American Society of Echocardiography Recommendations for Use of Echocardiography in Clinical Trials

A Report from the American Society of Echocardiography's Guidelines and Standards Committee and The Task Force on Echocardiography in Clinical Trials

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FDA, Food and Drug Administration; *LV*, left ventricular; *TEE*, transesophageal echocardiography.

I. INTRODUCTION

Echocardiography is one of the most commonly performed noninvasive diagnostic tests in patients with known or suspected cardiovascular diseases. Echocardiography provides comprehensive evaluation of the cardiovascular structure, function, and hemodynamics that characterize disease processes (readers are referred to published ACC/AHA/ASE guidelines[1-10] for an overview on clinical aspects of echocardiography). Moreover, there are no known side effects associated with echocardiography, even with frequent and repeat testing. Its real-time nature, portability, and relatively low cost make echocardiography adaptable to most clinical or research situations. Hence, echocardiography has been used successfully to provide mechanistic insights on therapeutic outcomes, and in some cases to measure functional and structural changes that are considered to be of therapeutic importance (ie, "surrogate" end points).

New advances in echocardiography bring increased opportunity and enormous potential to evaluate the cardiac effects of disease and its treatment repetitively and noninvasively in clinical trials (Table 1). Although many clinical studies have been performed to evaluate echocardiographic techniques per se, these are not the focus of this report. The purpose of this communication is to discuss the utility of echocardiography in enhancing the value of clinical trials by identifying potential mechanisms of clinical end points and determining surrogate end points and to offer recommendations regarding its use. In addition to physicians with expertise in echocardiography, this document is intended for project officers and others working with government or industrial sponsors who may not be familiar with echocardiography but need an in-depth overview of the types of information that can be provided by echocardiography and related techniques in clinical research.

As with other diagnostic techniques, the various sources of acquisition and measurement variability need to be considered in the application of cardiovascular ultrasound to clinical research. Data are presented in the following sections on reproducibility of echocardiography; however, diagnostic reproducibility and accuracy may vary according to the clinical or research context in which echocardiography is used. The importance of determining reproducibility for specific laboratories, readers, clinical trials, and potential changes over time is discussed later in this document.

II. TECHNIQUES IN CARDIOVASCULAR ULTRASOUND

The cardiovascular ultrasound examination ("echocardiography") offers several imaging and hemodynamic modalities.

Two-dimensional Echocardiography

Two-dimensional (2D) echocardiography is the backbone of echocardiography. By displaying anatomic structures in real-time tomographic images, comprehensive visualization of the components of the beating heart is achieved. The distance of ultra-

sound echoes along the vertical axis represents the depth of echo-producing structures, with brightness indicating the intensity of the returning echo. The examiner is required to obtain multiple, precisely oriented anatomic "slices" by aiming an ultrasound probe at the heart (cross-sectional scanning). Information regarding cardiac chamber size, wall thickness, global and regional systolic function, and valvular and vascular structures is readily available. B-mode imaging refers to cross-sectional 2D images displayed without motion. Such images can provide excellent detail of static structures and are used in vascular imaging to show high-resolution detail of atherosclerotic plaque and vascular structure.

M-mode Echocardiography

M-mode or motion-mode images are a continuous 1-dimensional graphic display that can be derived by selecting any of the individual sector lines from which a 2D image is constructed. M-mode echocardiography is useful for quantitating single dimensions of walls and chambers, which can be used to estimate chamber volumes and left ventricular (LV) mass when those structures are geometrically uniform. M-mode echocardiography also has high temporal resolution, which makes it useful for timing valve motion.

Doppler Echocardiography and Color Flow Imaging

The Doppler technique uses reflections from moving red blood cells to characterize blood flow in the central and peripheral circulation. Doppler echocardiography complements M-mode and 2D echocardiography by providing functional information regarding intracardiac hemodynamics, including systolic and diastolic flow, blood velocities and volumes, severity of valvular lesions, location and severity of intracardiac shunts, and assessment of diastolic function. There are 4 types of Doppler: pulsed-wave, continuous-wave, color flow mapping, and tissue Doppler. Pulsed-wave Doppler is useful for localizing and timing flow that is moving within the physiological range of velocities. Continuous-wave Doppler, which lacks spatial resolution, is useful for accurately measuring the gradients that drive pathological flow jets. Color flow mapping, by measuring velocity along each sector line of the 2D image and displaying the information as color-coded pixels, provides a composite picture of flow over a larger area; it is most useful for screening the valves for regurgitation and stenosis, imaging systolic and diastolic flow, detecting the presence of intracardiac shunts, and detecting coronary flow. Tissue Doppler detects the amplitude and phases of the relatively slow motion of the LV myocardium (usually at the base of the heart). It is useful as a means of studying diastolic function. Strain rate imaging[11-14] is a relatively new technique in echocardiography of potential utility for evaluation of systolic and diastolic LV function. This modality records myocardial tissue velocities to provide information about rates of local compression and expansion, and in contrast to endocardial excursion, it is free of tethering by adjacent myocardial segments.

