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January 26-27, 2017

The role of imaging in clinical trials

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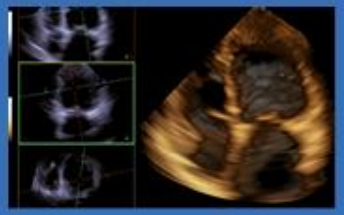

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Faculty disclosure

Alexandra Goncalves

I disclose the following financial relationships:

- **Academic cardiologist**
- **Employee of Philips Healthcare**

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- Cardiovascular disease is a worldwide epidemic
- The funding for research and development is limited

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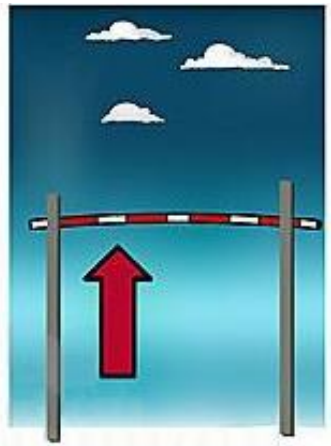
Clinical trials represent the most refined tool for drug/device development

$$ Regulations are more complex & Cost have become greater!!

- Proposed therapies must be compared against standard therapies
- Hard endpoints take time to occur
- Hard to get enough of the right types of patients timely



Surrogate markers

- *A surrogate endpoint is expected to predict clinical benefit (or harm, or lack of benefit) based on epidemiologic, therapeutic, pathophysiologic or other scientific evidence (FDA).*

Assessing response to therapy

- Early identification of responders and non-responders
- Early Go vs no Go
- Decision point in adaptive design
- Building evidence for validation or qualification

Cancer Informatics 2007:4 13–18

Surrogate markers

Smaller sample sizes

Shorter follow-up periods

↓ Financial cost

Effective therapies available to the public more quickly

CV Imaging as a Biomarker

- Detection
- Characterization
- Monitoring

Phenotyping /Patients selection

Time to progression

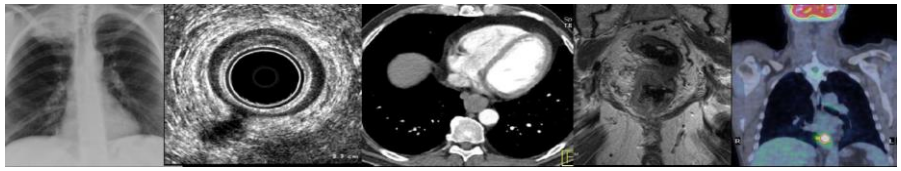


Table 1 | Imaging trials with cardiovascular clinical outcome end points

Type of trial	Trial name	End point(s)	Results[a]
ACE inhibitor (ramipril)			
Outcomes	HOPE[26]	Composite of cardiovascular death, MI, and stroke	22% reduction in HR of composite outcome in ramipril a over 5 years. No significant difference in cardiovascular outcomes with vitamin E supplementation (RR 1.05, 95 CI 0.95–1.16; *P*=0.33)
Imaging (substudy of HOPE)	SECURE[27]	Change in CIMT measured with ultrasonography	37% regression in mean maximum CIMT in ramipril arm over 4.5 years. No difference in CIMT progression for patients on vitamin E versus those on placebo
Statin (primary prevention; rosuvastatin)			
Outcomes	JUPITER[40]	Composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, and revascularization	43% reduction in HR of composite outcome in rosuvasta arm over 1.9 years
Imaging	ASTEROID[41]	Change in PAV measured with IVUS	0.98% regression in PAV in rosuvastatin arm over 2 yea
Imaging	METEOR[42]	Change in CIMT measured with ultrasonography	Statistically nonsignificant regression in CIMT in rosuvastatin arm from baseline over 2 years
Statin (secondary prevention; atorvastatin)			
Outcomes	PROVE IT–TIMI 22[37]	Composite of mortality, MI, stroke, hospitalization for unstable angina, and revascularization	16% reduction in HR of composite outcome in atorvasta arm over 24 months
Imaging	REVERSAL[38]	Change in PAV measured with IVUS	0.4% regression in PAV in atorvastatin arm over 18 mont
Imaging	ARBITER[39]	Change in CIMT measured with ultrasonography	5.4% regression in mean CIMT in atorvastatin arm over 12 months

R azzouk, L. & Farkouh, M. E E. Nat. Rev. Cardiol. 6, 524–531 (2009)

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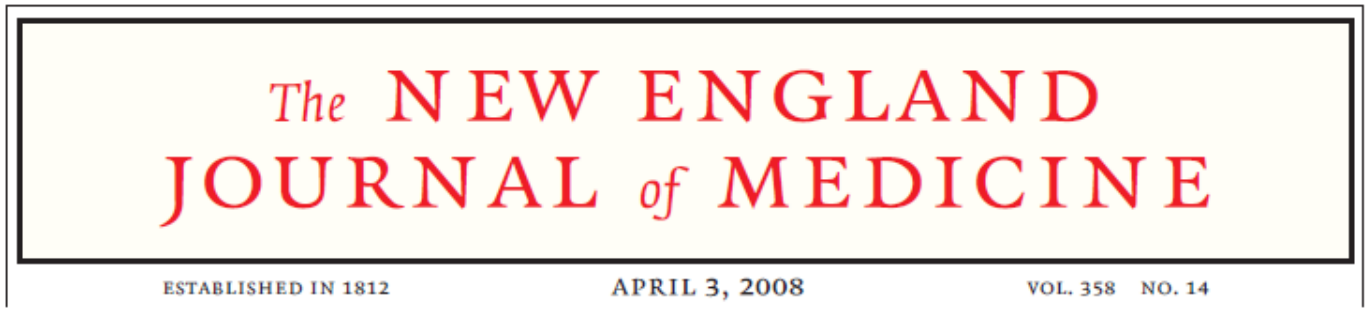
Lessons learned



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 3, 2008 VOL. 358 NO. 14

Simvastatin with or without Ezetimibe in Familial Hypercholesterolemia

John J.P. Kastelein, M.D., Ph.D., Fatima Akdim, M.D., Erik S.G. Stroes, M.D., Ph.D., Aeilko H. Zwinderman, Ph.D., Michiel L. Bots, M.D., Ph.D., Anton F.H. Stalenhoef, M.D., Ph.D., F.R.C.P., Frank L.J. Visseren, M.D., Ph.D.,

