

# AI-700-33 Reread Changes and Emphasis from the Original Blinded Reader Training Manual

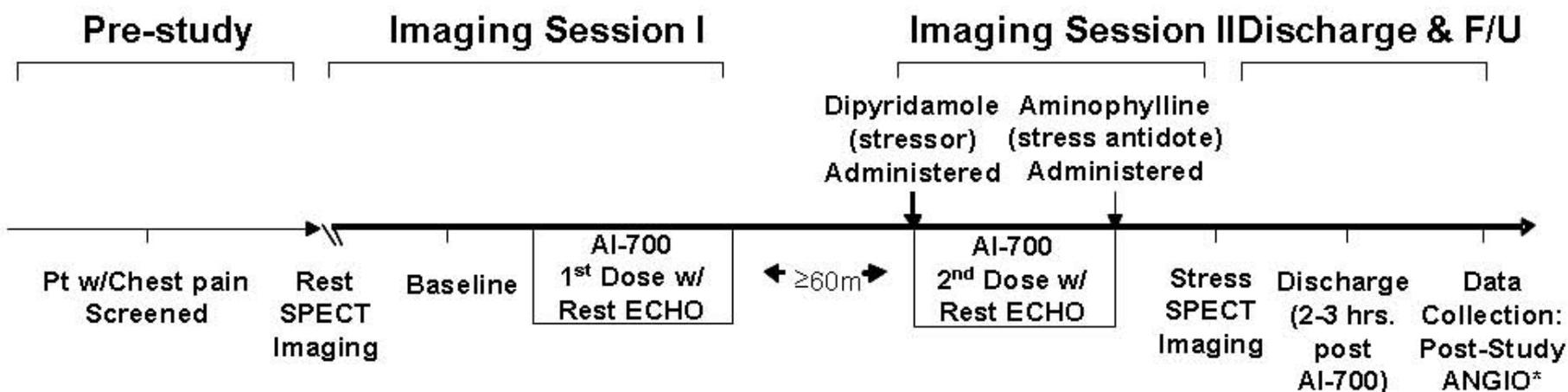
- **Blinded readers (2/3) in AI-700-32 with non-inferior accuracy were found to be predisposed towards more conservative reading as compared to the SPECT reader**
- **AI-700-33 reader retraining was focused on:**
  - **reducing bias towards conservative reading**
  - **improving sensitivity and maintaining accuracy**
- **No major changes in reader instructions**
- **Strategies were stressed to achieve retraining goals:**
  - **Schedule read sessions early in day**
  - **Read videotape and digital clips serially, not simultaneously**
  - **Spend majority of time deciding whether the patient has or does not have a defect(s)**
  - **Always read both rest and stress sessions completely**

\* Excerpts from Section 6.3.4 Reading Strategy, Revised Blinded Reader Training Manual

# ECHO Definitions

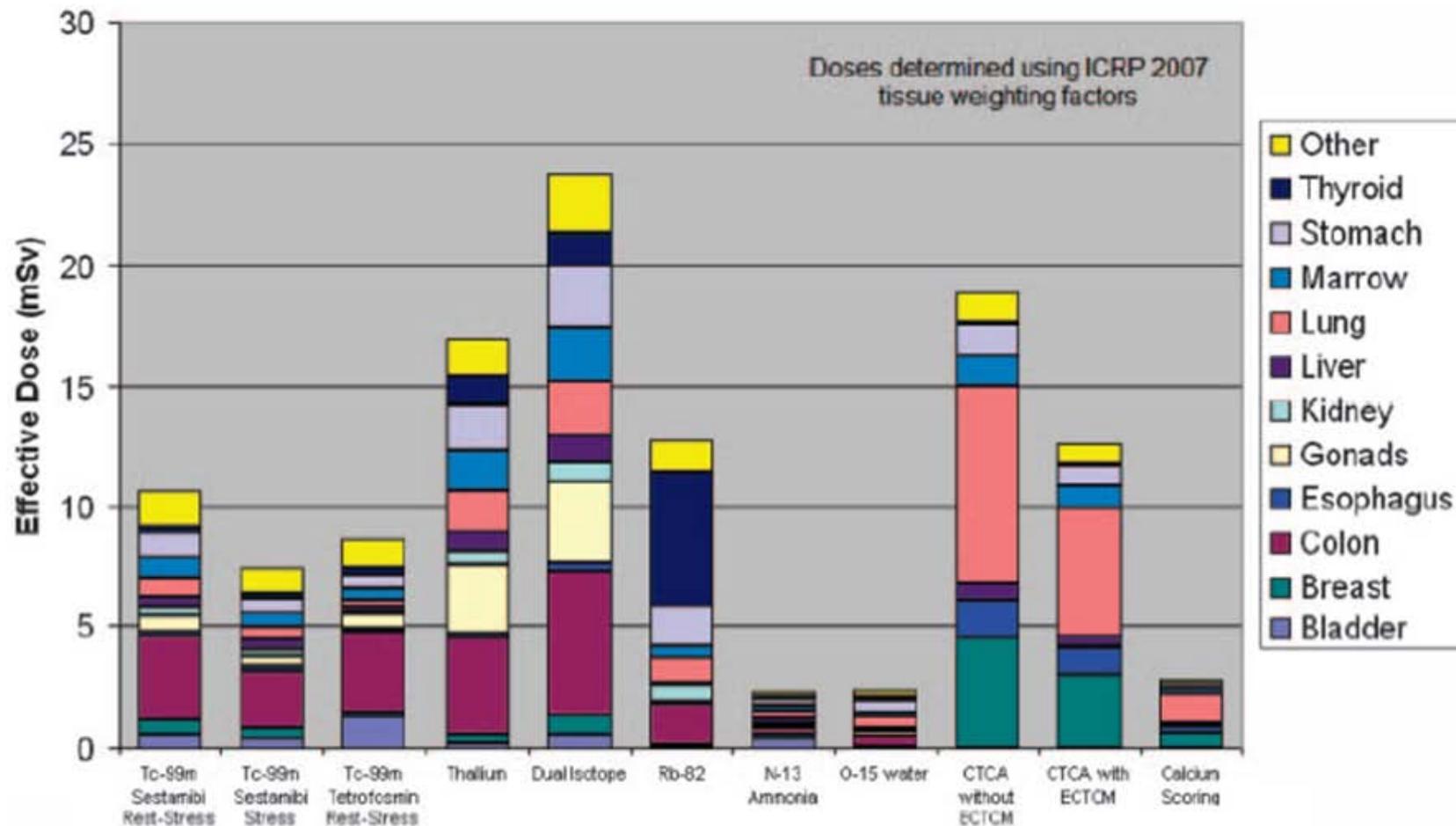
- **Normal Study:**
  - **Homogenous opacification during systole and diastole with normal wall motion.**
- **Abnormal Study:**
  - **A reversible defect is present if there is any evidence of an increase in extent or severity of the defect between the rest and stress sessions or during the stress session alone.**
    - **Reversible defects are often observed as subendocardial dark lines encompassing the inner 1/3rd of the myocardial segment, and may be associated with normal to hypokinetic wall motion abnormality. If both reversible and fixed defects are observed, the study was considered reversible.**
  - **A fixed defect is one in which there is no indication of inducible ischemia.**
    - **Transmural hypoechoic (dark) myocardium and wall motion abnormality noted during rest and stress. The defect does not worsen or extend with stress.**