Stress Echocardiography[7,15-17]

A stress echocardiogram[7] uses any combination of the above echocardiography modalities, before and during (or shortly after) a physical or pharmacological stress intervention. Most commonly, a treadmill or exercise bicycle is used for exercise echocardiography. Alternatively, in patients who are unable to exercise, stress testing can be performed with pharmacological agents that increase myocardial oxygen demand (eg, dobutamine, often given with atropine) or vasodilators that produce coronary steal. These tests may have utility primarily in the detection of myocardial ischemia and viability but may also be used to assess the efficacy of coronary revascularization or antianginal medication. Special interventions such as isometric handgrip, cold pressor (immersion of the hand in ice water), mental stress tasks, and cardiac pacing have also been used in some research applications. Hemodynamic changes with stress can be assessed by Doppler. Overall, the sensitivity and specificity of stress echocardiography for detection of coronary disease has been comparable to that of nuclear scintigraphy, and stress echocardiography has had excellent prognostic value for prediction of clinical outcome.[16]

Transesophageal Echocardiography

Transesophageal echocardiography (TEE) uses a miniature ultrasound probe mounted at the end of an endoscope. A physician inserts the probe into the esophagus and performs the examination while a nurse monitors the patient and administers sedative medications. Two-dimensional, M-mode, and Doppler techniques are performed during a TEE examination. TEE has the advantages of generally superior image quality to 2D echocardiography and better imaging of selected structures such as the left atrial (LA) appendage, pulmonary veins, and mitral regurgitant jets in patients with prosthetic mitral valves. However, TEE may be of limited utility in clinical trials because of its semi-invasive nature and added requirements for equipment and personnel. Nonetheless, in the STICH (Surgical Treatments for Ischemic Heart Failure) trial,[18] TEE is being used for assessment of mitral valve structure and regurgitation. TEE has been used successfully in clinical trials during surgery to evaluate and monitor cardiac function and in trials of atrial fibrillation treatment and closure of patent foramen ovale (PFO).

Three-Dimensional Echocardiography

Three-dimensional (3D) echocardiography provides displays of cardiac structures or flow and offers the display of any 2D imaging plane within the 3D data set.[19] Three-dimensional echocardiography can be performed in 2 ways: real-time acquisition or sequential acquisition and reconstruction of multiple 2D planes into a 3D model with a locator device. Real-time 3D technology has recently been introduced clinically and is currently being refined. Disadvantages of the non–real-time technique include nonsimultaneous acquisition and significant postacquisition reconstruction time. In clinical trials, 3D echocardiography offers the potential of improved quantitation of cardiac volumes and LV mass, which leads to greater accuracy, sensitivity, and reduced sample size.

Contrast Echocardiography

Commercially available contrast agents can be administered via venous injection to enhance the diagnostic quality of the echocardiogram.[20] Currently, contrast agents are only approved by the Food and Drug Administration (FDA) for LV opacification, although many clinical studies have evaluated their use to assess myocardial perfusion. Venous contrast injections are used to enhance LV endocardial borders and Doppler signals and to assess myocardial perfusion. The use of contrast may permit utilization of technically difficult studies and increase the yield of 2D echocardiography for assessment of global and segmental LV function. This advantage must be balanced against the expense, inconvenience, and need for an intravenous line.

Digital Acquisition and Storage

Clinical echocardiography is quickly moving from analogue videotape to digital acquisition and storage, and it is anticipated that multicenter clinical trials will also move in a similar direction. Digital acquisition and storage has many advantages in clinical trials, including high image quality, reproduction of images without loss of information, and long-term storage and transportability. Another important advantage is the ability to link study sites to core laboratories via the Internet or secure servers, with virtually no concern about geographic distance. In addition to elimating the mailing costs of physical media and reducing missing data, this facilitates rapid qualification of studies, quality control, and rapid data turnover. With digital acquisition, it is necessary to ensure that representative beats are obtained. Media used to transport the images (eg, compact disc, DVD, or magneto-optical disc) must be standardized so both the acquisition sites and central laboratory can view the images and calibration information.

III. ANATOMIC AND FUNCTIONAL QUANTITATION OF CARDIAC CHAMBERS

LV Linear Dimensions and Wall Thickness

These fundamental measurements are used for almost all clinical trials that incorporate echocardiography. Linear dimensions are obtainable from correctly aligned 2D and M-mode images. M-mode recordings provide better temporal resolution for accurate timing of motion of cardiac walls and valves, whereas 2D provides better spatial orientation. From LV chamber internal dimensions in diastole and systole, LV ejection fraction (EF) and fractional shortening can be readily determined, and the addition of wall thickness allows derivation of LV mass.

LV Volumes and EF

The use of single dimensions to accurately reflect volumes and global LV function requires symmetrical geometry and contraction of the LV, respectively, to minimize error. LV volume is one of the best prognostic parameters in patients after myocardial infarction and is a prerequisite for calculation of EF (the difference between end-diastolic and end-systolic volumes divided by end-diastolic volume), as well as LV mass (see below). Because 2D echocardiography is a tomographic technique, the slices it creates must be converted mathematically to volumes by one or more of several methods based on geometric models of the LV. These methods have been validated[21-23]; the accuracy of the prolate-ellipse, area-length, and truncated ellipsoid methods is limited to normally shaped and sized ventricles, whereas the biplane method of discs is accurate in abnormally shaped ventricles. Three-dimensional echocardiography methods are less geometry-dependent than 2D and may supplant 2D methods in the future.