Results questioned by the use of single-frame rather than moving images and a 17% rejection rate of ultrasound data

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Lessons learned

Results of the Predictors of Response to CRT (PROSPECT) Trial

Eugene S. Chung, MD; Angel R. Leon, MD; Luigi Tavazzi, MD; Jing-Ping Sun, MD; Petros Nihoyannopoulos, MD; John Merlino, MD; William T. Abraham, MD; Stefano Ghio, MD; Christophe Leclercq, MD; Jeroen J. Bax, MD; Cheuk-Man Yu, MD, FRCP; John Gorcsan III, MD; Martin St John Sutton, FRCP; Johan De Sutter, MD, PhD; Jaime Murillo, MD

Background—Data from single-center studies suggest that echocardiographic parameters of mechanical dyssynchrony may improve patient selection for cardiac resynchronization therapy (CRT). In a prospective, multicenter setting, the Predictors of Response to CRT (PROSPECT) study tested the performance of these parameters to predict CRT response.

Methods and Results—Fifty-three centers in Europe, Hong Kong, and the United States enrolled 498 patients with standard CRT indications (New York Heart Association class III or IV heart failure, left ventricular ejection fraction ≤35%, QRS ≥130 ms, stable medical regimen). Twelve echocardiographic parameters of dyssynchrony, based on both conventional and tissue Doppler–based methods, were evaluated after site training in acquisition methods and blinded core laboratory analysis. Indicators of positive CRT response were improved clinical composite score and ≥15% reduction in left ventricular end-systolic volume at 6 months. Clinical composite score was improved in 69% of 426 patients, whereas

Efforts aimed at reducing variability arising from technical and interpretative factors may improve the predictive power of these echocardiographic parameters in a broad clinical setting.

beyond current guidelines. Efforts aimed at reducing variability arising from technical and interpretative factors may improve the predictive power of these echocardiographic parameters in a broad clinical setting. (***Circulation*. 2008;117: 2608-2616.**)

Limitations of CV Imaging as a Biomarker

- Data collection and sharing
- Standardization of imaging acquisition protocols
- Standardized image measurement methods
- Standardized Image Review and Assessment
- Metadata standardization
- Quality review process

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PARAGONHF

Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction (PARAGON-HF)

This study is currently recruiting participants. (see Contacts and Locations)

Verified June 2016 by Novartis

Sponsor:
Novartis Pharmaceuticals

Information provided by (Responsible Party):
Novartis (Novartis Pharmaceuticals)

ClinicalTrials.gov Identifier:
NCT01920711

First received: August 8, 2013
Last updated: June 12, 2016
Last verified: June 2016
History of Changes

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ASE EXPERT CONSENSUS STATEMENT

Echocardiographic Imaging in Clinical Trials: American Society of Echocardiography Standards for Echocardiography Core Laboratories

Endorsed by the American College of Cardiology Foundation

Table 1 Categories of echocardiography use in clinical trials

Category	Description
A	Any study that includes FDA or other regulatory body oversight or is performed for registration. Although specific guidance for imaging is lacking, the FDA's general requirements for regulatory compliance mandate the highest level of best practices.
B	Studies that do not involve FDA or other regulatory body oversight but involve complex imaging or include echocardiographic measures as primary or secondary efficacy or safety endpoints.
C	Studies that do not involve regulatory oversight, complex imaging, or echocardiographic endpoints.

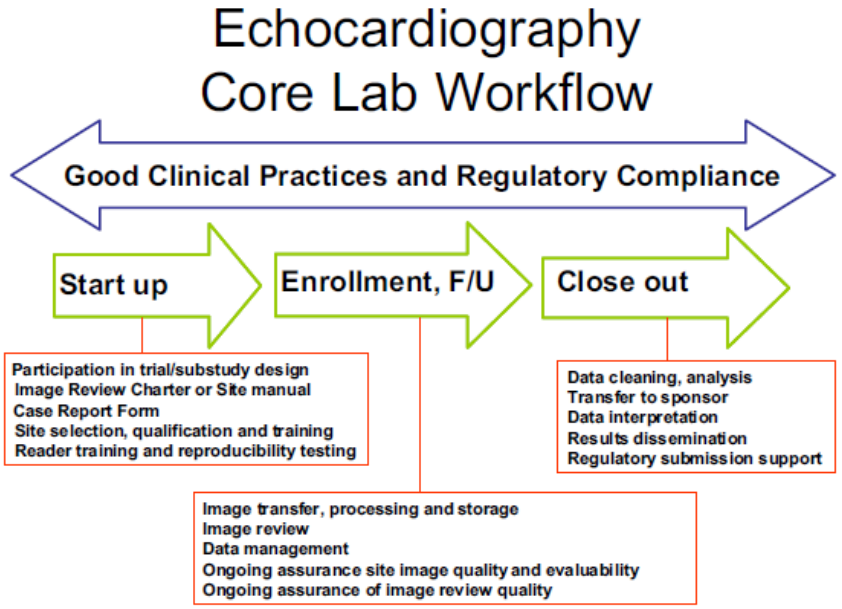

Figure 1 ECL work flow. *F/U*, Follow-up.

J Am Soc Echocardiogr. 2009 Jul;22(7):755-65

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Recommendations of the European Association of Echocardiography

How to use echo-Doppler in clinical trials: different modalities for different purposes

Maurizio Galderisi[1]*, Michael Y. Henein[2], Jan D'hooge[3], Rosa Sicari[4], Luigi P. Badano[5], Josè Luis Zamorano[6], and Jos R.T.C. Roelandt[7], on behalf of the European Association of Echocardiography

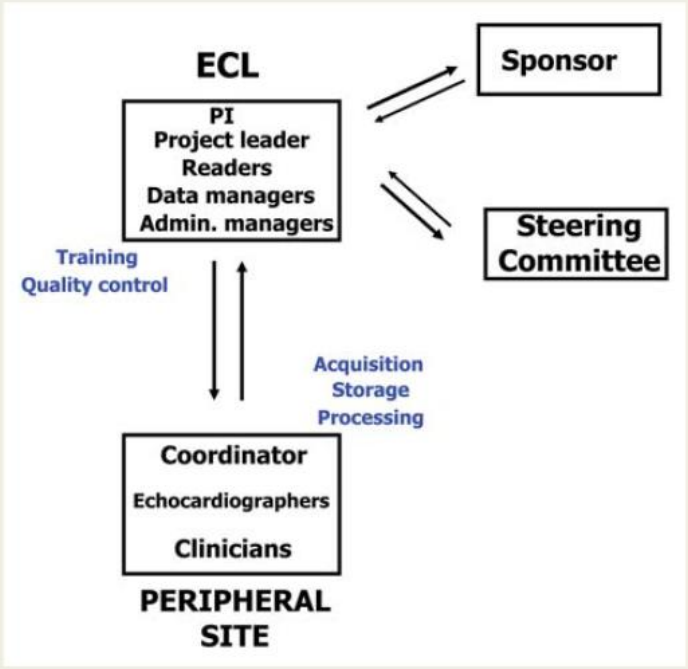

Figure 3 Structure and workflow of ECLs based quality assurance system.