# Overview of AI-700 Phase 3 Study Procedures



\*Data from off-study procedures

# Inter Modality Radiation Exposure by Effective Dose (Published reports)



# Diagnostic Cardiac Imaging Agents

Product	Imaging Use	Endpoints in Phase 3	N	Efficacy Results
Myoview <sup>®</sup> (1996)	Nuclear perfusion contrast agent	% Correct diagnosis (=agreement/accuracy) vs “Final clinical diagnosis”	252	64-80%
Definity <sup>®</sup> (2001)	ECHO contrast agent	LV opacification and improve LV endocardial border delineation	208	
Lexiscan <sup>®</sup> (2008)	Pharmacological stressor	Agreement with Adenoscan <sup>®</sup> (non-inferiority)	1871	61-64%
AI-700	ECHO perfusion imaging agent	Accuracy vs angiography/clinical history as truth (non-inferiority)	778	66-71%

# Number of Patients with Hypotensive Adverse Events by Onset Time (AI-700-23, -32, and -33)

Preferred Term	Onset Time				Total N = 911 n (%)
	1 <sup>st</sup> Dose to DIPY N = 911 n (%)	DIPY to 2 <sup>nd</sup> Dose N = 894 n (%)	2 <sup>nd</sup> Dose to Discharge N = 894 n (%)	Discharge to Follow-up N = 911 n (%)	
Hypotension	9 (1.0)	4 (0.4)	18 (2.0)	1 (0.1)	31 (3.4)
Blood pressure decreased	3 (0.3)	0	4 (0.4)	0	6 (0.7)
Blood pressure systolic decreased	0	0	1 (0.1)	0	1 (0.1)

If a patient had more than one occurrence of the same AE at 2 different timepoint categories, that patient was counted only once in the total column.

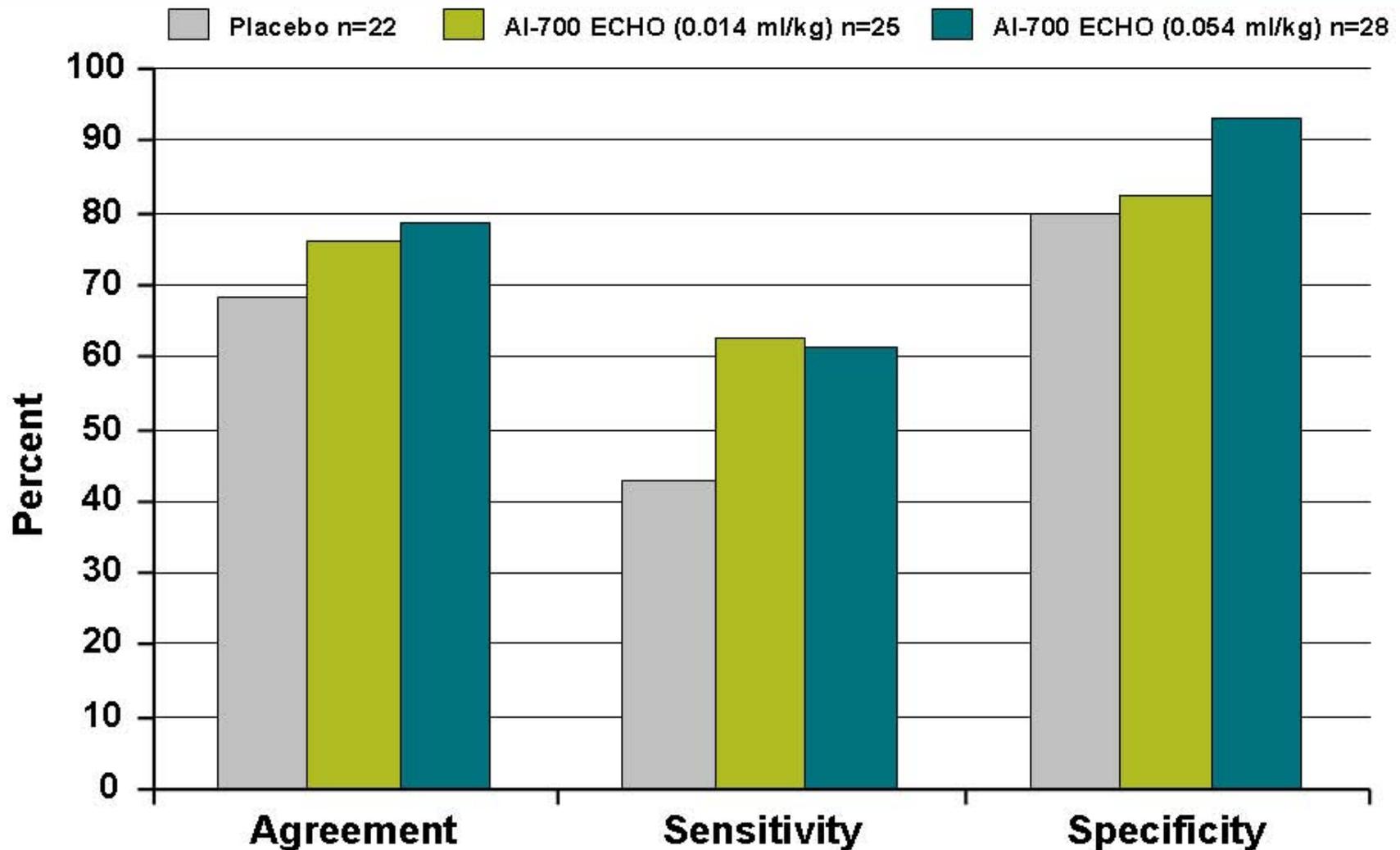
# Quality Control of SPECT Data and Blinded Readers

