

# Evaluation of Cardiotoxicity in Clinical Drug Development: Echo Core Lab Imaging

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# Echocardiography is Easily Accessible and Low Risk

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- Noninvasive and widely accessible
- No known side effects even with frequent and repeated testing
- Portable, relatively low cost



# Echo Provides Data on Cardiac Structure and Systolic Function

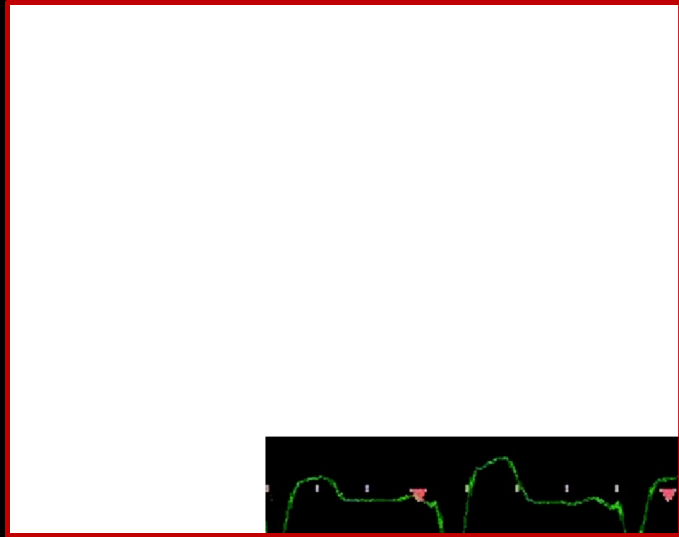
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- Anatomic and functional quantification of cardiac chambers
  - LV linear dimensions, wall thickness
  - LV mass, volumes, and ejection fraction (EF)
  - RV mass, function, and pressure
  - LA and RA size, volume, and function
  - Valvular structure and function



# Echo Provides Data on LV & RV Diastolic Function and Hemodynamics

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# Core Lab Echocardiography has Played a Major Role in Advancing Cardiovascular Research

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- Numerous studies establish core lab quantitative echo as the modality to assess cardiac remodeling
  - Coronary disease, heart failure, drug toxicity, device and drug effects
  - SAVE, DEFIANT, MIRACLE, MIRACLE-ICD, REVERSE, InSync MARQUIS III CRT-ICD , COMPASS-HF, ACTION, CARDIA, LIFE, CHS, VALIANT, V-HEFT, PRESERVE, CHARM
- Standardized process with integrated quality assurance

# Guidelines to Establish Standards in Core Lab Echocardiography

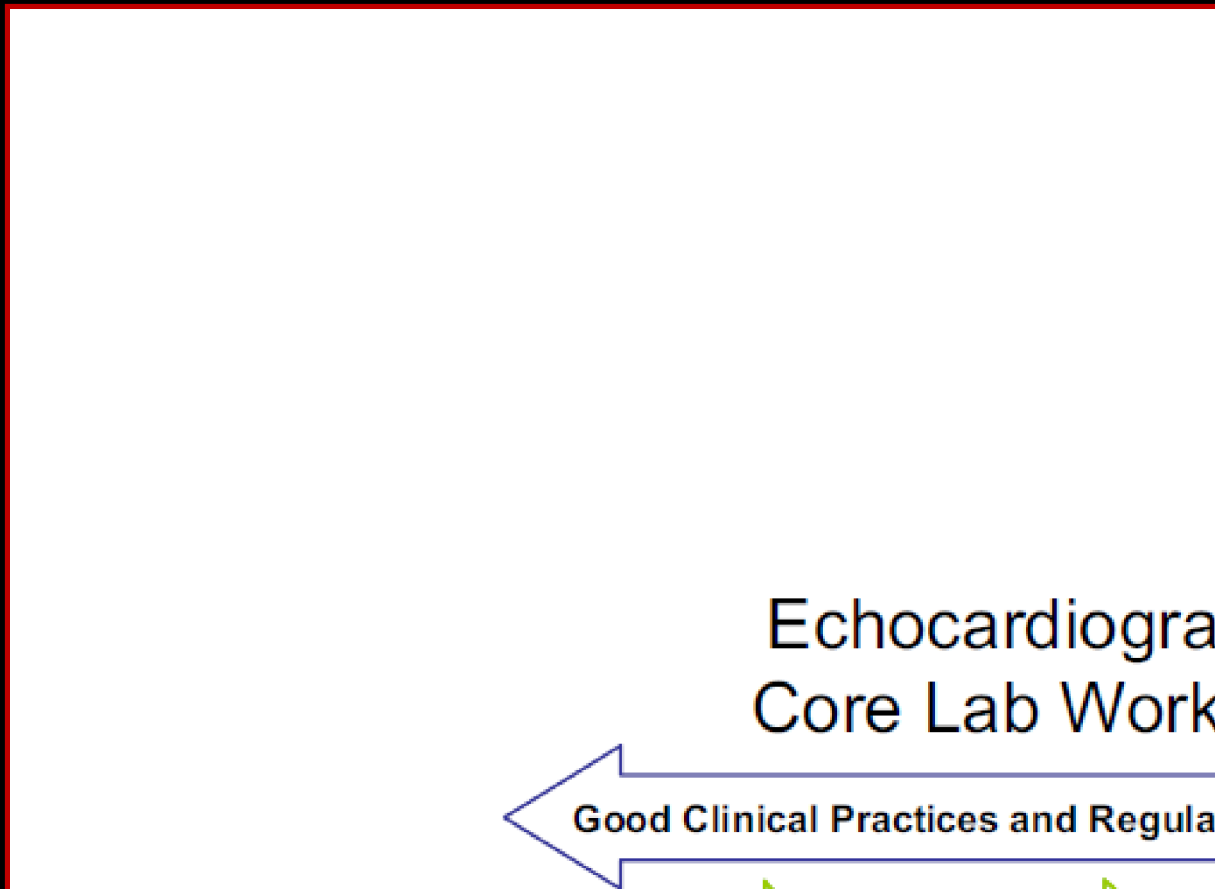
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# Core Lab Goals and Logistics

