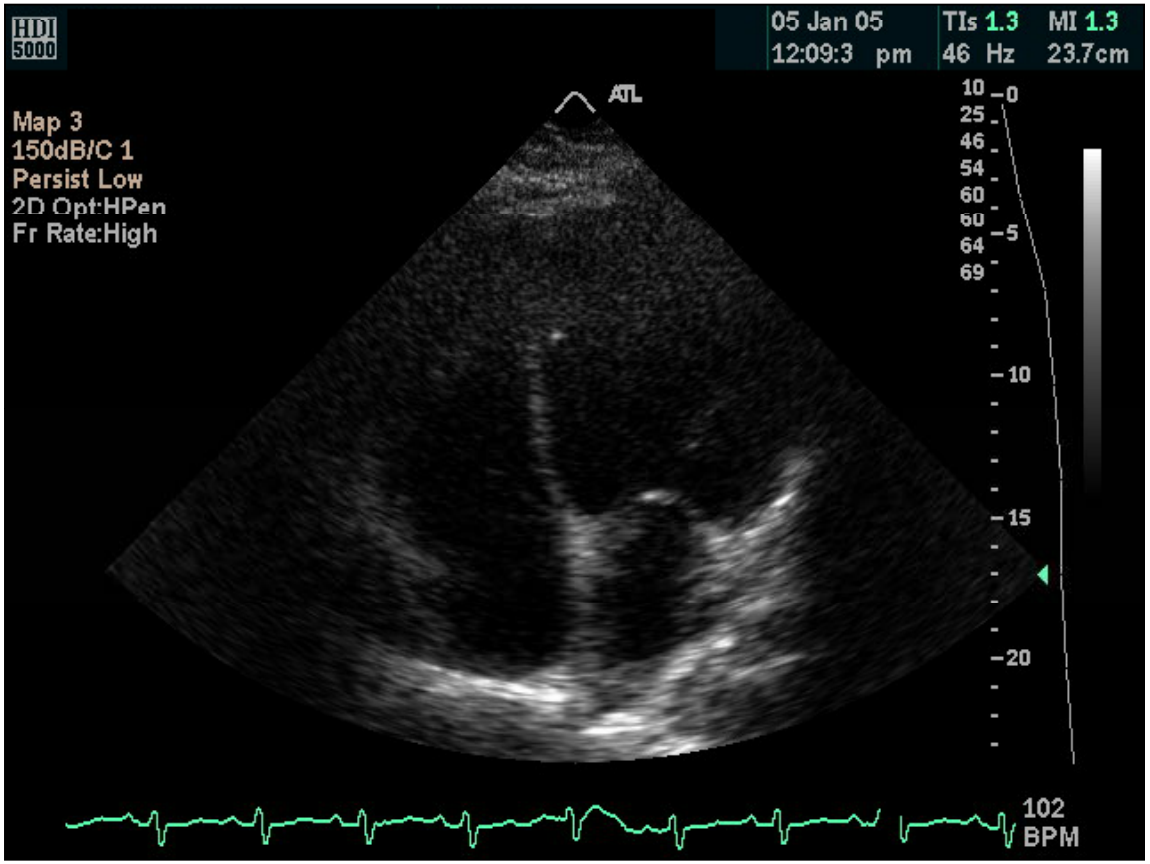
Is There LV Dysfunction?