- **SPECT Core Lab (Yale University)**
  - ASNC's certification lab for accreditation of nuclear cardiology laboratories
  - Phase 3 sites without prior accreditation required to meet Core Lab's standards
- **SPECT imaging data:**
  - Acquired under Core Lab's guidelines consistent with Imaging Guidelines for Nuclear Cardiology Procedures, Part 2, ASNC
  - Inspected by the Core Lab for count density, patient motion, and confirmation to guidelines
  - Could be rejected by Core Lab for uninterpretability and excluded from the mITT population
- **Independent expert nuclear cardiologists**
  - Blinded to patient histories and other SPECT, ECHO, and ANGIO results
  - Consistently trained for definition of terms and scoring
  - Provided with raw cines, tomographic slices, gated cines, and quantitative analysis

# Intracarotid Administration in Rats – Escalating Dose Phase

- Doses: 0.035X, 0.35X, 1.4X, and 1.8X the HD
  - Doses diluted to a total dose volume of 0.3-0.5 mL/kg.
- 3M per dose level
- Parameters: clinical observations, clinical chemistry and hematology
- At 1.8X
  - Clinical signs included yawning, licking, lateral or dorsal recumbency, circling, labored breathing, increased respiration rate, increased muscle tone, vocalization, hypersensitivity, weakness and erect fur
  - All animals survived until the end of the study (1 day).
- 1.4X was the maximum tolerated dose

# Efficacy of AI-700 ECHO Compared to Non-Contrast ECHO (AI-700-21)



SPECT was used as truth standard in AI-700-21.

# Serum Chemistry Parameters: Renal (Studies AI-700-32 and -33)

Parameter	Baseline	Discharge	Follow-up
<b>BUN (mg/dL)</b>			
n	766	711	727
Mean (SD)	18.7 (6.7)	17.8 (6.1)	18.2 (6.3)
Median	18.0	17.0	17.0
Minimum, Maximum	6.0, 76.0	6.0, 69.0	6.0, 60.0
<b>Creatinine (mg/dL)</b>			
n	766	711	727
Mean (SD)	1.0 (0.5)	1.0 (0.3)	1.0 (0.3)
Median	0.9	0.9	1.0
Minimum, Maximum	0.2, 12.3	0.4, 2.6	0.5, 3.1
<b>Uric Acid (mg/dL)</b>			
n	766	711	727
Mean (SD)	6.3 (1.6)	6.2 (1.6)	6.3 (1.6)
Median	6.1	6.1	6.2
Minimum, Maximum	2.7, 14.0	2.7, 14.1	2.5, 12.7