Table I **Top-ten procedures recommended from EAE for quality control of clinical trials.**

1. To choose the ECLs on the basis of the head and team experience in both ultrasound technique and clinical trial planning and performance
2. To involve the head and the ECLs in the study design
3. To standardize 'hands on' training of echocardiographers either onsite or at centralized meeting before starting the clinical trial
4. To monitor echocardiographers of the peripheral sites for technical quality (acquisition, storage, and processing) of their echo studies
5. To overview quality of the study acquisition at peripheral sites with the head of the core laboratory
6. To minimize the number of readers in ECLs in order to improve reproducibility of measurements
7. To check the reader variability of ECLs by periodical joint reading sessions with the head
8. To maintain an optimal level of communication between ECLs and peripheral sites throughout the time course of the study
9. To maintain an optimal level of communication between ECLs and both study sponsor and steering committee throughout the time course of the study
10. To involve head and investigators of both ECLs and peripheral sites in data analysis, presentation, and publication

J Am Soc Echocardiogr. 2009 Jul;22(7):755-65

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Table 3 Doppler echocardiographic variables and indices suggested as possible primary and secondary echo endpoints suggested from EAE in specific settings of clinical trials

Disease	Primary echo endpoints	Secondary echo endpoints
Arterial hypertension	LV mass	RWT, MFS, *E*/*e*' ratio, LA volume, GLS
Systolic heart failure	2D/3D LVEF, DT, PAPs	*E*/*e*' ratio, MR severity, TAPSE
Heart failure with normal EF	*E*/*e*' ratio, LA volume	GLS, PAPs
Acute myocardial infarction	2D/3D LVEF, DT, *E*/*e*' ratio, GLS	LA volume, TAPSE, 3D RVEF
Atrial fibrillation and stroke	*E*/*e*' ratio, LA volume	LAA flow velocities, MR severity
Cardiac toxicity of chemotherapy	2D/3D LVEF, *E*/*e*' ratio, GLS	TAPSE, 3D RVEF

2D, two-dimensional; 3D, three-dimensional; DT, deceleration time of E velocity; *E*/*e*' ratio, ratio of transmitral E velocity to tissue Doppler-derived early diastolic velocity of the mitral annulus; GLS, global longitudinal strain by speckle-tracking echocardiography; LA, left atrial; LAA, left atrial appendage; LV, left ventricular; LVEF, LV ejection fraction; MFS, mid-wall fractional shortening; MR, mitral regurgitation; PAPs, pulmonary arterial systolic pressure; RV, right ventricular; RWT, relative wall thickness; RVEF, right ventricular EF; TAPSE, tricuspid annular plane systolic excursion.

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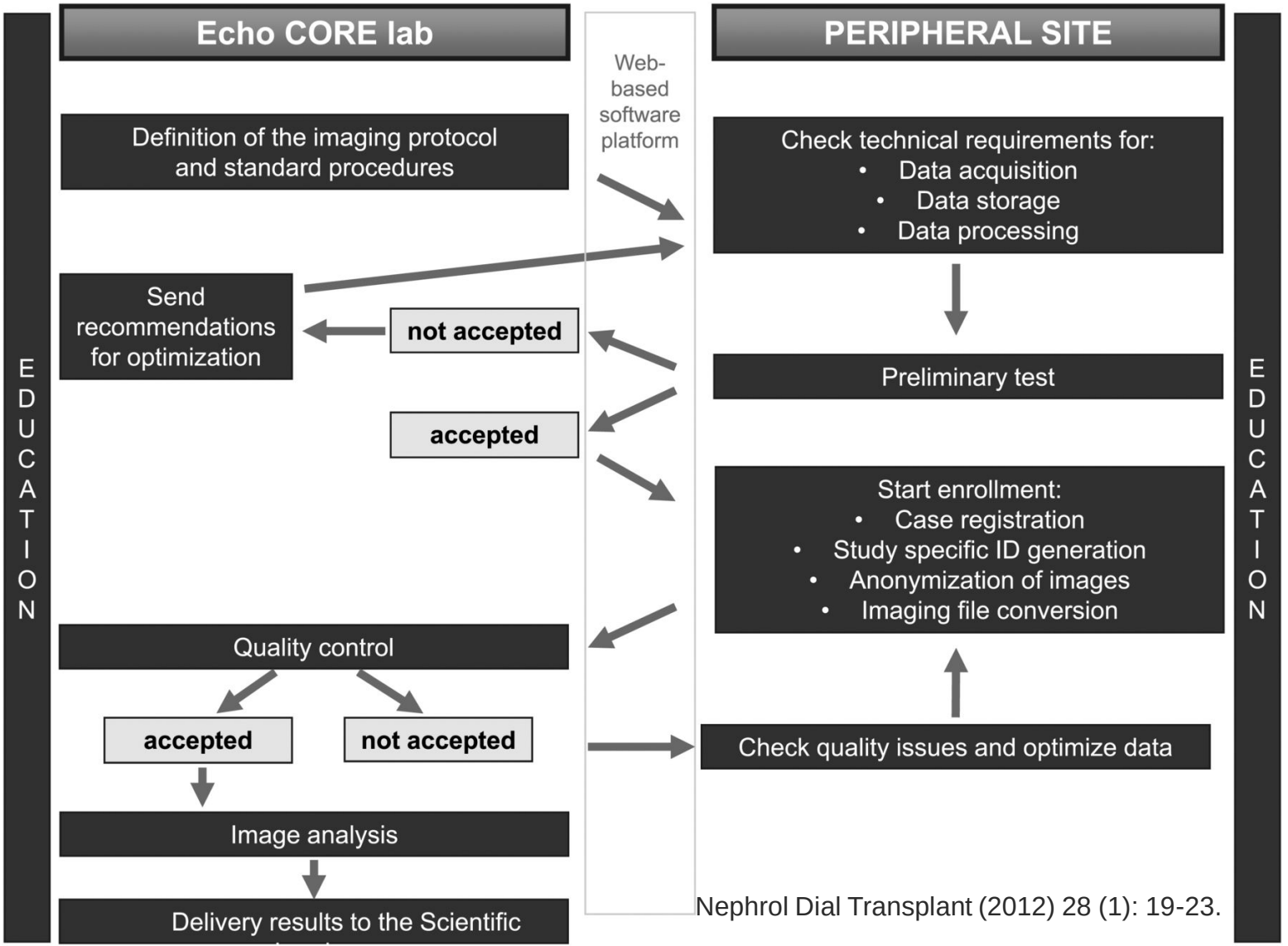