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- Goals of core lab is to ensure robust, precise echo data and to minimize variability to answer the study objective



# Core Lab and Sites Need to Have Bidirectional Communication

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- Involve core lab PI early and throughout trial (study design and echo analysis plan)
- Monitor quality control throughout study
- Ensure adequacy of late-model equipment
- Improve and maintain high echo data quality
- Establish manual of operations
- Dedicated personnel training (webcasts, instructional videos, face-to-face meetings)



# Core Lab Has Established Data Quality and Standards

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- Create rigorous image analysis plan
  - Personnel training plans, analysis tools, measurements, analytic plans, quality assessment tools
- Establish standard method for image transfer
- Maintain core lab log, secure environment for data storage
- Develop case report forms for data entry
- Perform regular data QA (range limit checks, double entry)
- Perform regular QC measures to decrease variability

# Limitations of Echocardiography – Variability

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- Variability, variability, variability
- Patient habitus, comorbidities can affect acoustic windows and image quality
- Suboptimal endocardial visualization and foreshortened LV apical views limit accurate measurements
- Under or overgaining can also affect endocardial definition
- Geometric assumptions (linear dimensions and LV mass)

# Potential Sources of Variability

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- Intra-reader and inter-reader
- Intra-sonographer and inter-sonographer
- Beat-to-beat
- Biologic (day-to-day)
- Reader (temporal) drift
- Unmeasurable data (e.g. missing secondary to poor image quality)

# Core Lab Goals are to Minimize Variability

1. Standardized “hands-on” training of echocardiographic sonographers and readers
2. On-site observation of experienced sonographers by trained physician echocardiographers
3. Strategies to optimize image quality, including using latest generation echocardiographic equipment and recording images digitally, if possible
4. Centralized reading, ideally with a highly experienced single adjudicator, or limited number of final adjudicators; minimize number of sonographers and readers
5. Blind duplicate readings for documenting intrareader and interreader and sonographer variability during the pilot phase and throughout the study
6. Periodic reader review sessions and adjudication of duplicate studies in which measurement variability exceeds a predetermined

# Special Considerations in Drug Cardiac Toxicity Studies

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- Rapid initiation and completion of clinical trials necessitates short time frame for training and standardization
- Use of control group for statistically significant comparison in cardiac parameter as opposed to arbitrary cutpoint

# Directions to Advance Quantitative Echocardiography

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- Contrast agents to improve endocardial definition
- Sensitive measures of cardiac function (strain, strain rate)
- 3D volumetric analysis may also improve accuracy