BUN = blood urea nitrogen

# Creatinine Kinase Values (AI-700-32, -33)

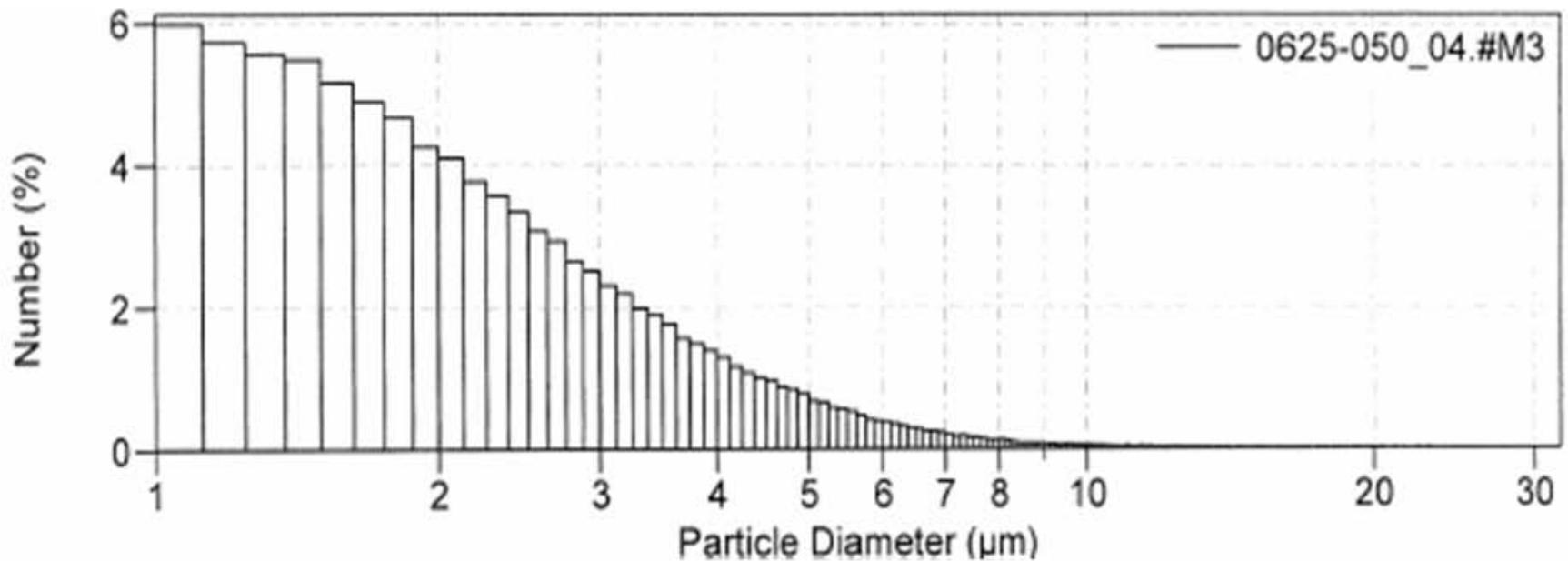
<b>Baseline</b> \ <b>Post dose</b>	<b>≤1.5 mg/dL</b>	<b>&gt;1.5 mg/dL</b>
<b>≤1.5 mg/dL</b>	<b>721</b>	<b>10</b>
<b>&gt;1.5 mg/dL</b>	<b>3</b>	<b>20</b>

Note: Patient with highest creatinine value (12.3 mg/dL at baseline) had no follow-up measurements. An additional 13 patients had baseline measurements only, all ≤1.5 mg/dL.

# Particle Size Distribution Specifications

Parameter	Specification
Mean Diameter	2.0-2.6 $\mu\text{m}$
Particles 2-8 $\mu\text{m}$	50-60 %
Particles $\leq 10 \mu\text{m}$	$\geq 99.0\%$
Particles $\leq 20 \mu\text{m}$	NLT 100.0%
Total Number of Particles	$1.5\text{-}2.7 \times 10^9$ particles/mL

