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Core Lab Analysis of Baseline Echocardiographic Studies in the STICH Trial and Recommendation for Use of Echocardiography in Future Clinical Trials

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Abstract

Background—The Surgical Treatment for Ischemic Heart Failure (STICH) randomized trial was designed to identify an optimal management strategy for patients with ischemic cardiomyopathy. Baseline echocardiographic (Echo) examination was required for all patients.

Aims—The primary aim of this report is to describe the baseline STICH Echo Core Lab data. The secondary aim is to provide recommendations regarding how Echo should be used in clinical practice and research based on the experience gained from Echo in STICH.

Method—Between September 2002 and January 2006, 2,136 patients with an ejection fraction (EF) ≤ 35% and coronary artery disease amenable to coronary artery bypass grafting were enrolled. Echo was acquired by 122 clinical enrolling sites and measurements were performed by the Echo Core Lab after a certification process for all clinical sites.

Results—Echo was available for analysis in 2,006 (93.9%) patients; 1734 (86.4%) were men and mean (SD) age was 60.9 (9.5) years. Mean left ventricular (LV) end-systolic volume index measureable in 72.8% was 84.0 (30.9) mL/m^2, and EF was 28.9 (8.3) % with 18.5% of patients having EF >35%. Single plane measurement of LV and left atrial volume was similar to their volume by biplane measurement (r= 0.97 and 0.92, respectively). Mitral regurgitation severity by visual assessment was associated with a wide range of effective regurgitant orifice area (ERO), while ERO ≥ 0.2 cm^2 indicated at least moderate mitral regurgitation by visual assessment. .

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Deceleration time (DT) of mitral inflow velocity had a weak correlation with EF (r=0.25), but was inversely related to estimated pulmonary artery systolic pressure (r = −0.49).

Conclusion—In STICH patients with ischemic cardiomyopathy, Core Lab analysis of baseline Echo demonstrated a wide spectrum of LV shape, function, and hemodynamics as well as feasibility and limitations of obtaining essential Echo measurements. It is critical that utilization of Echo parameters in clinical practice and research needs to balance the strengths and weaknesses of the technique.

INTRODUCTION

The Surgical Treatment for Ischemic Heart Failure (STICH) trial, supported by the NHLBI, National Institutes of Health, is an international randomized trial designed to test two specific hypotheses in patients with left ventricular (LV) dysfunction and coronary artery disease (CAD).[1] The first hypothesis (H1) tested whether coronary artery bypass grafting (CABG) would result in improved long-term survival compared with intensive medical therapy alone. The second hypothesis (H2) tested whether combining a surgical ventricular reconstruction (SVR) procedure with CABG would improve survival free from cardiac hospitalization in comparison with CABG alone in patients with reduced LV ejection fraction (EF) and dysfunctional anterior segments. The STICH protocol required that all patients undergo baseline, 4-month follow-up, and 2-year follow-up echocardiography (echo) and measurements be performed by an Echo Core Laboratory (Lab). The primary outcome data in H2 patients (499 assigned to CABG vs 501 to CABG + SVR) showed no over-all benefit from the addition of SVR to CABG despite a more significant reduction in LV volumes and increase in EF with SVR.[2] The outcome results in H1 patients (602 assigned to medical therapy vs 610 to CABG) showed no statistically significant benefit for CABG in the primary outcome of all cause mortality. However, patients assigned to CABG compared to those assigned to medical therapy alone had lower rates of death from cardiovascular causes and of death from any cause or hospitalization for cardiovascular causes. [3] Knowledge of LV structure, function (volumes, EF, and diastolic function), and hemodynamics in STICH patients would help us to better understand the outcome of tested treatment strategies in future subgroup analyses. Since the STICH trial was conducted at 122 clinical sites in 26 countries, we made a substantial effort to standardize and maintain the quality of echocardiograms of study patients. Our experience in operating the Echo Core Lab in this large clinical trial had provided insights into how echocardiography should be used in clinical trials and subsequent implementation of trial data in our clinical practice.

Therefore, the aims of this report are 1. to provide feasibility of obtaining quality baseline echo data for the entire STICH trial cohort as well as for H1 and H2 separately, 2. to provide pertinent baseline echo data analyzed by Echo Core Lab in these patients, and 3. to provide recommendations for the use of echocardiography in clinical practice and trials.

METHODS

Patients

Between September 2002 and January 2006, 2,136 patients with an EF of 35% or less and coronary artery disease amenable to CABG were enrolled into STICH. The qualifying LVEF for enrollment was determined by clinical sites using any of available imaging modalities within 3 months of enrollment. More detailed inclusion and exclusion criteria have been published.[1, 2].

Design and Quality Assurance of the Echo Core Lab

The Echo Core Lab team that analyzed Echo studies for STICH (Appendix) consisted of experienced physician echocardiographers (with level 3 training and more than 5 years of practice) and sonographers (with more than 3 years of clinical sonography). They were instructed in the goals of the STICH trial and measurement standards. A manual of operation for echo was produced to standardize the sequence, duration, and technique of echo studies at all clinical sites in 26 countries. Each site was asked to submit 1 to 3 echo studies that demonstrated all of the required components of echo in order to be certified before patient enrollment began. When the initial echo studies did not meet minimal criteria for measurements of LV volumes, LVEF, mitral regurgitation (MR) severity, diastolic function, and tricuspid regurgitation velocity, additional studies were requested until the requirements were met.

Once an echo study arrived at the Echo Core Lab, it was transferred directly, if in digital format, to the Echo Core Lab's workstation (Digiview; Digisonics Inc. Houston, Texas) for measurements and archiving; if the study was in an analogue format, it was digitized first and then transferred. Echo measurements were performed by Echo Core Lab sonographers and were approved by Echo Core Lab physician staff. The qualitative assessments including MR severity, regional wall motion abnormalities, and grading of diastolic function severity were performed primarily by a physician member.

Echocardiographic Measurements

All measurements and analyses were performed without knowledge of clinical or other laboratory data. An average of 3 cardiac cycles was used for sinus rhythm, and an average of 3 to 5 cardiac cycles was used for atrial fibrillation. If arrhythmia or poor image quality prevented quantitative measurements, LVEF was estimated visually. Interobserver variability in measuring LV volumes was determined in a subset of patients. The following parameters were measured mostly according to the recommendation of the American Society of Echocardiography.[4]

LV Dimensions—LV dimensions were measured from the 2D parasternal long-axis view of the LV at the junction of the head of the papillary muscle and chordae. Long-axis dimension of the LV was measured from the apical 4-chamber view. The LV sphericity index was calculated as the ratio of the LV short-axis dimension and the maximum long-axis dimension. .

LV Volume and LVEF Measurement—LVEF was measured primarily by the Simpson's volumetric method whenever possible. Either a combination of apical 4- and 2-chamber views (preferentially) or a combination of apical 4-chamber and long-axis views was used. If 2 apical views were not available, only 1 apical view was used for the Simpson's single plane method. The LV endocardial border was traced contiguously from one side of the mitral annulus to the other, excluding the papillary muscles and trabeculations. LV end-diastolic volume (LVEDV) was measured at the time of QRS when LV cavity was largest and LV end-systolic volume (LVESV) when LV was smallest. They were indexed by the body surface area. When the definition of the LV endocardial border was not satisfactory from any apical view, LVEF was determined by visual estimation.