18 Year Old Man with Super Obesity (BMI=58.3) and Dyspnea

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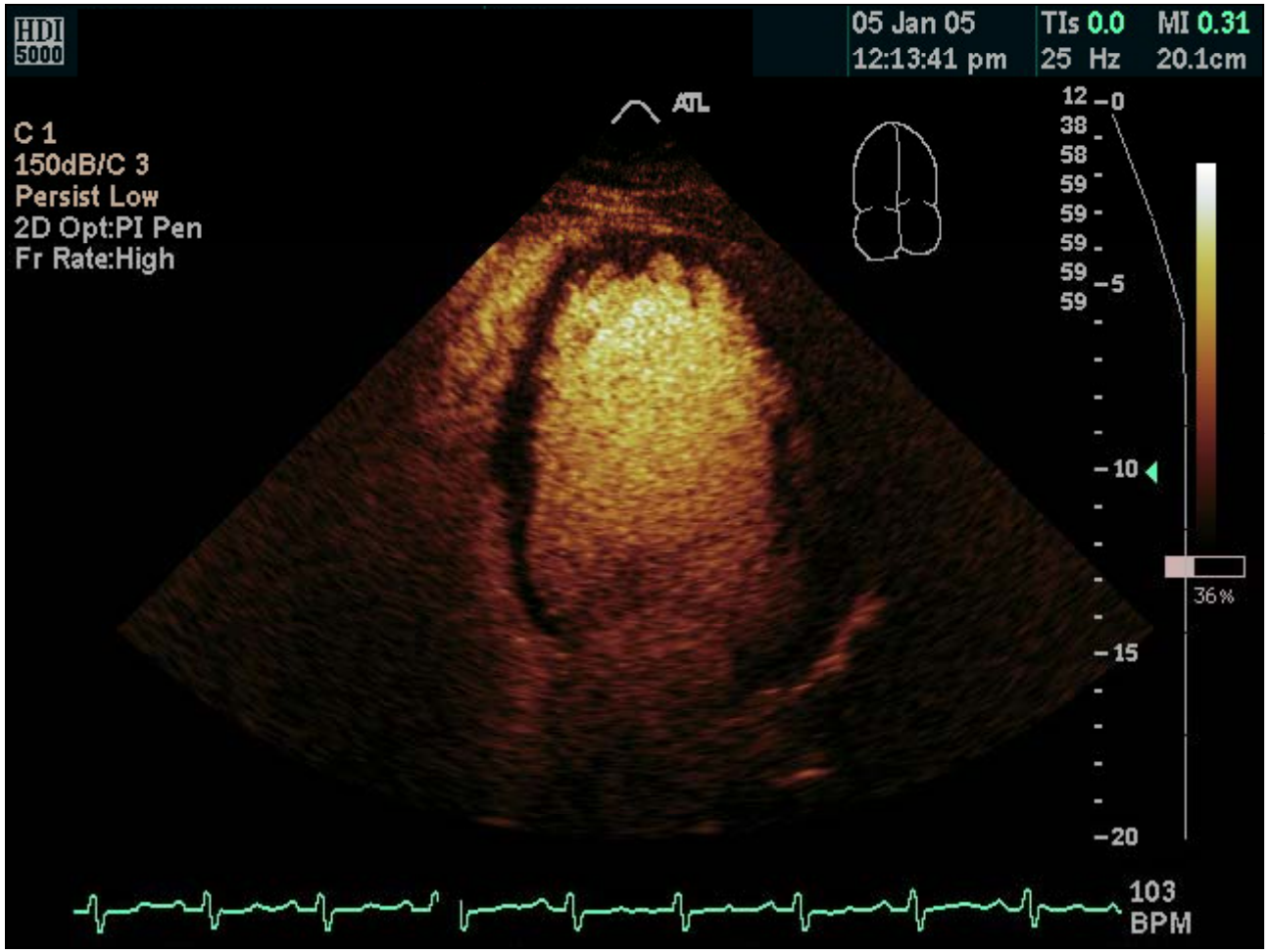
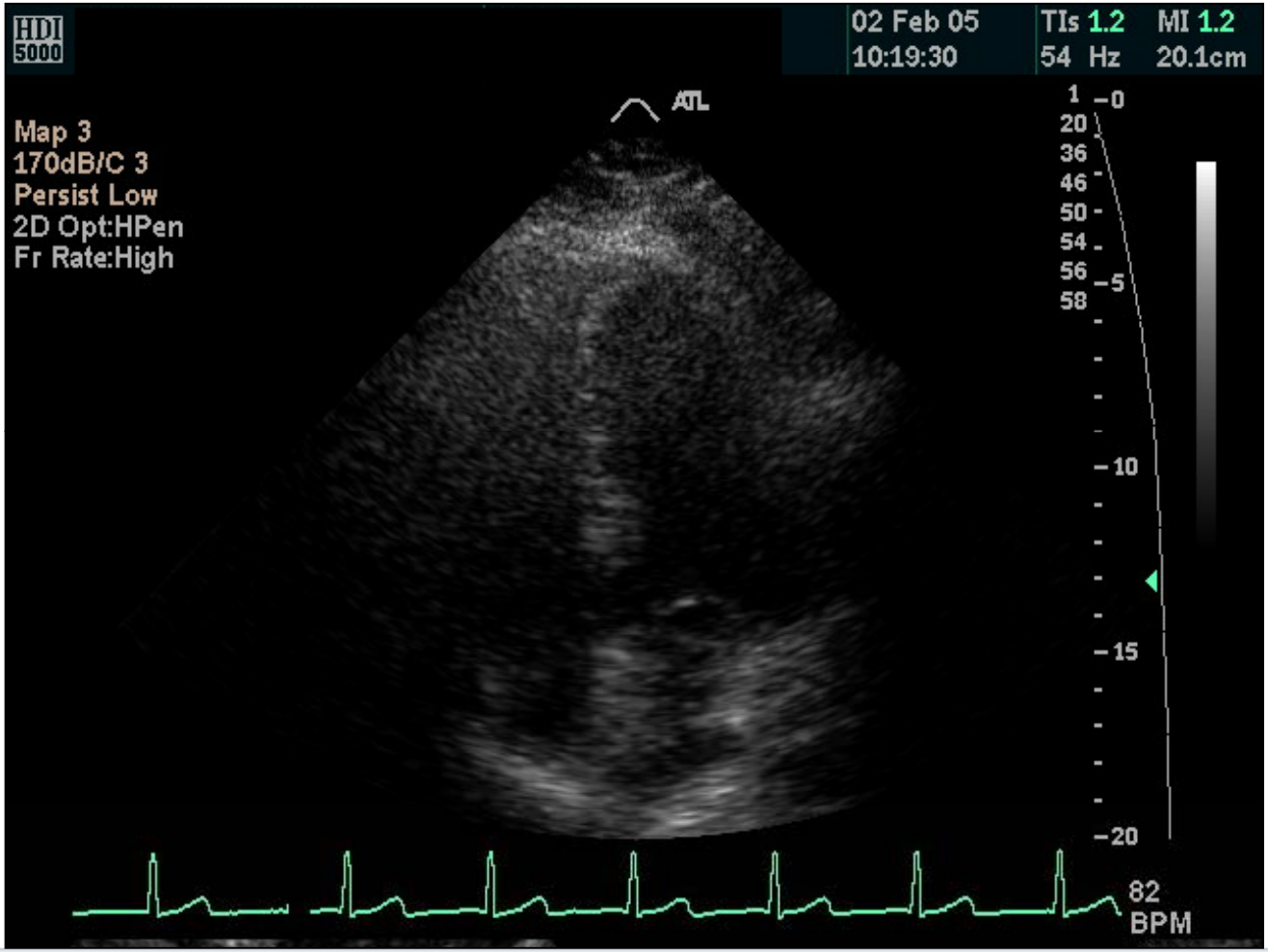
Contrast Enhanced Image