Nephrol Dial Transplant (2012) 28 (1): 19-23.

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Valvular heart disease

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STATE-OF-THE-ART PAPER

Paravalvular Leak After Transcatheter Aortic Valve Replacement

The New Achilles' Heel? A Comprehensive Review of the Literature

Philippe Généreux, MD,*†‡ Stuart J. Head, MSc,§ Rebecca Hahn, MD,*† Benoit Daneault, MD,*†
Susheel Kodali, MD,*† Mathew R. Williams, MD,*† Nicolas M. van Mieghem, MD,‖
Maria C. Alu, MM,* Patrick W. Serruys, MD, PhD,‖ A. Pieter Kappetein, MD, PhD,§
Martin B. Leon, MD*†

- *Given the limitations of the current literature, the nature and strength of the relationship between PVL and mortality are still to be determined.*
- *Future studies should standardize the evaluation of PVL and ensure an appropriate classification of its severity.*

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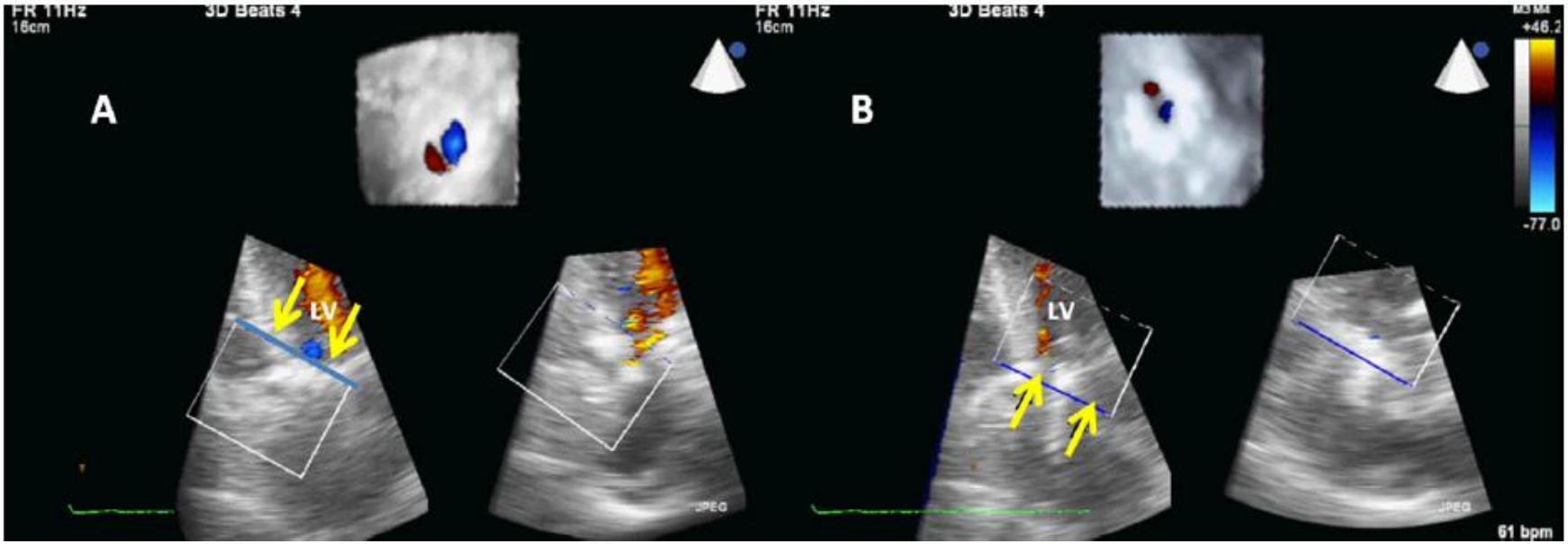
Three-Dimensional Echocardiography in Paravalvular Aortic Regurgitation Assessment after Transcatheter Aortic Valve Implantation

Alexandra Gonçalves, MD, Carlos Almeria, MD, Pedro Marcos-Alberca, MD, PhD, FESC, Gisela Feltes, MD, Rosana Hernández-Antolín, MD, PhD, Enrique Rodríguez, MD, José C. Silva Cardoso, MD, PhD, Carlos Macaya, MD, PhD, FESC, and José Luis Zamorano, MD, PhD, FESC, *Madrid, Spain; Porto, Portugal*