LV Regional Wall Motion—LV regional wall motion was analyzed visually using the standard 16-segment model. On the basis of the contractility of each segment, a wall motion score was assigned: 1 = normal, 2 = hypokinesis, 3 = akinesis, and 4 = dyskinesis. The wall motion score index was calculated as an average of the individual wall motion scores of

each visualized segment. If more than 2 segments were not visualized or wall motion abnormalities were global, wall motion analysis was not performed.

Left atrial volume—Left atrial (LA) volume was measured using the area-length method (= A1 × A2 / length) using the apical four chamber view and the apical long or the two chamber view. A1 is LA area from the apical four chamber view, A2 is LA area from the apical two or long axis view, and length is LA long axis dimension of the line drawn from the center of mitral annulus to the posterior wall of LA from an apical view. LA volume was also calculated from the apical 4 chamber view only using the following modified area-length method: A1 × A1 / length.

Stroke Volume and Cardiac Output—Stroke volume (SV) was calculated by two methods: one from the LV outflow tract (LVOT) using the following formula [3]: $SV = LVOT\ area \times LVOT\ TVI$ where TVI is the time velocity integral, and another from the LV volumes measured by the single or biplane Simpson's method: $SV = LVEDV - LVESV$. Cardiac output was calculated as the product of SV and heart rate.

MR Severity—The severity of MR was primarily determined by the physician's visual assessment of width, depth, and area of mitral regurgitation jet. In addition, effective regurgitant orifice (ERO) was determined using the PISA (proximal isovelocity surface area) method, as previously described[4, 5] whenever possible.

Pulmonary Artery Systolic Pressure—Pulmonary artery systolic pressure (PASP) was estimated from the peak tricuspid regurgitation (TR) velocity, obtained by continuous-wave Doppler echocardiography, and estimated right atrial pressure, as previously described.[6, 7]

Determination of Diastolic Function—Mitral inflow velocities were recorded by placing a small sample volume at the tip of mitral valve during diastole. Early diastolic velocity (E), late diastolic velocity with atrial contraction (A), and deceleration time (DT) of E velocity were measured from the inflow velocity recording.[4, 8] A velocity was not available for patients with atrial fibrillation. Mitral annulus velocities were measured using tissue Doppler imaging by placing a sample volume over the medial and/or lateral annulus to determine early diastolic velocity (e′) and late diastolic velocity with atrial contraction (a ′). In patients with sinus rhythm, diastolic function was graded as follows: Grade 1 = relaxation abnormality (no elevation of filling pressure), E/A less than 0.8 and DT greater than 240 msec; grade 2 = pseudonormalized filling (relaxation abnormality and mild elevation of filling pressure), E/A 0.8 to 1.5 and DT 160 to 240 msec; and grade 3 = restrictive filling (relaxation abnormality and marked elevation of filling pressure), E/A more than 1.5 and DT less than 160 msec. Diastolic function was regarded normal if medial or lateral e′ velocity was greater than 8 or greater than 10 cm/sec, respectively. If there was discrepancy among diastolic parameters in grading, function was classified as "indeterminate." Diastolic function was not graded in patients with atrial fibrillation.

Tei Index—The LV Tei index, or LV index of myocardial performance, was derived from the mitral inflow tract and LVOT velocity time intervals as previously described.[9].

Statistics

Continuous variables were summarized as mean (SD) and categorical variables were summarized as a percentage of the group total. Two-sample *t* tests were used to compare echocardiographic continuous variables. The χ^2 was used to compare categorical data. Because there was some overlap between the H1 and H2 patient groups and the statistical tests we used require independent samples, 74 patients included in both groups were

excluded from the statistical analysis. Pearson correlation coefficients are presented when describing relationships among echo parameters.

RESULTS

Of the total 2,136 patients, a baseline echo was available for analysis in 2,006 patients (93.9 %). Their mean age was 60.9 [9.5] years and 86.4% were male. Atrial fibrillation was present in 85 patients (5%). Table 1 shows echo variables and their values measured by the Echo Core Lab as well as the number of patients in whom each variable could be measured.

LV Dimensions and Sphericity Index

The mean LV end-diastolic dimension and LV long-axis dimension were significantly longer in H2 patients than the dimensions in H1 patients (p=.03 for end-diastolic dimension and P=.007 for long-axis dimension). The sphericity index was similar in H1 and H2 patients (p= 0.26). There was no significant difference between H1 and H2 patients in LV end-systolic dimension (p=.84).

LV Volumes and Ejection Fraction

In 873 of 2,006 patients (43.5%), a reliable delineation of the LV endocardial border was feasible from 2 apical views; in 587 patients (29.3%) border detection was possible from a single apical view only. Therefore, in 1,460 (72.8%) patients LVEDV and LVESV (hence, EF) were measured using the Simpson's method. When those 1,460 patients with volume measurement were compared with 546 patients without volume measurement, the latter group was older and heavier with more patients with hypertension or diabetes (Table 2).

Interobserver variability for measuring LV volumes was assessed in 67 patients (approximately 1 in 20 patients in whom LV volumes could be measured) and was determined to be good (r = 0.92) with the mean difference and the mean percentage difference of 8.9 (24.8) mL and 4.6 (11.6) %, respectively for LVEDV, and of 7.6 (23.3) mL and 6.8 (17.9) % for LVESV. Table 1 shows LV volumes, their indexes, and EF in H1 and H2 patients separately as well as their mean values (SD) in all patients. LV volumes were measured by both biplane and single plane Simpson method in 182 randomly selected patients and were highly correlated, as shown in Figure 1 (LVES, r = 0.97; LVED, r = 0.96). When LV volumes were correlated with LVEF, LVESV had a better correlation with LVEF than LVEDV (Figure 2). Although LVEF ≤35% was an enrollment criterion, LVEF measured by the Core Lab was greater than 35% in 18.5 % of patients (10.6 % had 35 < LVEF ≤40 % and 7.9 % had LVEF >40 %). The distribution of LVEF in STICH patients is shown in Figure 3.

Left Atrial Volume

There was no significant difference in mean LA volume index [41.9 (15.2) vs 42.8 (16.8) mL/m^2] whether measured by the biplane area-length method or from a single apical four chamber image, respectively (Figure 4).

Right Ventricular Systolic Function

Right ventricular systolic function was visually assessed in 1,838 patients; 1,387 (75.5%) had normal function; 237 (12.9%) had mildly reduced function; 156 (8.5%) had moderately reduced function; and 58 (3.2%) had severely reduced function.

SV and Cardiac Output

SV from the LVOT was available for 1,028 patients with a mean value of 64.9 (19.6) mL. In the 964 patients with data available, cardiac output and index were 4.5 (1.4) L/min and 2.3 (0.7) L/min/m^2, respectively. There was a statistically significant ($p<0.0001$), but a weak correlation between cardiac output and LVEF ($r= 0.26$). Mean stroke volume obtained from (LVEDV – LVESV) was 61.9 (19.6) mL. The correlation between two methods was modest ($r= 0.37$, $p < 0.0001$).