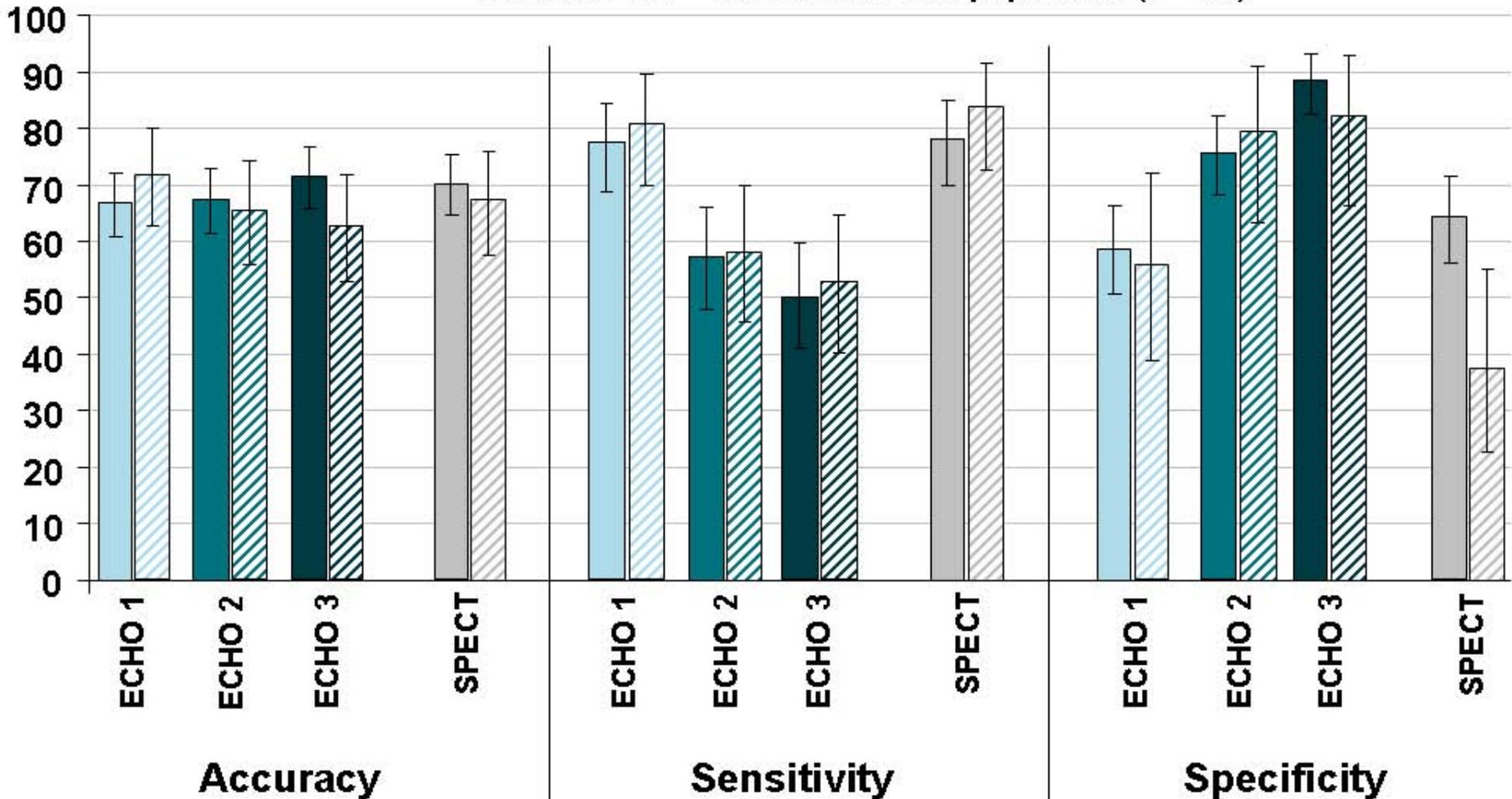
# Particle Size Distribution Example



# ANGIO/LVG Subgroup (AI-700-32)

Solid Bars = MITT Population (n=285)

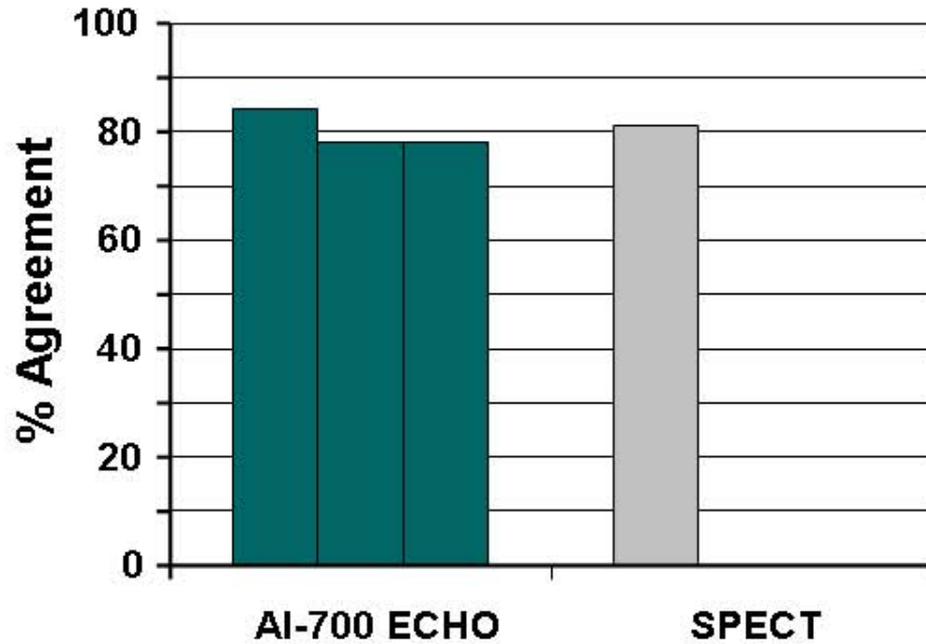
Hatched Bars = ANGIO/LVG Sub-population (n=109)



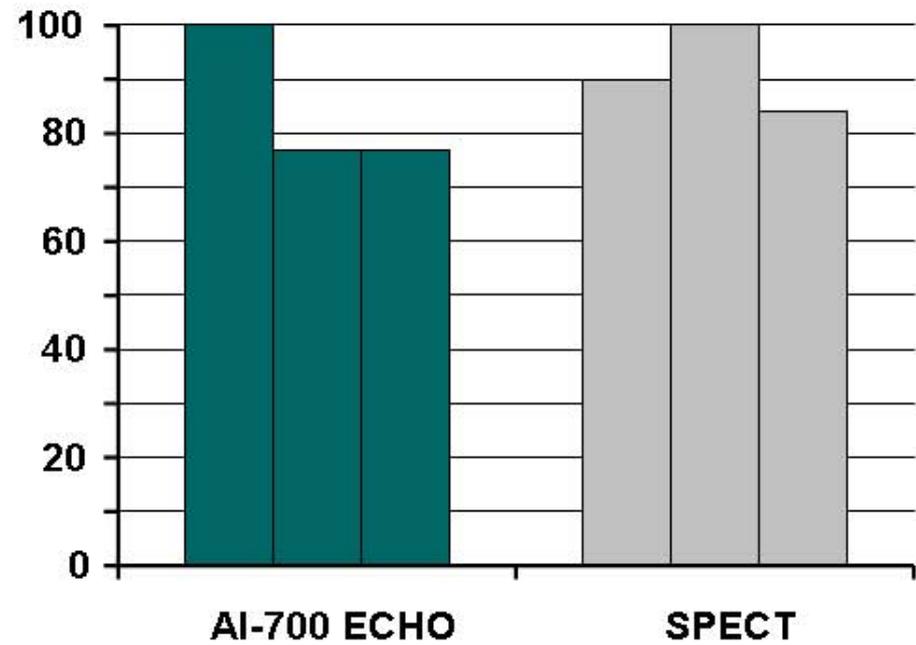
Error bars designate 95% confidence intervals.