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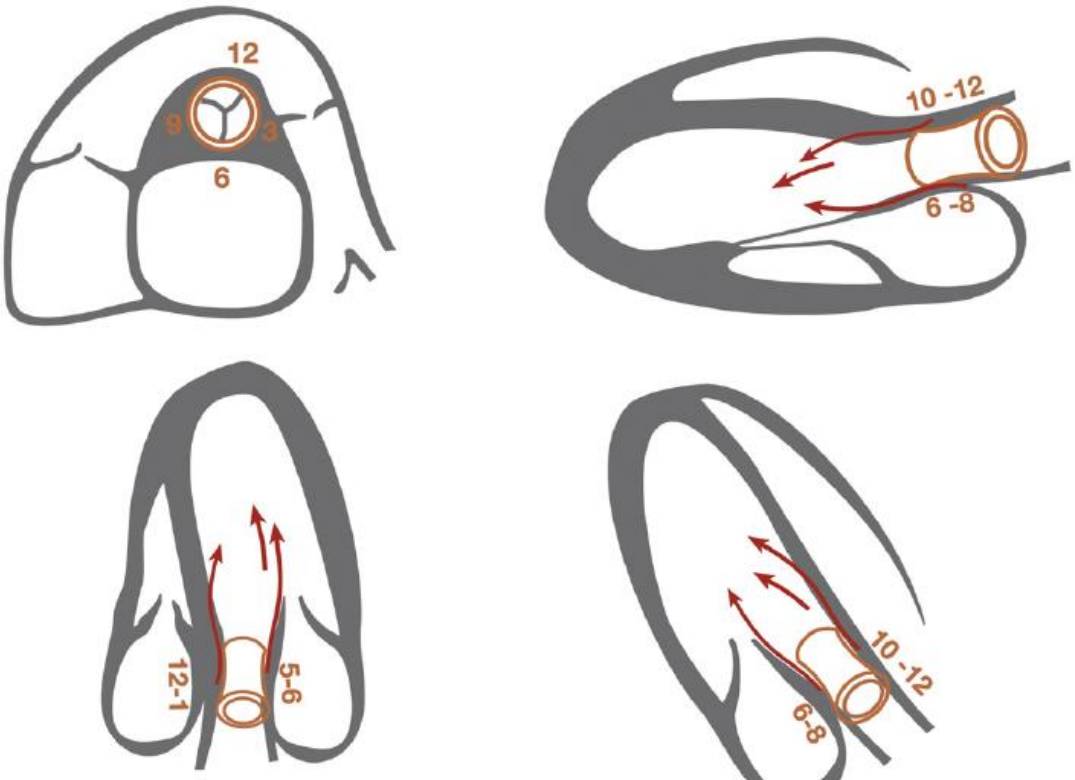
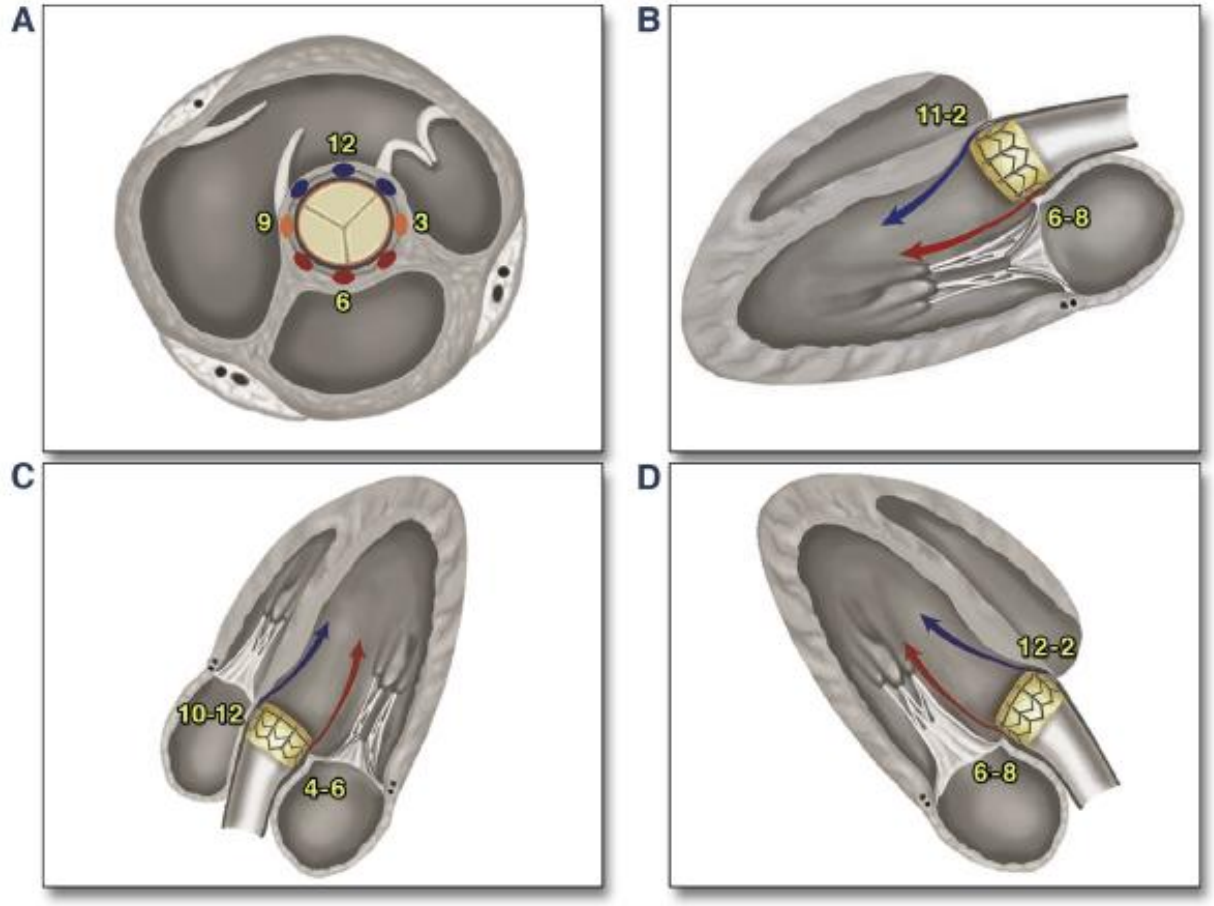


Assessment of Paravalvular Regurgitation Following TAVR

A Proposal of Unifying Grading Scheme

Philippe Pibarot, DVM, PhD,* Rebecca T. Hahn, MD,† Neil J. Weissman, MD,‡ Mark J. Monaghan, PhD§

FIGURE 3 Location of the PVR Jets in the Different Transthoracic Echocardiographic Views