Mitral Regurgitation (MR) Severity

The determination of MR severity by visual assessment of color flow imaging was feasible for 1,852 patients (92.3 % of received Echo studies) and the distribution of MR severity in STICH patients is shown in table 1. There was a modest correlation between the severity of MR by visual assessment of color flow imaging and effective regurgitant orifice(ERO), which was measured in 169 patients ($r = 0.67$; $P<.001$). However, there was a wide range of ERO for each grade of MR severity (Figure 5). When ERO was 0.2 cm^2 or greater, MR was at least moderate by visual interpretation in most patients.

Diastolic Function and Filling Pressure

Baseline diastolic function assessment was feasible in 1,634 patients, and function was found to be abnormal in almost all patients enrolled in the trial. Only 5 of 1,634 patients had normal diastolic function. Diastolic function parameters including early diastolic mitral inflow (E) and annulus (e′) velocities, and E/e′ ratio as well as the number of patients in each diastolic dysfunction category are shown in Table 1. There was only a weak correlation ($r=0.25$) between LVEF and the DT of mitral inflow velocity, a noninvasive surrogate for pulmonary capillary wedge pressure, as shown in Figure 6. However, there was a gradual increase in LVESV [150 (60), 154 (55), 180 (60); $p <0.001$] and decrease in LVEF [30.8 (8.2), 30.6 (7.9), 25.6 (7.4); $p <0.001$] as diastolic dysfunction worsened from grade 1,2, to 3, respectively.

Pulmonary Artery Systolic Pressure (PASP)

PASP was elevated with a mean value of 42.8 (15.5) mmHg and correlated best with noninvasive estimates of diastolic filling pressure, E/e’ ($r=0.54$) and deceleration time of early diastolic mitral inflow velocity ($r= −0.49$) (Figure 7). It was found to have a moderate correlation with LA volume ($r=0.34$) and a weak correlation with LVEF ($r= −0.21$) and LVESV ($r=0.17$) but no correlation with the Tei index ($r= −0.06$).

DISCUSSION

The STICH trial is the largest cardiac surgery trial assessing different treatment strategies in patients with ischemic cardiomyopathy and provided a unique opportunity to study the cardiac structural, functional, and hemodynamic characteristics in this common, high-risk population. The baseline echo study in more than 2,000 STICH patients demonstrated that there is a wide spectrum of cardiac structure, systolic and diastolic function, and hemodynamic parameters in patients with ischemic cardiomyopathy. There was a weak correlation between LVEF and non-invasively derived diastolic filling pressure and echo parameters for diastolic filling pressure were closely related to pulmonary artery systolic pressure These data will be helpful in understanding the clinical outcomes of medical versus CABG with or without SVR treatment strategies in STICH patients. Although LV volume has been one of most important prognostic variables in patients with myocardial infarction or dilated cardiomyopathy, patients with smaller LV volume created by SVR did not have improved outcomes compared to CABG without SVR in either the composite of death or

cardiac hospitalization or in total mortality.[2] Understanding of this paradox and the relationship between systolic and diastolic function among patients with ischemic cardiomyopathy will be critical for optimizing medical and surgical management strategies and defining clinical expectations for this growing patient population.

Echocardiography is commonly employed in clinical trials since it is widely available and provides functional as well as structural information of the heart essential for clinical trials. However, many factors affect the quality and completeness of echocardiography which may have a profound impact on the interpretation of the trial. From our experience of performing Echo Core Lab measurements in the STICH trial with a large number of patients with ischemic cardiomyopathy, clinically relevant insights into the use of echo in clinical practice as well as in clinical trials are provided.

LV Volume Measurement

LV volume and LVEF are the basic parameters for defining LV structure and systolic function, used commonly as components of inclusion criteria as well as secondary endpoints for cardiovascular or heart failure trials. The ability of echo to provide reliable LV volume and LVEF depends on how well the LV endocardial border is defined. In the STICH, the LV endocardial border could be traced in 72.8%. The proportion of STICH patients in whom LV volume measurement by the Simpson's method was feasible is similar to that (67.5 % – 79.2%) obtained in more than 2,000 subjects for Olmsted County diastolic function studies.[10, 11] Inability to measure LV volumes by echo is due to multiple factors which preclude adequate visualization of the LV endoardial border. One remedy is to use contrast agent which allows superior visualization of the border. The use of a contrast agent, however, requires additional cost and an intravenous access which are limiting factors in a large clinical trial. However, in clinical practice where LV volume and EF are the critical information needed, a contrast agent should be used whenever LV border is not adequately visualized.. Three dimensional echo also holds a promise to provide more reliable LV volume measurements than 2-dimensional echo [12, 13] if technical expertise for 3-D echo is more generalized and its resolution is more refined. Other cardiac imaging modalities such as cardiac magnetic resonance (CMR) imaging or radionuclide (RN) imaging have a higher feasibility to provide LV volumes and/or EF, but are less often available for a large scale clinical trials. For that reason, in the STICH, CMR and RN were obtained whenever feasible, but not mandated. The fact that the patients in whom LV volume measurement was not possible were heavier with more hypertension and diabetes may have an impact on the interpretation and application of clinical data of a trial which uses echo LV volumes as an inclusion criterion or an end-point of the study. One interesting aspect of LV volume measurement by echo in the STICH was that LV volumes measured using the biplane Simpson's method were very close to those measured using the single-plane method in the same patient. Therefore, at least for the patients with enlarged heart, the use of single-plane volume measurement (preferably, from the apical 4 chamber view) appears to be suffient for clinical use and to be more feasible and less variable in serial volume measurements during follow-up of a specific patient. When LVEDV and LVESV were correlated with LVEF, there was a much tighter correlation with LVESV. White and his colleagues[14] also demonstrated that LVESV was more powerful predictor than LVEDV after acute myocardial infarction. Most clinical trials studying systolic heart failure also have used a change in LVESV as a means to define reverse remodeling.[15, 16] In the VALIANT trial echo substudy,[17] both baseline end-diastolic volume and end-systolic volume were independently predictive of the combined end points of death, myocardial infarction, cardiac arrest, or stroke. Therefore, the STICH baseline data support the use of LVESV (as opposed to LVEDV) as a marker of LV remodeling extent in clinical trials of systolic heart failure

LV Ejection Fraction

Patient entry criterion for the STICH was a site-reported LVEF ≤35% within 3 months that could be determined using any of the following modalities: left ventriculography, RN imaging, CMR imaging, or echo. The baseline LVEF measured by the Echo Core Lab, however, was greater than 35% in 18.5 % of STICH patients. The difference in LVEF between clinical sites and the Echo Core Lab can be related to different imaging methods, interobserver variability, different timing of imaging modalities, or interpretation error. LVEF can change drastically with an alteration in preload and/or afterload. It is possible that LVEF improved after its initial determination at the time of recruitment 2–3 months prior to baseline echo. Test-retest reliability of measuring LVEF by Echo was shown to be ± 5% [18] and a similar portion of patients was found to have LVEF >35% by baseline cardiac MRI or radionuclide imaging studies analyzed by the respective Core Lab (from communication among STICH imaging Core Labs, but unpublished). Whether this subgroup of patients with LVEF >35 % have a different response to treatment or outcome compared with the group with LVEF ≤35 % will be a subject of subsequent analyses. LVEF is the single most important criterion for various drug and device therapy which are expensive and sometimes can be harmful. It is possible that we are providing an unnecessary and potentially harmful therapy based on this single measurement which has a significant variability regardless of which imaging modality is being used. The medical community may consider creating clinical Imaging Core Labs to provide more standardized measurements values when they are used for a major clinical decision.