# Intra-reader Reproducibility

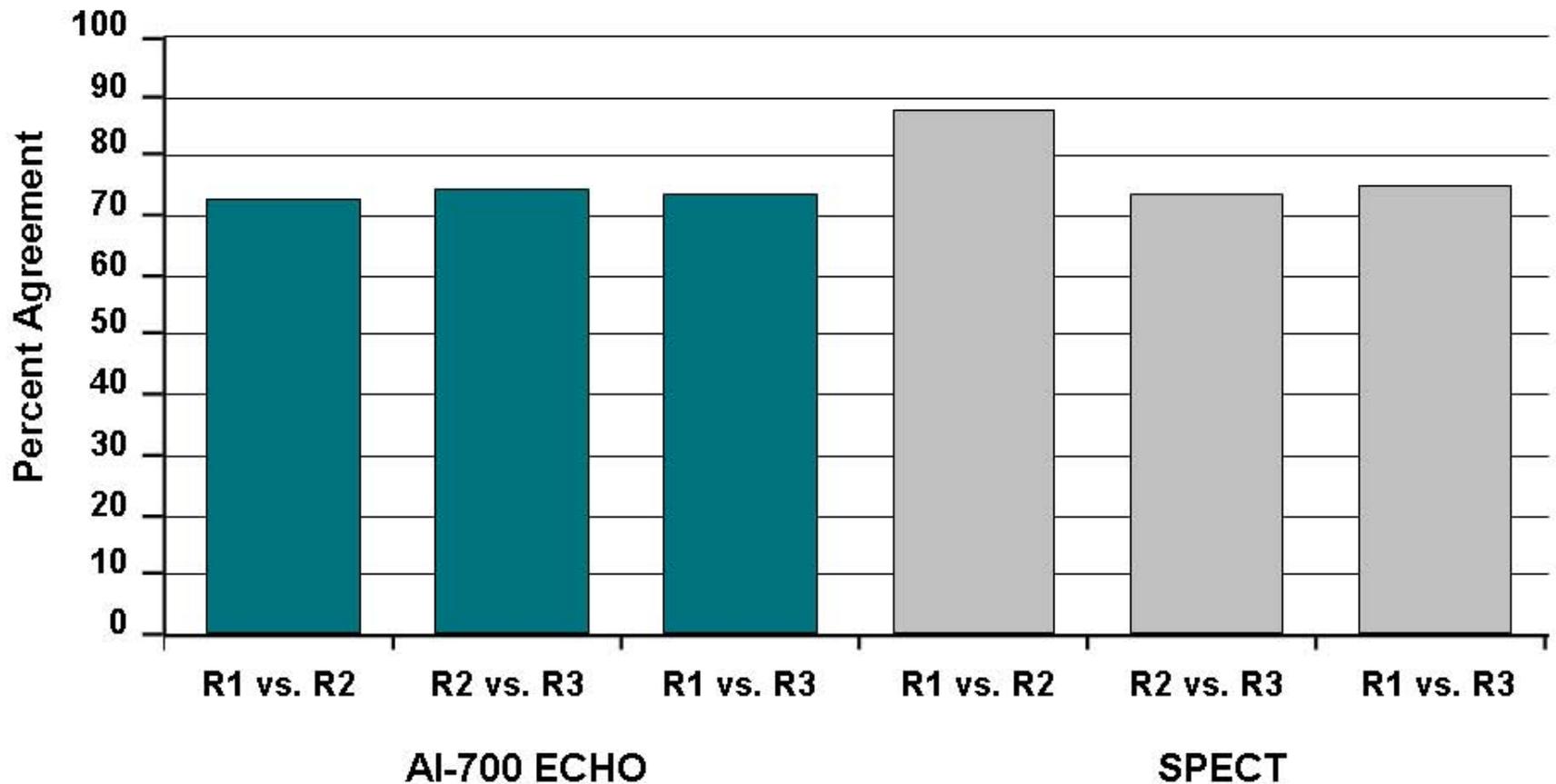
AI-700-32



AI-700-33

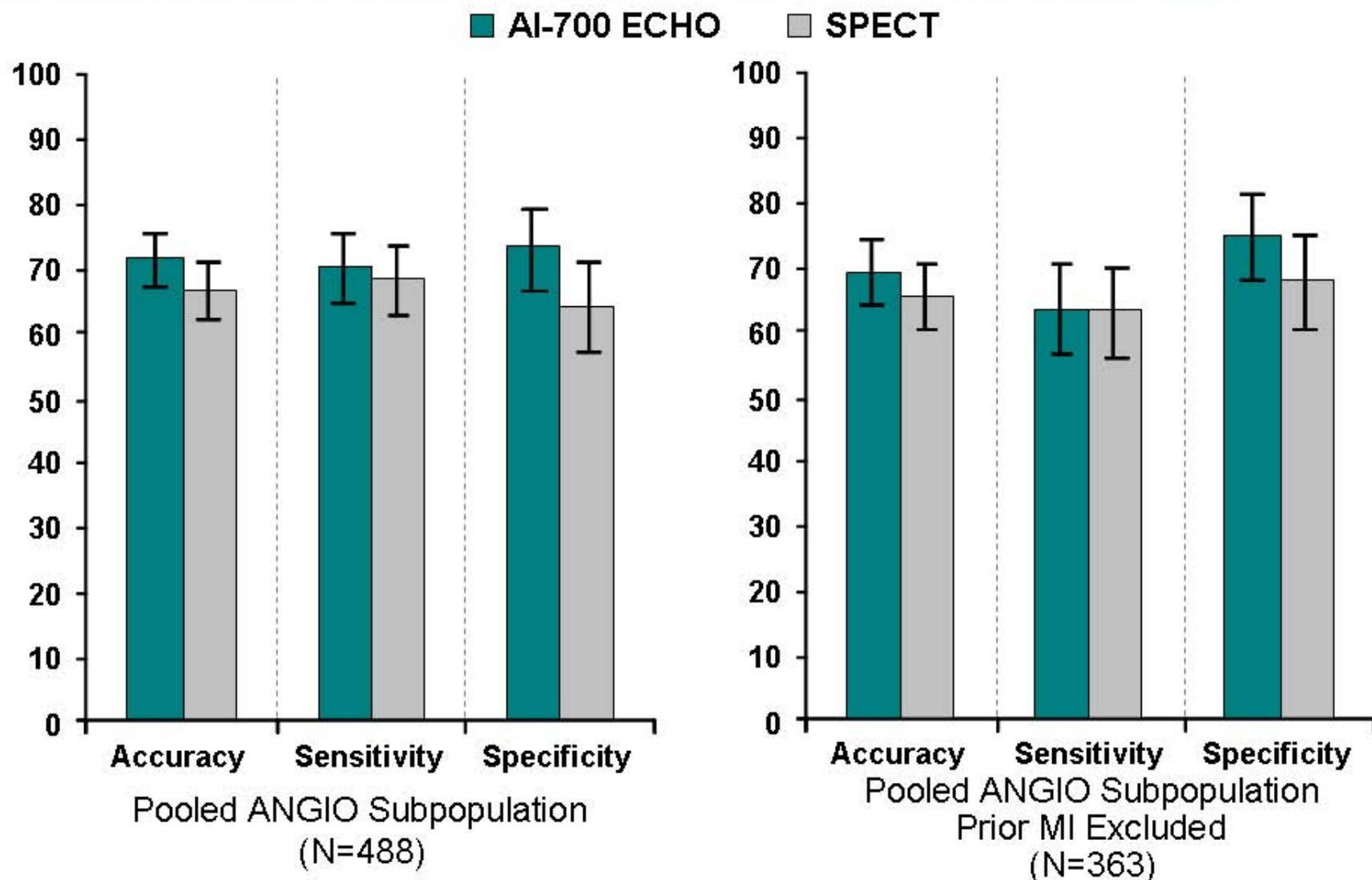


# Inter-reader Agreement (AI-700-33)

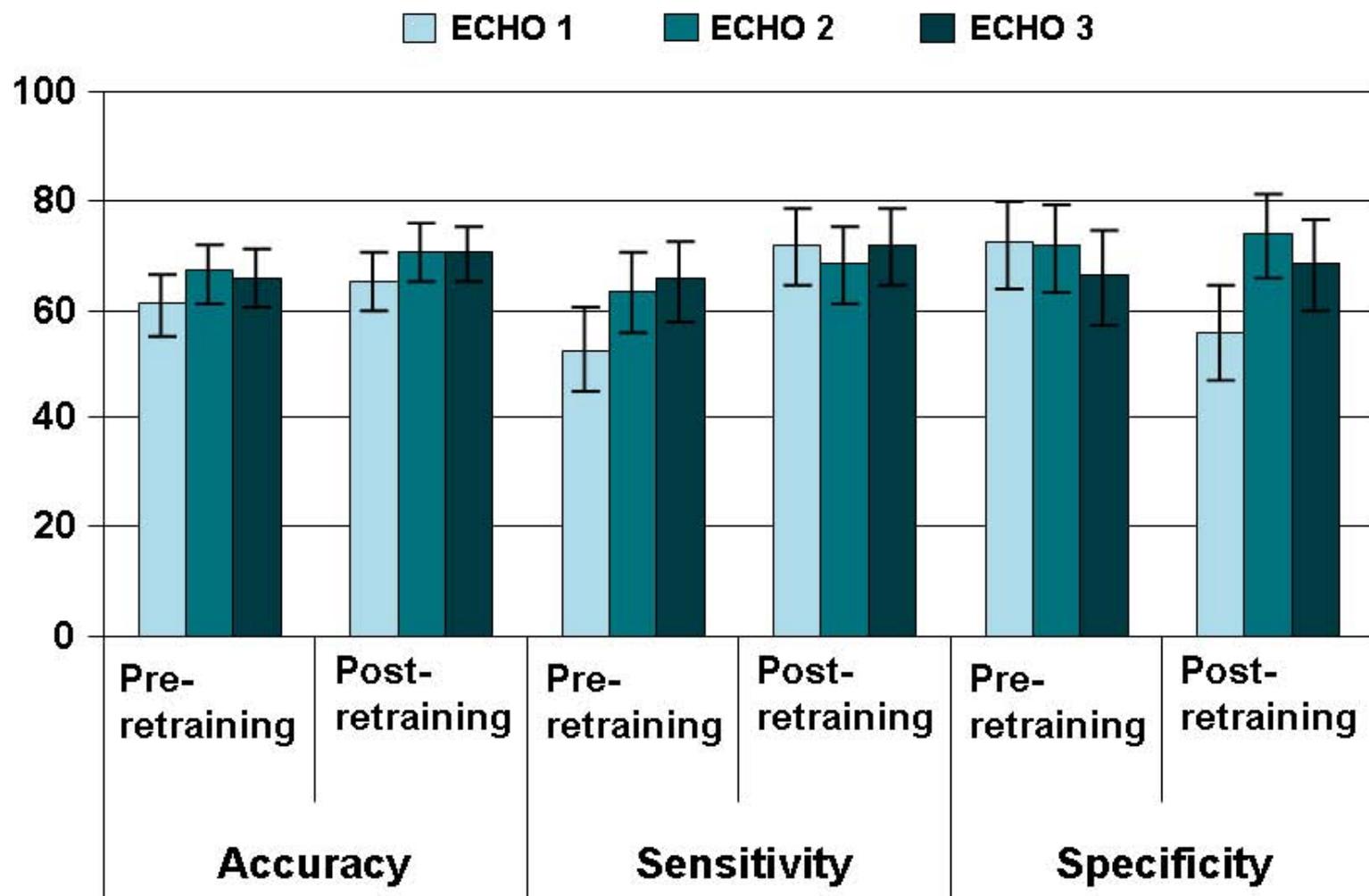


A similar comparison cannot be made for Inter-reader agreement in AI-700-32 due to the single SPECT reader.