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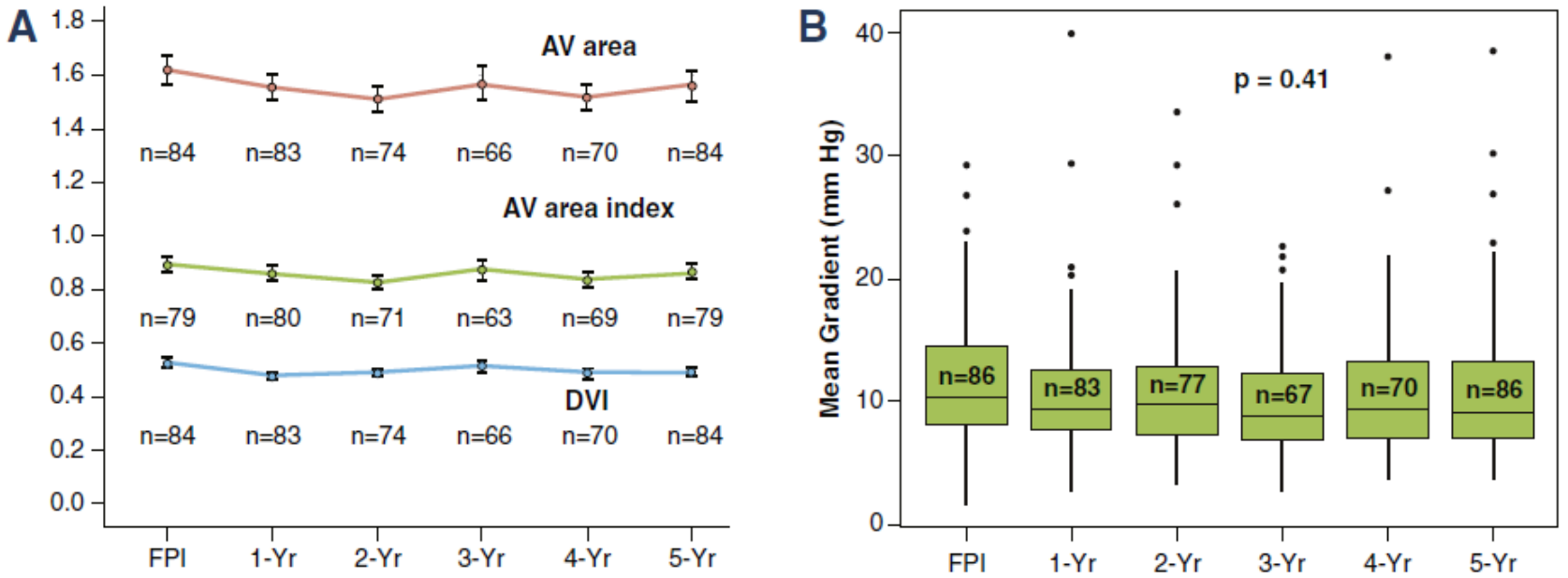
Long-Term Valve Performance of TAVR and SAVR

A Report From the PARTNER I Trial

Melissa A. Daubert, MD,[a] Neil J. Weissman, MD,[b] Rebecca T. Hahn, MD,[c] Philippe Pibarot, DVM, PhD,[d] Rupa Parvataneni, MS,[e] Michael J. Mack, MD,[f] Lars G. Svensson, MD, PhD,[g] Deepika Gopal, MD,[f] Samir Kapadia, MD,[g] Robert J. Siegel, MD,[h] Susheel K. Kodali, MD,[c] Wilson Y. Szeto, MD,[i] Raj Makkar, MD,[h] Martin B. Leon, MD,[c] Pamela S. Douglas, MD[a]

FIGURE 3 Valve Hemodynamics and Left Ventricular Mass Index of TAVR



J Am Coll Cardiol Img 2017;10:15–25

Implementation of Echocardiography Core Laboratory Best Practices: A Case Study of the PARTNER I Trial

Pamela S. Douglas, MD, FASE, Robert A. Waugh, MD, Gerald Bloomfield, MD, Gary Dunn, MBA, LaGia Davis, MS, CCRP, Rebecca T. Hahn, MD, FASE, Philippe Pibarot, DVM, FASE, William J. Stewart, MD, FASE, Neil J. Weissman, MD, FASE, Irene Hueter, PhD, Robert Siegel, MD, Stamatios Lerakis, MD, D. Craig Miller, MD, Craig R. Smith, MD, and Martin B. Leon, MD, *Durham, North Carolina; New York, New York; Quebec City, Quebec, Canada; Washington, District of Columbia; Los Angeles and Stanford, California; Atlanta, Georgia*

Table 1 Intraclass correlation coefficients demonstrating close correlation of measurements and high reproducibility across all readers for continuous variables

Reader type	Analysis	Biplane LVEF	Visual LVEF	Mean AV gradient	Peak AV gradient	AVA
Sonographer	Intraobserver	0.70-0.87	0.95-0.99	0.99-1.00	1.00	0.91-1.00
	Interobserver	0.89	0.88	0.97	0.97	0.90
Physician	Intraobserver	0.56-0.94	0.98-0.99	0.99-1.00	0.99-1.00	0.95-0.97
	Interobserver	0.92	0.95	0.99	0.99	0.95
Pairwise comparisons		649	1,101	1,065	1,077	1,059

Intraclass correlation coefficients ranging from 0.92 to 0.99 and κ statistics from 0.58 to 0.85 for key variables.

- A high standard of measurability and reproducibility can result from extensive quality assurance efforts in both image acquisition and analysis.
- These results provide a reference for future studies of aortic stenosis patients and should encourage the wider use of echocardiography in clinical research.