LA volume measurement

LA volume has been shown to be prognostic in patients with various cardiovascular disorders and is a main component of assessing diastolic function. [19, 20] Again, reliable LA volume measurement depends on the accurate detection of LA wall border and good quality apical views of the LA. There are several different methods to measure its volume: prolate-ellipse, area-length, and biplane Simpson's. Most of the investigators who measured LA volumes have employed the area-length method, which uses a combination of the apical four chamber view along with an apical two chamber or long axis view. The area-length method was used in the Echo Core Lab for STICH. Because of the finding that LV volumes by the single plane Simpson method were similar to those by bi-plane method, we also compared LA volumes measured from two apical views with those from one apical view (the four chamber view). The correlation was again sufficiently encouraging to suggest that a single plane method be further considered and evaluated for use in future clinical practice and research. The similarity between the single plane and the biplane methods in LV and LA volume measurements highlights the notion that doing more measurements may not necessarily make more accurate results.

Diastolic Function and Filling Pressures vs Systolic Function

Many studies have shown that diastolic filling parameters are one of the most significant prognostic factors in patients with systolic dysfunction.[21–23] In this study of contemporary patients with ischemic cardiomyopathy, diastolic dysfunction was observed in nearly all patients, but the extent of dysfunction was variable with mild, moderate, or severe dysfunction in 37%, 36%, and 26% of patients, respectively. The patients with the most severe diastolic dysfunction had larger LV volumes and lower LVEF compared to patients with mild or moderate diastolic dysfunction. However, DT and E/e' which have been shown to correlate well with pulmonary capillary wedge pressure and to have a strong prognostic value in patients with systolic HF[21–24] were found to have a weak correlation with LVEF and LV volume in the STICH population while PASP estimated from TR velocity was correlated most closely with diastolic filling parameters among various echocardiographic parameters including LV volumes and LVEF. Our data are consistent with other studies in

different patient populations.[25, 26] Diastolic filling pressure reflects final hemodynamic manifestation of combined abnormalities of LV, and it is possible that diastolic parameters provide incremental to or even better prognostic information than systolic parameters in patients with ischemic cardiomyopathy.

Mitral Regurgitation in Ischemic Cardiomyopathy

In ischemic cardiomyopathy, tenting of the apically displaced mitral leaflets and tethering of chordae tendinae result in varying degrees of MR which is an important contributor to morbidity and mortality.[27–29] However, despite marked dilatation of the LV, only 25% of patients in our study were found to have grade 2 or greater MR. It is possible that a bias existed against patients with a severe degree of mitral valve regurgitation participating in this trial because physicians might have opted for surgical treatment rather than randomizing the patient in this trial. However, despite the known important prognostic value of MR, surgical treatment of MR or mitral valve repair in the setting of ischemic cardiomyopathy has not been shown to improve patients' survival compared with medical therapy.[30] The STICH trial provides an opportunity to assess the impact of medical therapy, CABG, or CABG + SVR on the natural history of functional MR in the setting of ischemic cardiomyopathy. Although measured by PISA in only a subset of 169 patients, there was a wide range of ERO for each grade of visually assessed MR severity although there was a significant correlation. It has been shown that patients with ERO> 0.2 cm^2 have reduced survival after myocardial infarction, and ERO> 0.2 cm^2 in this study was associated with at least a moderate degree of MR by visual assessment. McCully and his associates have shown that visual assessment overestimates the MR severity compared to ERO (or ERO underestimates compared to visual assessment) in functional MR [31] as shown in STICH. When there is a discrepancy between MR severity assessments, a further testing such as transesophageal echo and/or an integrated approach along with clinical correlation is required.

If a specific treatment strategy results in reducing MR severity and reversing the underlying determinants of MR, it is logical to expect that this treatment may correlate with an improvement in symptoms and survival of patients with MR. Although reduction of LV volume in response to a given therapeutic modality (medically or surgically) is expected to parallel the reduction of MR, there has not been a large prospective study of ischemic cardiomyopathy patients to monitor the immediate and long-term impact of medical or surgical treatment on the severity of MR. ERO and MR volume measurements are more objective in serial follow-up of patients. We recommend that both visual assessment and PISA method for MR severity be performed in all patients with MR. The impact of SVR on LV remodeling process is not well known and even worsening of MR after SVR has been reported.[32] A more recent report, however, suggested that mitral valve repair was not found to be necessary in conjunction with SVR.[33] Comprehensive serial (4- and 24-month follow-up) echo data in STICH patients will be able to correlate changes in structural and functional parameters with the extent of change in the severity of MR as well as be able to evaluate the mechanism and effects of volume reduction SVR surgery as well as of CABG on MR.

Echo Core Lab for clinical trials

Echocardiography is an operator and patient dependent imaging modality with multiple factors to influence the accuracy of its measurements while it is the most widely available and versatile technique to provide structural, functional, and hemodynamic information of the heart. The interpretation of the trial data depends on the accuracy and the reliability of echo measurements when it is used for determination of inclusion and/or as an end-point in a clinical trial. Although more costly, measurement of echo variable in a standardized way by

Echo Core Lab minimizes measurement variability and improves the precision of study results.[34] The superiority of Core Lab interpretation for reducing variability and enhancing study outcome has been reported.[35–37] Moreover, the American Society of Echocardiography has published a document emphasizing the importance of high quality imaging and measurement for clinical trials,[38] and an expert consensus document regarding the responsbilities and best-practices of Echo Core Lab participating in clinical trials.[34]

LIMITATIONS

Although vigorous efforts at standardization were made in the Echo Core Lab, echo measurements were performed and approved by several sonographers and physician echocardiographers, resulting in potential measurement variability. However, the large scale of the STICH trial did not allow analysis by a single sonographer and a single physician. Interobserver variability in LV volume measurements was small and acceptable. An important limitation inherent to echo and a large clinical trial involving a large number of clinical sites was that not all echo parameters were obtained or able to be measured in all patients. LV volumes and LVEF could not be measured quantitatively in 27% of patients because of difficulty in visualizing the entire endocardial border of the LV. Use of contrast echo might have improved visualization, but was not performed in this trial.

The severity of MR, RV dysfunction, and LV regional wall motion abnormalities were assessed visually. However, the visual assessment was done by a small group of experienced physician echocardiographers and is still the most widely accepted method of assessing MR. From the comprehensive echo data from the STICH trial, we expect to gain a better understanding of which variables have most prognostic power in patients with ischemic cardiomyopathy, and how these variables change after different treatment strategies. Baseline echo data and correlations among systolic function, diastolic function, MR, RV function, and PASP reported herein will serve as a reference to answer those clinically valuable questions

CONCLUSIONS

In this contemporary STICH trial of a large number of patients with ischemic cardiomyopathy, baseline echo analyzed by Echo Core Lab demonstrated a wide spectrum of LV shape, function, and hemodynamic parameters as well as feasibility and limitations of obtaining essential Echo measurements. Utilization of echo parameters in clinical practice and research needs to incorporate the variability and limitations of Echo measurements described in this report.