# Strain Imaging is a Promising Tool

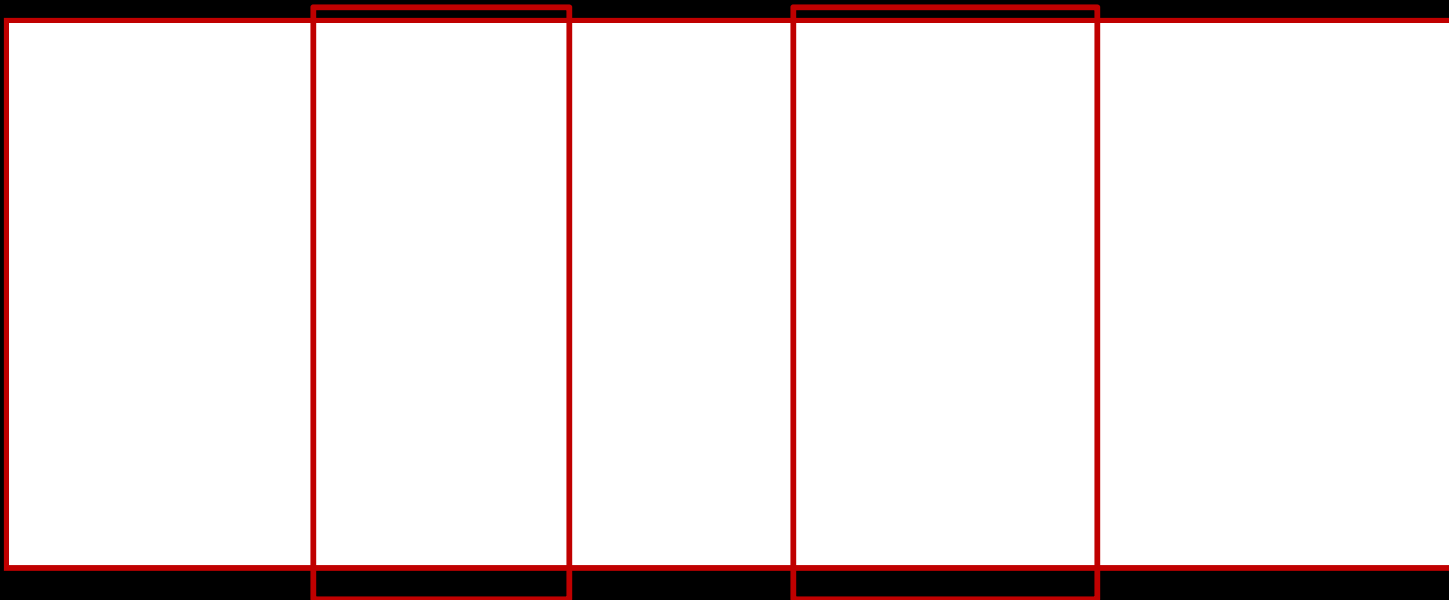
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- Strain imaging measures cardiac deformation; regional and global assessment of cardiac function
- 2D methods are angle independent and more reproducible
- Strain imaging can detect subclinical dysfunction in amyloidosis, hypertrophic cardiomyopathy
- Smaller studies in chemotherapy population show significant decline in strain or strain rate despite normal LVEF
- Requires post-hoc analysis; need for widely accepted vendor independent methodology

# 3D Echo May Overcome Some Limitations in Variability

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- Improved accuracy and reproducibility with 3D echo-based LV volume and EF measurements
- Not affected by wall motion abnormalities or shape





# Summary

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- Echo is easy to use, portable, and safe
- Established core lab methods to reduce variability; established as a robust tool
- Limitations are in variability and image quality in select groups
- Advancements in strain imaging and 3D echo may overcome these limitations





Additional slides

# Core Lab Echocardiography is a Validated Methodology to Reduce Variability

- Compared with local site readings, core lab measurements have significant prognostic value
  - ACTION study – **A** Coronary disease Trial Investigating Outcome with Nifedipine GITS
  - 7016 chronic stable angina patients, median f/u 4.9 years
  - Core Lab superior in reducing variability – LVEF SD 6.4% versus local lab SD 9.2%

	Local EF (40 to 72%)	Core Lab EF (38 to 59%)
All cause death	1.38 (1.02-1.87)	2.51 (1.90-3.32)
MI	1.14 (0.83-1.58)	1.77 (1.31-2.38)
Heart Failure	2.23 (1.32-3.75)	4.50 (2.83-7.14)
Primary endpoint (efficacy)	1.22 (1.01-1.46)	1.79 (1.51-2.13)
Primary endpoint (safety)	1.28 (1.02-1.60)	2.03 (1.65-2.49)

# Limitations of Echocardiography – Variability

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- In other studies, greatest sources of variability was with repeated echo measurements



RER = Repeated echo recording

RVM = Repeated video measurement

# Limitations of Echocardiography – Variability

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- Need to develop robust and contemporary measures of systolic and diastolic cardiac function and remodeling
- Predictors of Response to CRT (PROSPECT) trial with marked variability in measures of dyssynchrony