# Pooled Analysis: AI-700 ECHO Majority is Comparable to SPECT Majority for Detection of “Ischemic Disease”

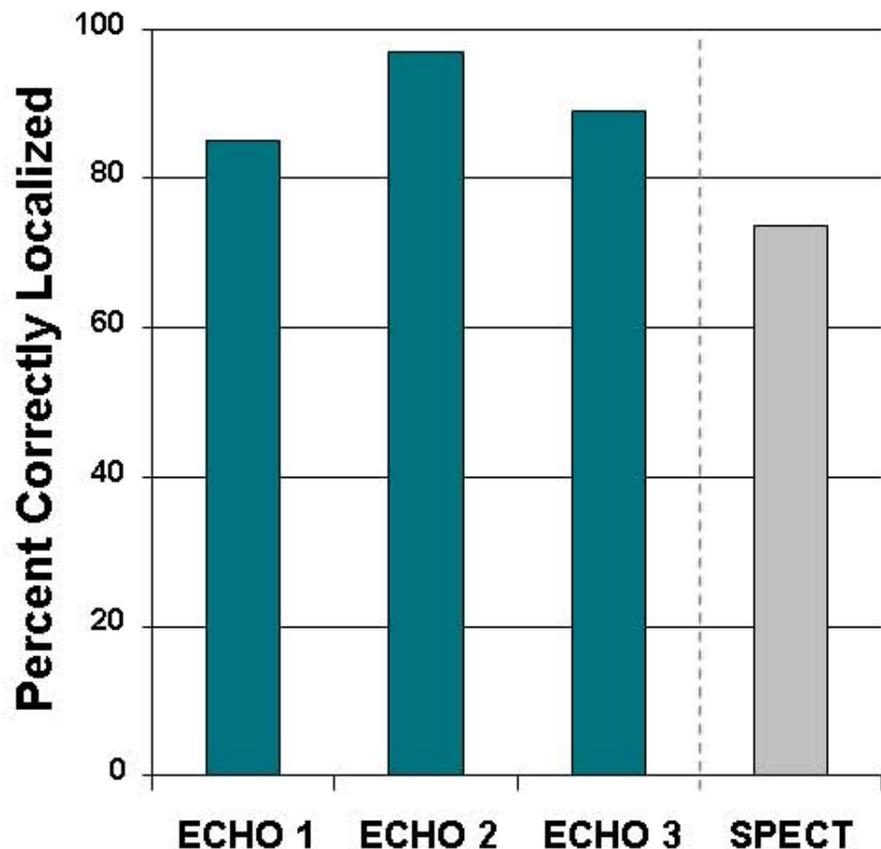


# Pre-retraining Diagnostic Performance (n=304; AI-700-33)

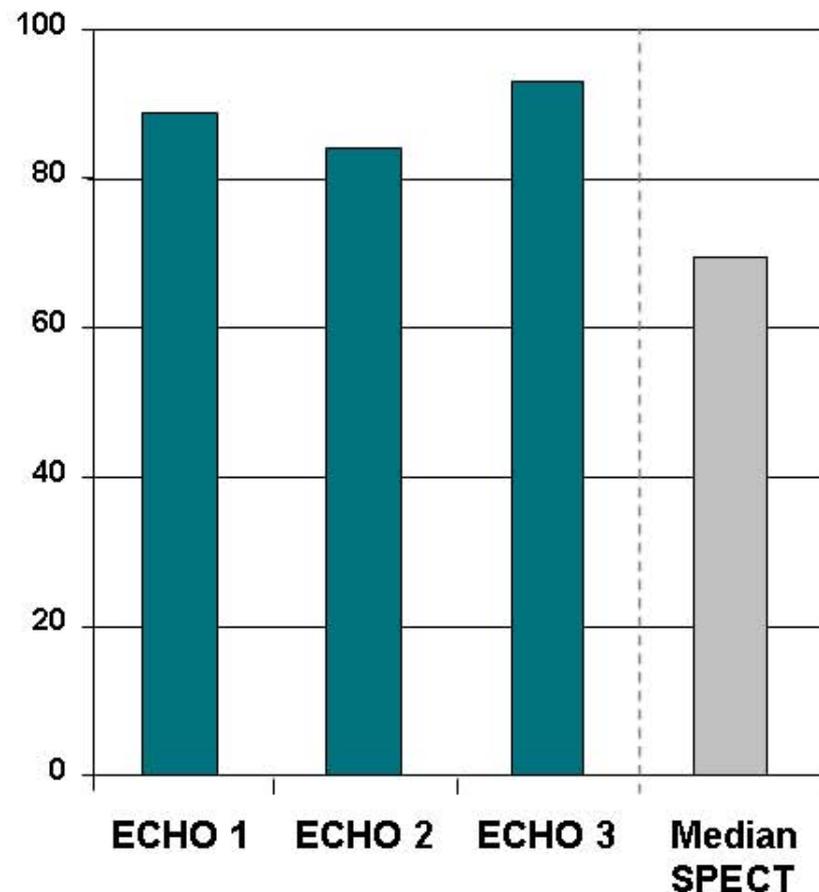


# Percent of CAD+ Patients Correctly Localized in ANGIO Subpopulation

## AI-700-32



## AI-700-33



# Go to Further Diagnostic Testing

	<b>Yes</b>	<b>No</b>	
<b>AI-700 ECHO</b>	<b>50</b>	<b>50</b>	<b>100</b>
<b>SPECT</b>	<b>50</b>	<b>50</b>	<b>100</b>

\*Non-diagnostic  
50% disease prevalence

# Go to Further Diagnostic Testing

	Yes	No	
AI-700 ECHO	50	50	100
SPECT	50	50	100
Non-contrast ECHO	50+15*	35	100

\*Non-diagnostic  
50% disease prevalence