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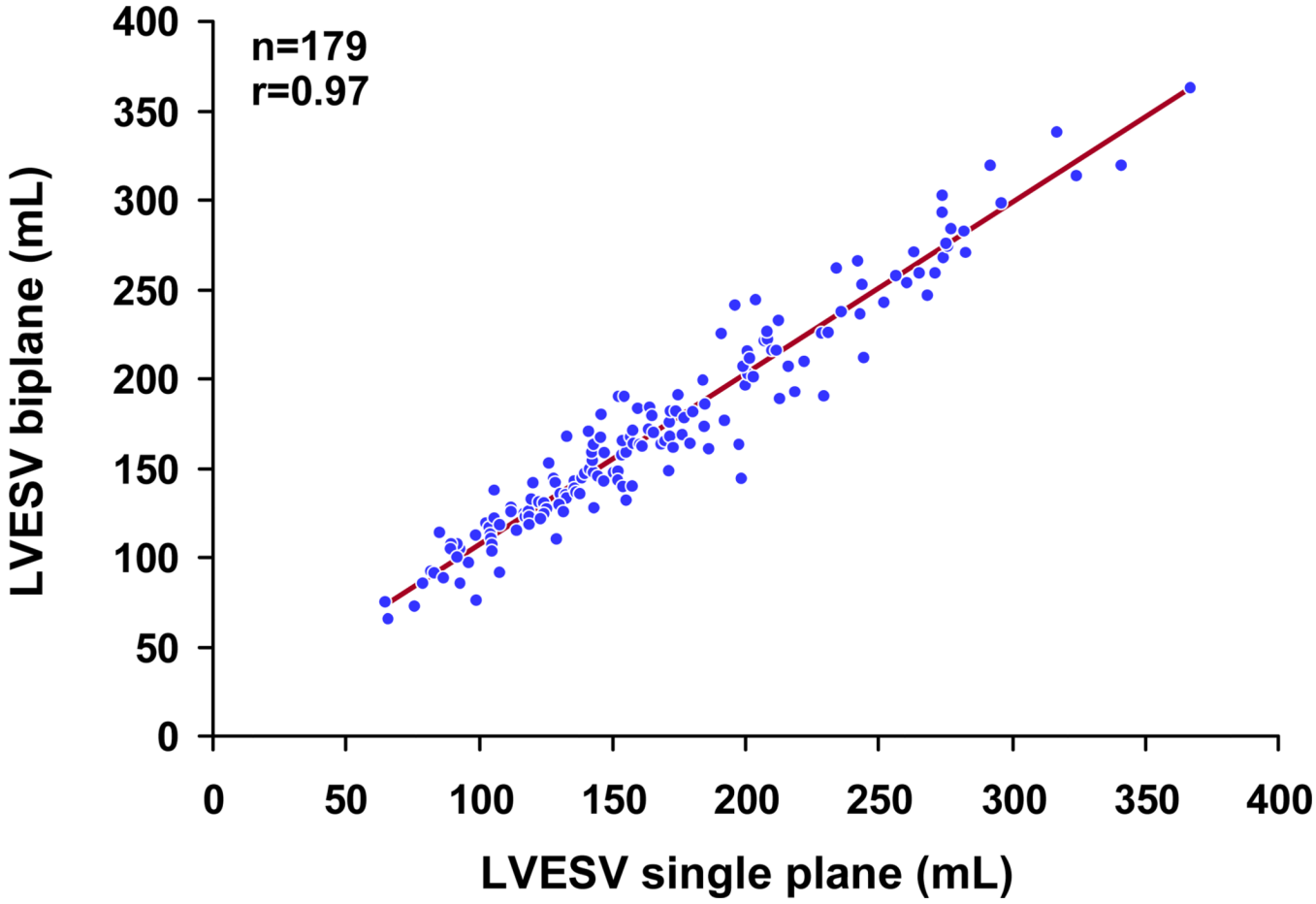
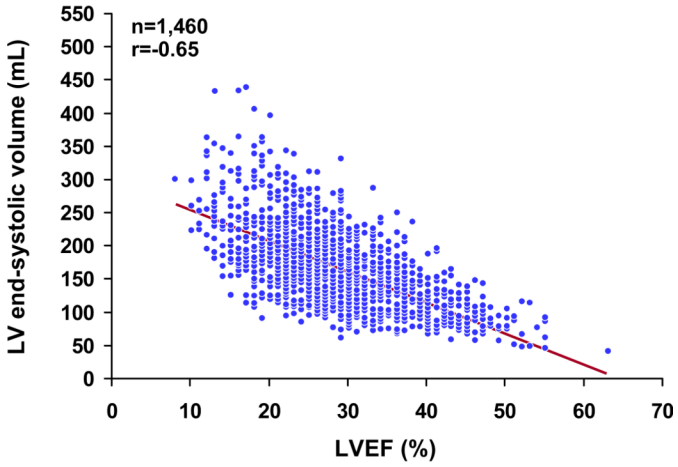


Figure 1.
Correlation between left ventricular (LV) end-systolic volume(ESV) measured by biplane and single-plane Simpson method.

2 A



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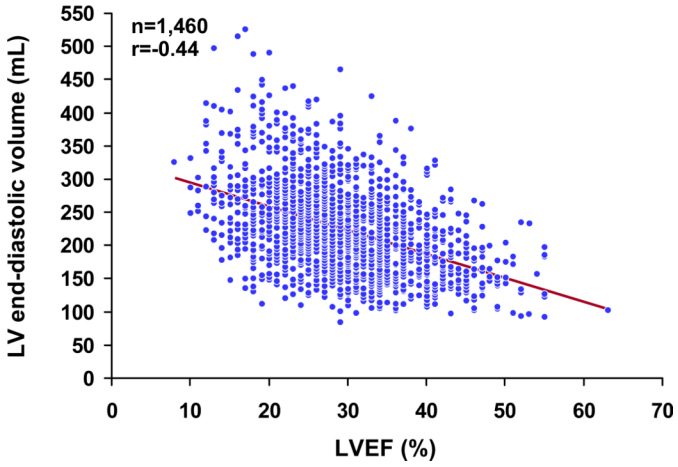

Figure 2.
Correlation between left ventricular (LV) ejection fraction (LVEF) and LV endsystolic volume (A) and LV end-diastolic volume (B). LV endsystolic volume has a better correlation than LV enddiastolic volume with LVEF.