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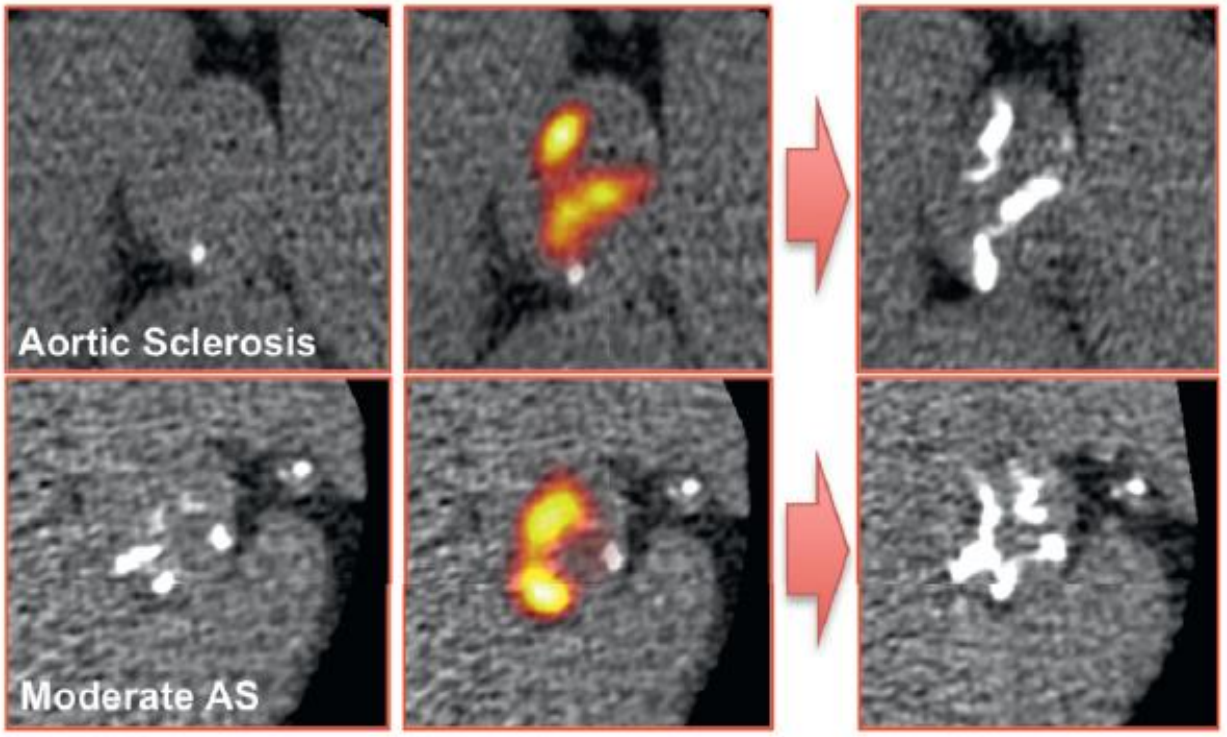
Valvular ^{18}F-Fluoride and ^{18}F-Fluorodeoxyglucose Uptake Predict Disease Progression and Clinical Outcome in Patients With Aortic Stenosis

FIGURE 1 Valvular ^{18}F-Fluoride Uptake Predicts the Progression of Calcification in Aortic Stenosis



18F-fluoride and 18F-FDG predicted disease progression and adverse clinical outcomes in aortic stenosis.

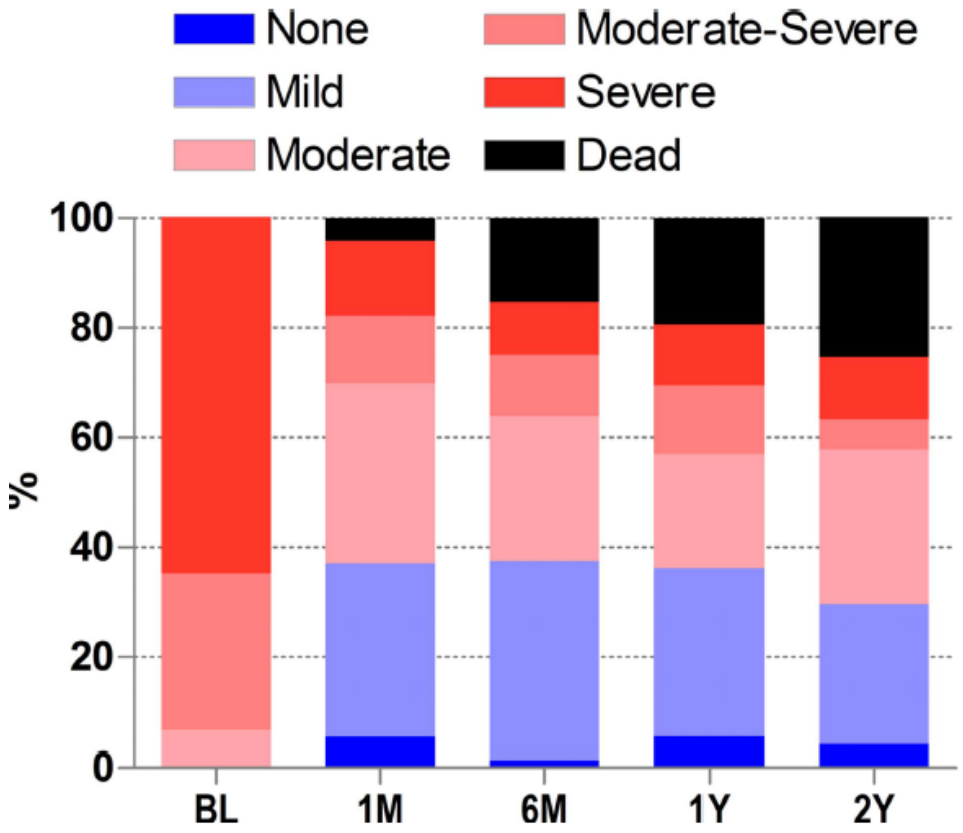
J Am Coll Cardiol. 2015 Sep 8;66(10):1200-1

openheart

Two-year outcomes after percutaneous mitral valve repair with the MitraClip system: durability of the procedure and predictors of outcome

Stefan Toggweiler,[1] Michel Zuber,[1,2] Daniel Sürder,[3] Patric Biaggi,[2,4] Christine Gstrein,[2] Tiziano Moccetti,[3] Elena Pasotti,[3] Oliver Gaemperli,[2] Francesco Faletra,[3] Iveta Petrova-Slater,[3] Jürg Grünenfelder,[2,4] Peiman Jamshidi,[1] Roberto Corti,[2,4] Giovanni Pedrazzini,[3] Thomas F Lüscher,[2] Paul Erne[1,2]

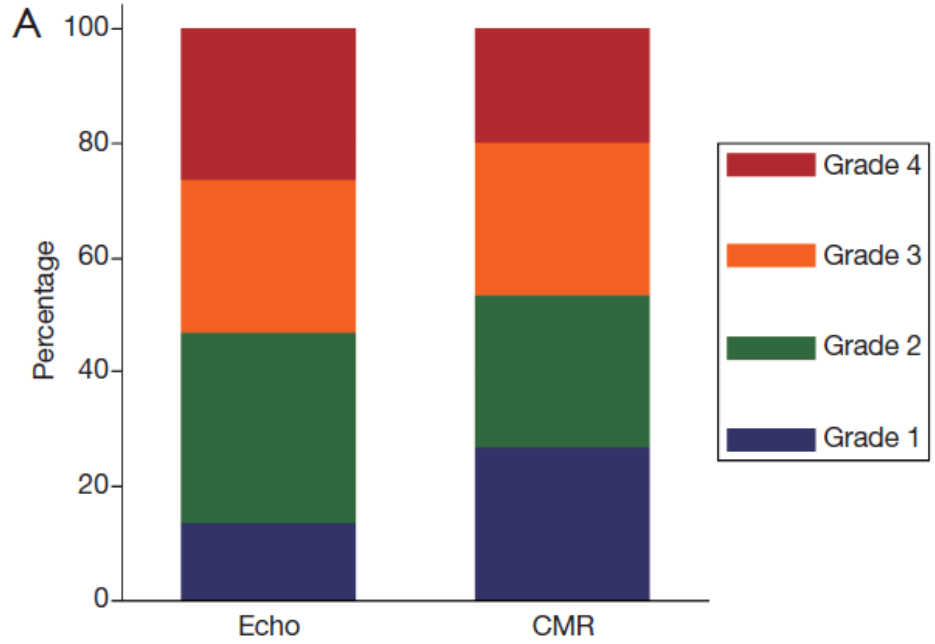
A mean transmitral gradient <3 mm Hg at baseline, an LAVI <50 mL/m2 and reduction of MR to less than moderate were associated with favourable outcome.