Severe Global Hypokinesis

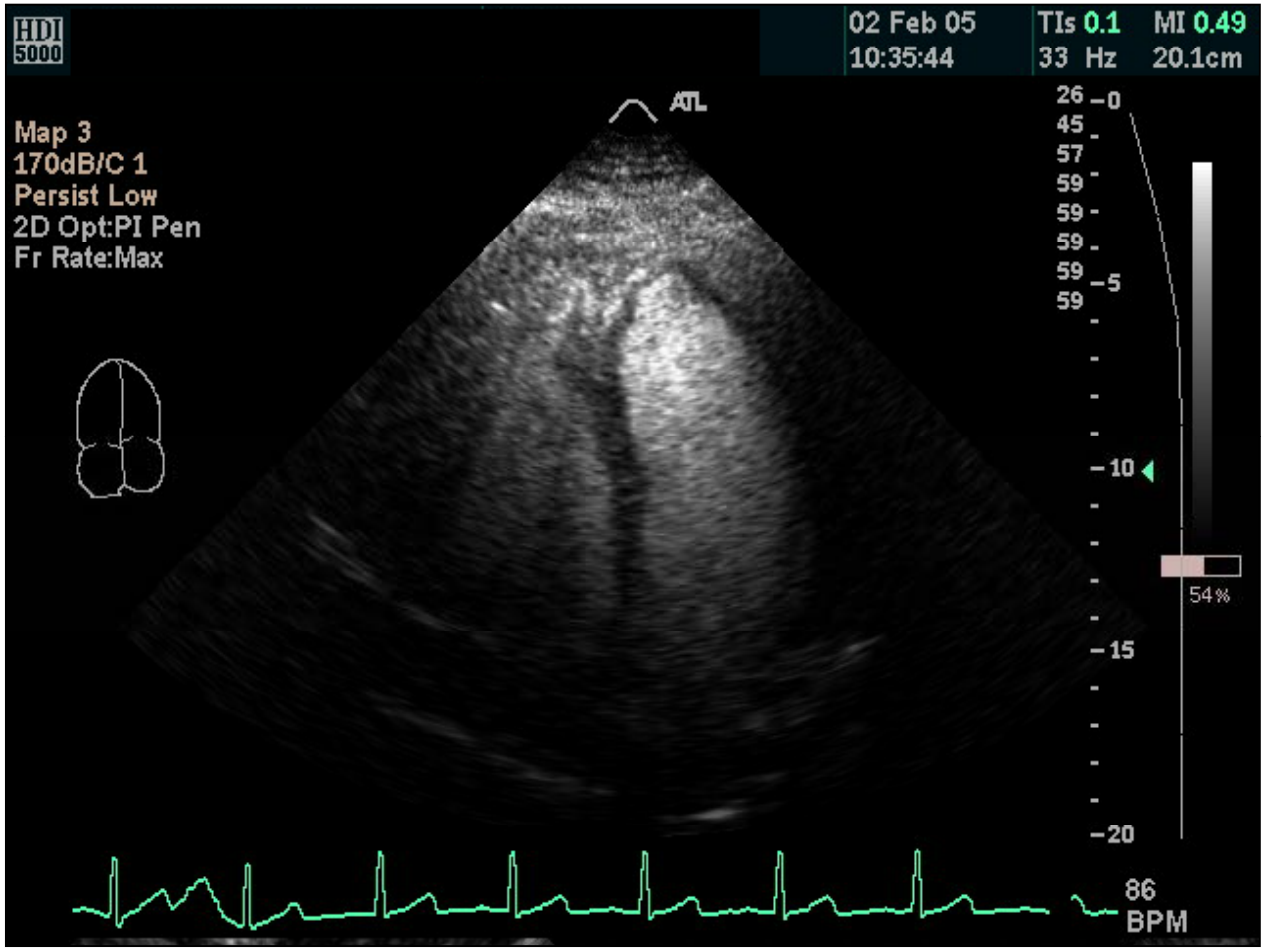


34 Year Old Super Obese Woman (BMI=64): Is LV Function Normal?



Contrast Enhanced Image

Clearly Normal LV Function



Apparent Under Utilization of Contrast Echocardiography

- **Prospective single center study demonstrated suboptimal baseline echocardiograms in:[1]**
  - –6% of outpatients
  - –18% of inpatients
  - –21% in the ICU
- **ASE Consensus statement estimates suboptimal echocardiograms at 15-20%[2]**
- **Current contrast use in ~2% of echocardiograms**

1 Kurt et al. Impact of Contrast Echocardiography. J Am Coll Cardiol 2009;53
2 Mulvagh SL, et al. ASE consensus statement on the clinical applications of ultrasonic contrast agents in echocardiography. J Am Soc Echocardiogr 2008;21:1179-201

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DEFINITY® Benefit-Risk Summary

- **Strong and consistent safety profile**
- **SAEs are rare; lower or similar to reported rates for other cardiovascular imaging modalities**
- **Use of DEFINITY® shown to favorably impact patient management**
- **Current use of contrast is low compared to published rates of suboptimal echocardiograms**
- **Data from post-marketing studies, pharmacovigilance & literature suggest Product Label should be revised**

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Labeling Recommendation

Dana Washburn, MD
VP, Clinical Development & Medical Affairs
Lantheus Medical Imaging

Lantheus Recommendations

1. **Removal of Boxed Warning**
   - Not warranted according to guidance (21 CFR 201.57(c)(1))
   - Relevant safety information appears elsewhere in the label (Highlights and Warnings Sections)
2. **Remove language from Warnings Section regarding monitoring requirements and risk associated with specific disease states**
3. **Include summary of 3 post-marketing study results**

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