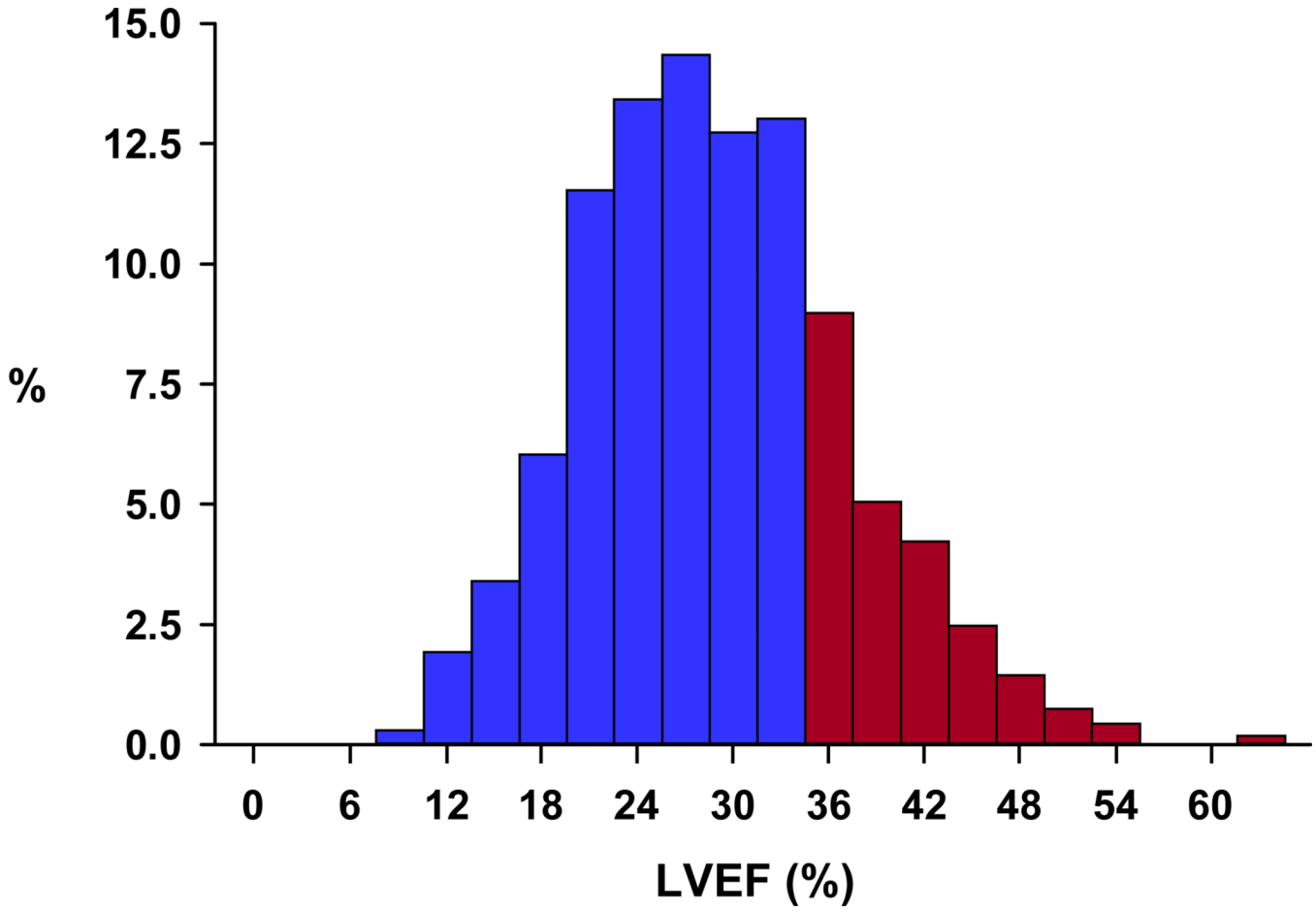

Figure 3.
Distribution of left ventricular ejection fraction (LVEF) measured by the Echo Core Lab. LVEF was >35% in 20 % of the patients.

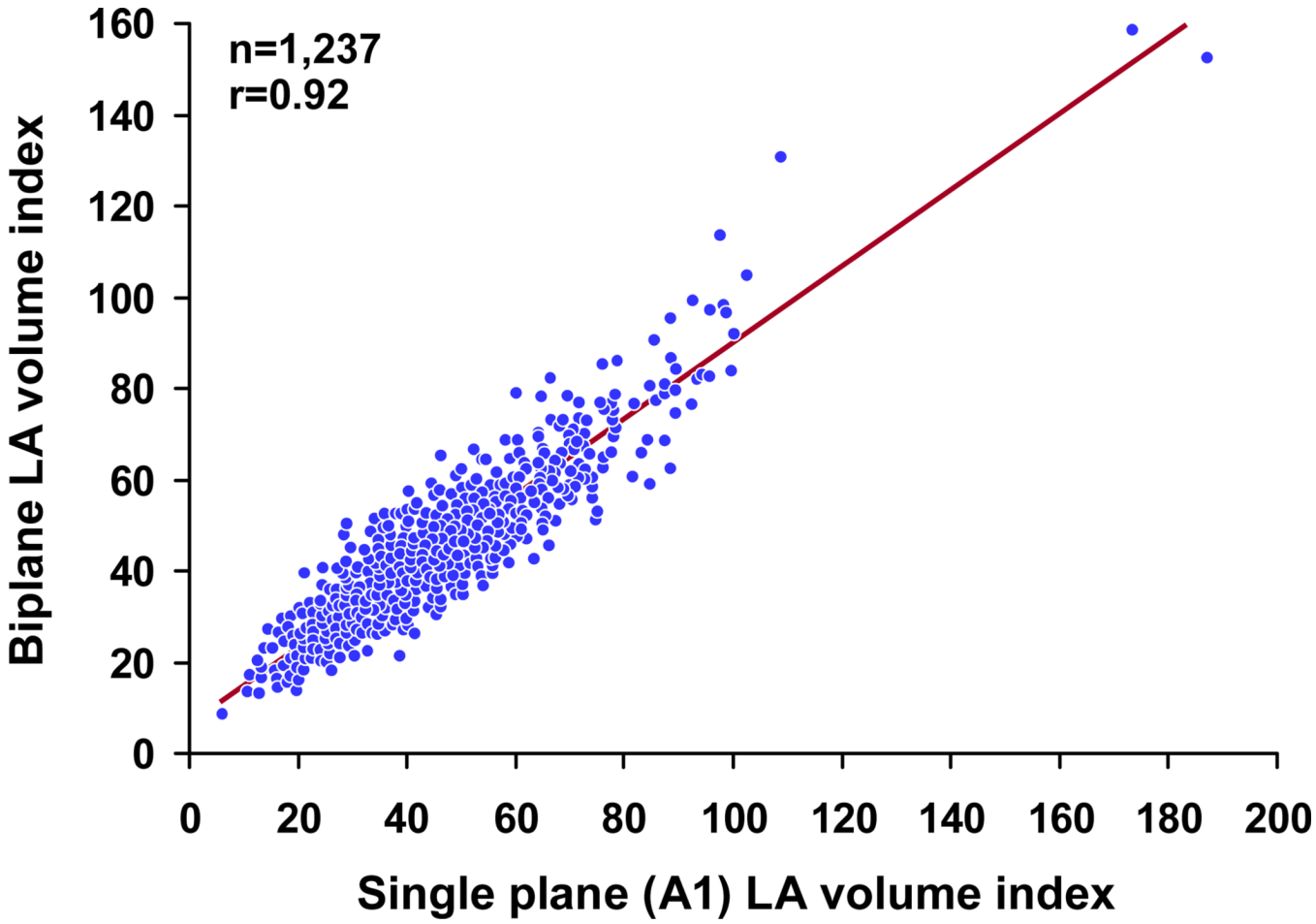

Figure 4.
Correlation between biplane and single plane LA volume index.