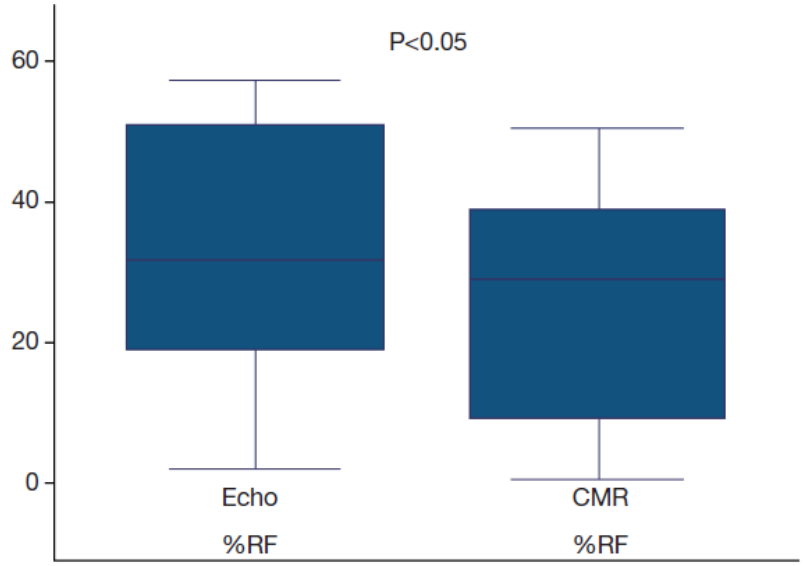
Quantitation of mitral regurgitation after percutaneous MitraClip repair: comparison of Doppler echocardiography and cardiac magnetic resonance imaging

Christian Hamilton-Craig[1,2,3], Wendy Strugnell[1], Niranjan Gaikwad[1], Matthew Ischenko[1], Vicki Speranza[1], Jonathan Chan[4], Johanne Neill[1], David Platts[1,2], Gregory M. Scalia[1,2], Darryl J. Burstow[1,2], Darren L. Walters[1,2]

Differences in MR severity by echo and CMR



Differences in RF by echo and by CMR



Technical limitations exist for both techniques, and quantitation remains a challenge in some patients.

Ann Cardiothorac Surg 2015;4(4):341-351

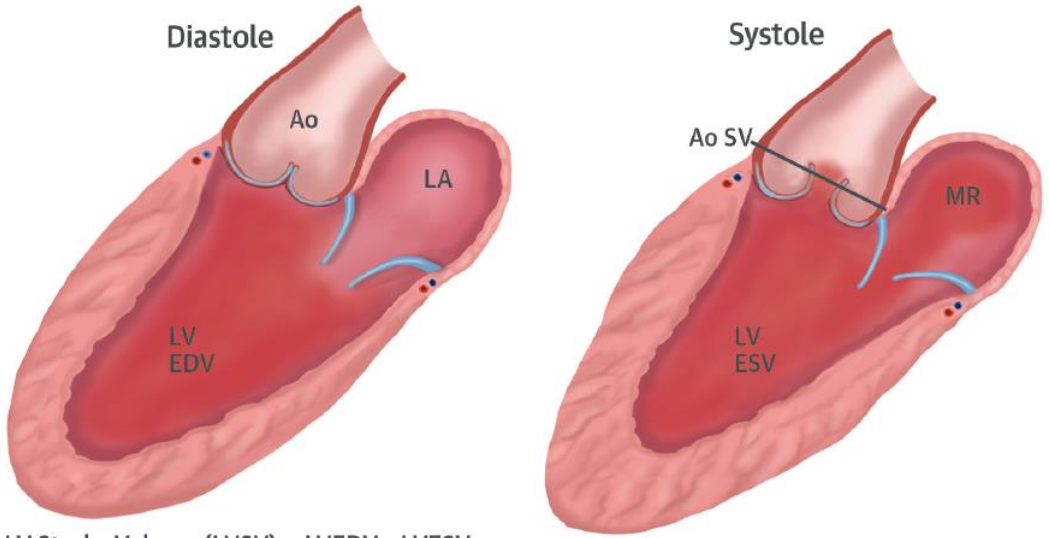
Current Assessment of Mitral Regurgitation

Not Making the Grade*

Saibal Kar, MD, Rahul Sharma, MD

We hope that in the future the severity of MR will not be characterized categorically as mild/moderate/severe but rather as a continuous variable incorporating regurgitant volume/fraction.

FIGURE 1 Schematic Diagram Showing the Principle of Estimation of Mitral Regurgitant Volume Using Cardiac MRI



LV Stroke Volume (LVSV) = LVEDV - LVESV
Mitral Regurgitation Volume = LVSV - AoSV

J Am Coll Cardiol. 2015 Mar 24;65(11):1089-91

Overcoming Limitations of CV Imaging as a Biomarker

- Control groups; High quality and uniform image
- Imaging experts involved in the design of the CT
- Image data interpreted consistently by experienced reviewers
- Uniform measurement methodology and variability avoidance from commercial equipment
- Metadata standardization
- Expert quality review process; Applying statistical methods to reduce variability

Conclusion

- There is an increasing role for the use of CV imaging outcomes as surrogates for clinical end points.
- Functional and anatomical imaging modalities need to be optimized in the design of cardiovascular trials.
- There is an increased emphasis on the relationship between the results of imaging studies and clinical outcomes.

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Thank you very much for your attention

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