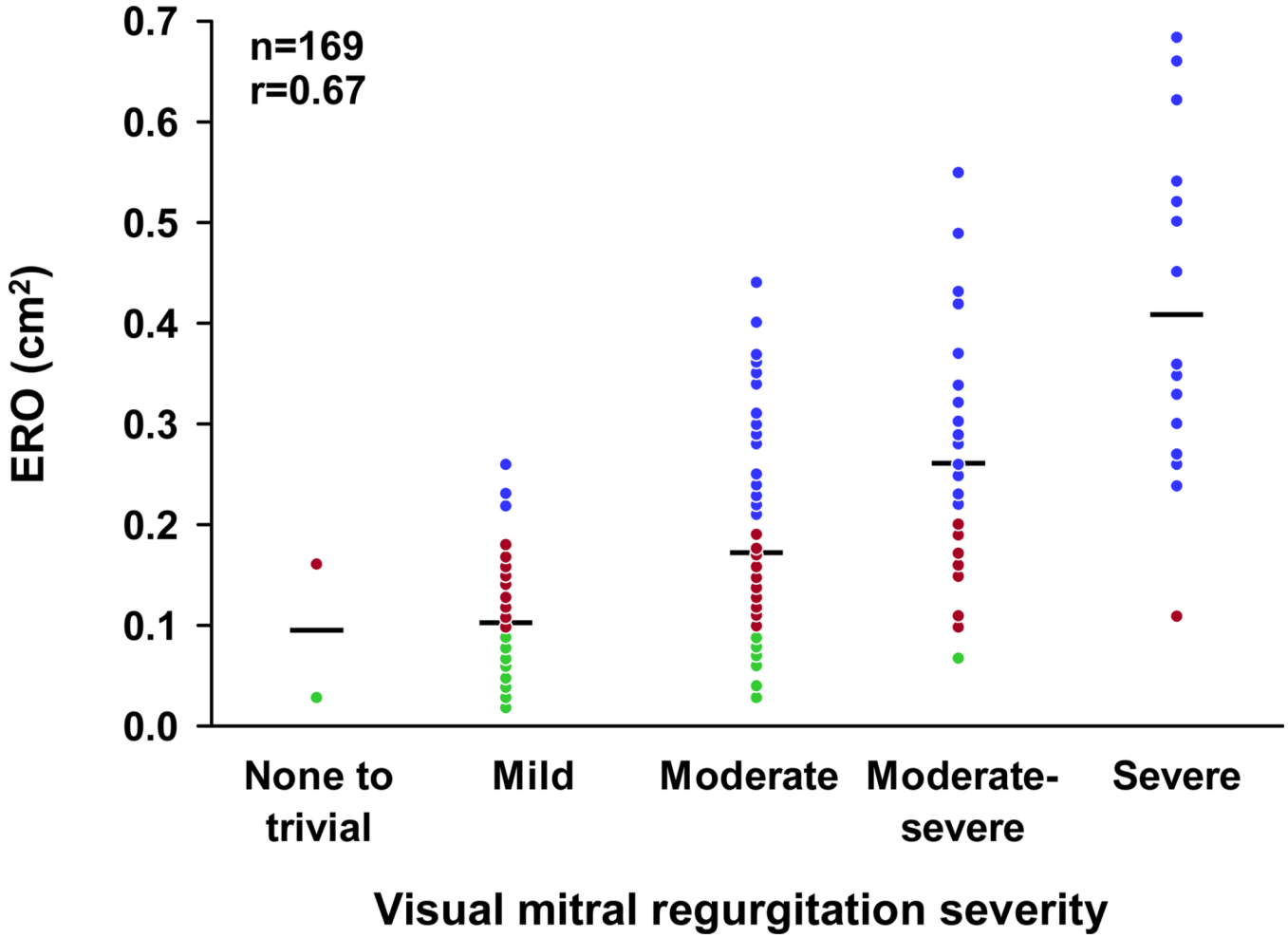

Figure 5.
Effective regurgitant orifice (ERO) vs visual determination of mitral regurgitation (MR) severity using color flow imaging.

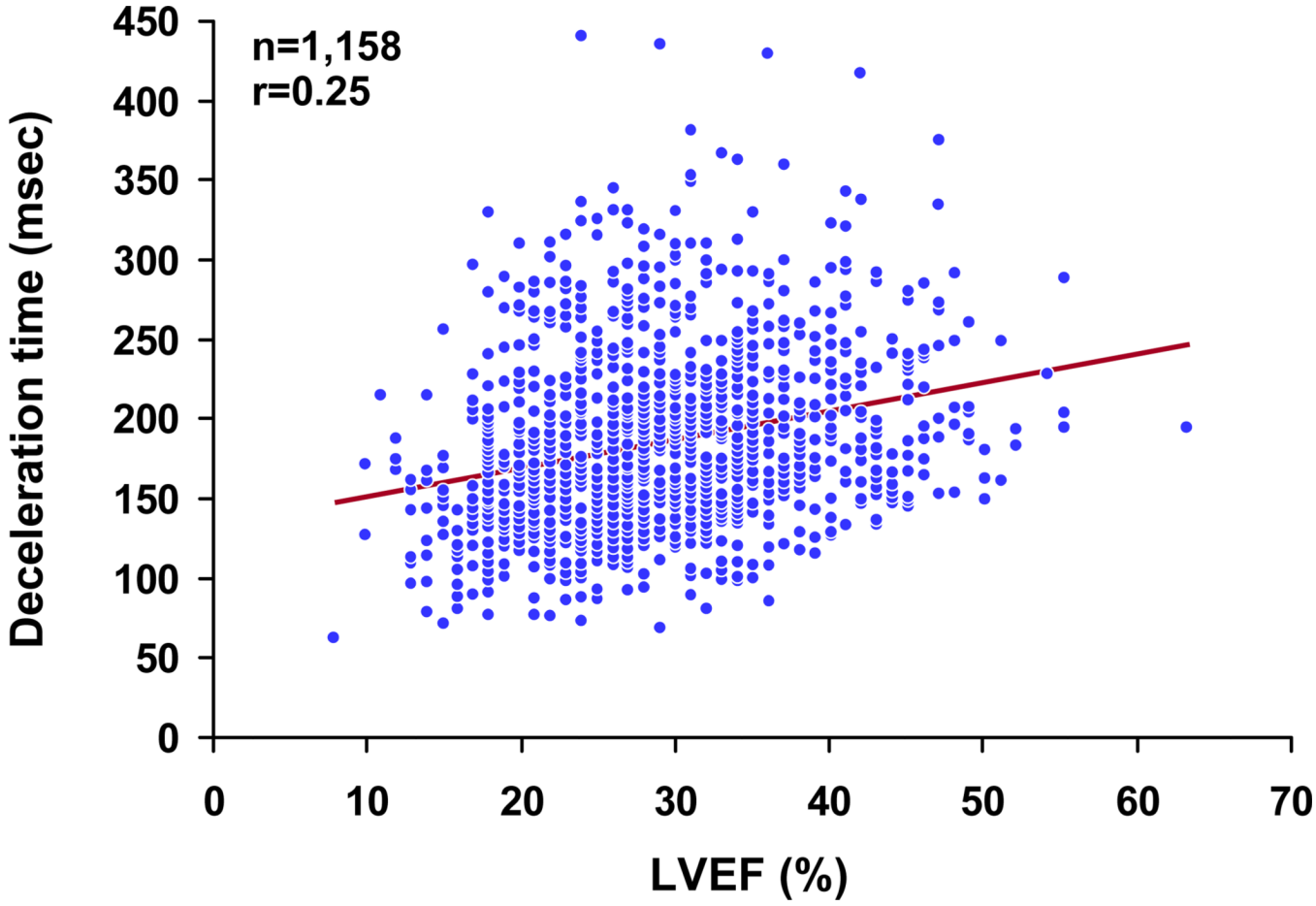

Figure 6.
Correlation between left ventricular ejection fraction (LVEF) and mitral inflow deceleration time.

TABLE 1

Baseline echocardiographic parameters and their values

	Overall (N=2006)		Hypothesis 1 (n=1,144)		Hypothesis 2 (n=936)	
Measurement	**No. of Patients**	**Value[a]**	**No. of Patients**	**Value[a]**	**No. of patients**	**Value[a]**
LVED dimension, cm	1,432	6.3 (0.8)	804	6.3 (0.8)	680	6.4 (0.8)
LVES dimension, cm	1,352	5.4 (0.9)	767	5.3 (0.9)	635	5.3 (0.9)
LV long-axis dimension, cm	1,506	9.2 (1.0)	846	9.2 (1.0)	721	9.3 (1.0)
Sphericity index (diastole)	1,154	0.69 (0.09)	648	0.69 (0.09)	551	0.68 (0.09)
LVEDV, mL	1,460	222.4 (68.8)	806	220.4 (67.3)	710	225.0 (69.4)
LVESV, mL	1,460	160.7 (60.4)	806	160.2 (60.1)	710	161.0 (60.3)
LVEDV index, mL/m^2	1,460	116.3 (34.6)	806	115.6 (33.8)	710	117.0 (35.5)
LVESV index, mLl/m^2	1,460	84.0 (30.9)	806	84.1 (30.7)	710	83.8 (31.2)
LVEF, %	1,460	28.9 (8.3)	806	28.5 (8.5)	710	29.5 (8.1)
LA volume index, mL/ m^2	1,237	41.9 (15.2)	696	41.7 (14.7)	596	42.1 (15.6)
Global hypokinesis[c]	1,985	227 (11%)	1,130	149 (13%)	929	88 (9 %)
Wall motion score index	1,758	2.2 (0.3)	981	2.3 (0.3)	841	2.2 (0.3)
Deceleration time, msec	1,492	186.2 (56.2)	842	189.2(8.2)	708	183.3 (53.4)
MV E velocity, m/sec	1,635	0.73 (0.25)	920	0.72 (0.26)	778	0.73 (0.25)
MV A velocity, m/sec	1,535	0.67 (0.24)	860	0.67 (0.24)	736	0.68 (0.24)
E/A ratio	1,532	1.3 (1.1)	859	1.4 (1.3)	734	1.3 (0.9)
e′ or Ea septal velocity, m/sec	1,002	0.05 (0.02)	592	0.04 (0.02)	450	0.05 (0.02)
e′ or Ea lateral velocity, m/sec	971	0.06 (0.03)	573	0.06 (0.03)	436	0.06 (0.03)
Septal E/Ea or E/e′ ratio	920	17.6 (9.6)	544	18.1 (9.7)	413	16.8 (9.3)
Diastolic function[c]	1,992		1,132		934	
Normal		5 (0.3 %)		3 (0.3 %)		2 (0.2 %)
Grade 1		604 (30 %)		362 (32 %)		268 (29 %)
Grade 2		590 (30 %)		304 (27 %)		311(33 %)
Grade 3		433 (22 %)		253 (22 %)		194 (21 %)
Grade 4		2 (0.1 %)		1 (0.1 %)		1 (0.1 %)
Indeterminate		358 (18 %)		209 (18 %)		158 (17 %)
Mitral regurgitation[c]	1,990		1,138		926	

Measurement	Overall (N=2006)		Hypothesis 1 (n=1,144)		Hypothesis 2 (n=936)	
	No. of Patients	Value[a]	No. of Patients	Value[a]	No. of patients	Value[a]
Grade 0		514 (26 %)		316 (28 %)		227 (24)
Grade 1		871(44 %)		465 (41 %)		437 (47)
Grade 2		306 (15 %)[b]		174 (15 %)[b]		142 (15)[b]
Grade 3		110 (6 %)[b]		58 (5 %)[b]		52 (5)[b]
Grade 4		51 (3 %)[b]		30 (3 %)[b]		24 (3)[b]
Indeterminate		138 (7 %)[b]		95 (8 %)[b]		44 (5)[b]
TR velocity, m/sec	596	2.9 (0.5)	342	2.9 (0.5)	274	2.8 (0.5)
PASP, mm Hg	430	42.8 (15.5)	241	43.4 (15.8)	205	41.7 (15.0)

Abbreviations: LA, left atrial; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MV, mitral valve; PASP, pulmonary artery systolic pressure; TR, tricuspic regurgitation.

[a]Values are shown as mean (SD) unless otherwise indicated.

[b]The *P* value tests differences between hypothesis 1 and hypothesis 2 patients where there is no overlap (n=1,044; n=863).

[c]Values are shown as No. (%) for categorical variables.

TABLE 2

Comparison of patients with and without echocardiographic volume measurement

	Have volume measurements (N=1460)	Do not have volume measurements (N=546)	P
Age	60.6±9.51	61.8±9.54	0.0104
Female sex	13.6 (198)	13.6 (74)	0.9960
Weight (kg)	78.3±14.0	83.4±19.3	<0.0001
Body Mass Index (kg/m2)	27.0±4.19	28.6±5.56	<0.0001
Myocardial infarction	82.7 (1208)	78.4 (428)	0.0253
Stroke	7.3 (106)	5.3 (29)	0.1210
Hypertension	58.2 (849)	65.0 (355)	0.0052
Atrial flutter fibrillation	11.9 (174)	13.2 (72)	0.4406
Diabetes	34.5 (504)	43.8 (239)	0.0001
Previous CABG	2.5 (37)	3.7 (20)	0.1757
Previous PCI	15.0 (219)	16.8 (92)	0.3083
NYHA Class I	10.4 (152)	9.7 (53)	0.6469
NYHA Class II	46.2 (675)	49.5 (270)	
NYHA Class III	39.2 (573)	37.0 (202)	
NYHA Class IV	4.1 (60)	3.8 (21)	
Visual EF*	0.28±0.08	0.29±0.08	0.1415
MR grade 0	33.6 (490)	41.9 (229)	0.0083
MR grade 1	46.7 (682)	42.7 (233)	
MR grade 2	15.8 (230)	12.5 (68)	
MR grade 3	3.5 (51)	2.4 (13)	
MR grade 4	0.5 (7)	0.5 (3)	

* EF is available for 1453 subjects with volume measurements and 517 subjects without volume measurements