Prolate-ellipse. The so-called cube formula is based on a model of the LV as a prolate ellipse of revolution where $V = 4/3\ \pi\ L/2 \times D_1/2 \times D_2/2$, where D_1 and D_2 are orthogonal minor axes; L is the long axis, which equals $2 \times D$; and $D_1 = D_2$. Hence, the volume approximates D^3, which has been taken as the single linear dimension representing the short axis of the LV at the tips of the mitral valve.

Area-length and truncated ellipsoid. The area-length formula (so-called bullet formula) for LV volumes ($V = 5/6\ AL$, where A = LV short-axis area and L = LV long axis) assumes a bullet shape of the LV. The truncated ellipsoid formula assumes that the ventricle resembles a truncated ellipsoid. Both methods use the parasternal cross-sectional short-axis image at the level of the papillary muscles. Similar to volumes obtained from linear dimensions, these methods are also subject to error in the case of

distortions of LV geometry. In patients in whom only a low parasternal window can be obtained, the short-axis view will distort LV geometry, resulting in gross overestimation of LV volume by either of these formulas. In these patients, it is better to use the prolate-ellipse formula with linear dimensions taken from anatomically correctly oriented apical views or a parasternal long-axis view, with care taken to obtain the minor dimension perpendicular to the long axis, which will be angulated on the monitor screen.

Correct alignment of short-axis images (for the 2D bullet formula) is characterized by a circular image just at the level of minimal motion of the mitral valve structures (indicating a level between mitral tips and chordae tendineae). Linear dimensions from 2D-targeted M-mode echocardiography should be derived through the center of this circular image, whereas optimal 2D linear dimensions (for cavity and walls) are obtained perpendicular to the septum and posterior wall in the parasternal long-axis view that shows the largest LV cavity area.

Method of discs (Simpson's Rule). This method summates volumes of multiple cylinders of equal height along the LV. It is the most useful in obtaining LV cavity volumes in the presence of distorted LV geometry. However, a technical trade-off is incurred, because apical views (preferably paired biplane views) of the LV must be used. These views, which image the LV endocardium in lateral (poor, relative to axial) resolution, generally result in larger LV cavity volumes than the parasternal short-axis view required by the bullet formula, which images the LV endocardium mostly in axial (good) resolution. Moreover, it is sometimes difficult to identify the epicardial contour with certainty. Myocardial areas and derived volumes can be subject to substantial error. Hence, this method is not optimal for measurement of LV mass.

Method of multiple diameters. LV EF and volumes can also be measured by the multiple diameter method,[24,25] which uses the average of several diameters of the LV measured at end diastole and end systole from the parasternal long-axis and apical views. The diameter method is helpful in situations in which the apical views are suboptimal for adequate tracing of the endocardial contour or if the tomographic plane foreshortens the LV cavity. Its main advantage is incorporation of the parasternal long-axis view, which is available in the majority of patients. This method was applied by the SOLVD (Studies of Left Ventricular Dysfunction) investigators in an evaluation of LV remodeling.[26]

LV Mass

The single largest application of echocardiography in epidemiology and in therapeutic trials has been the estimation of LV mass in free-living populations[27-33] and its change with antihypertensive therapy in clinical trials.[34,35] All LV mass algorithms, whether based on M-mode, 2D, or 3D echocardiography, are based on subtraction of LV cavity volume from the volume enclosed by the LV epicardium to obtain an LV muscle "shell" volume. This shell volume is then converted to mass by multiplying by myocardial density (1.04 g/mL). To obtain the shell volume, the echocardiogram must be capable of imaging the interface between the LV blood pool and endocardium, as well as between the epicardium and pericardium. In principle, all the methods described above for LV volumes should be able to obtain LV volumes enclosed by the endocardium, as well as by the epicardium, thus allowing calculation of the shell volume and LV mass. However, in cases in which the shell volume is obtained by use of linear dimensions of LV cavity and septal wall thickness, cubing these linear dimensions can multiply even small errors. However, LV mass obtained with this method (LV mass = $0.8 \times (1.04[(Dd + PW + VS)^3 - (Dd)^3] + 0.6$g, where Dd = diastolic dimension, PW = posterior wall thickness, and VS = septal thickness) has been well validated by necropsy ($r = 0.90$, $P < 0.001$).[37] Moreover, if care is taken to obtain accurate primary dimension measurements in an experienced core laboratory, good reproducibility of LV mass can be obtained.[38] Linear dimensions can be obtained from either 2D-targeted M-mode images or directly from correctly aligned 2D images.[38,39] Utilization of 2D linear dimensions overcomes the common problem of oblique parasternal images that result in overestimation of cavity and wall dimensions from M-mode echocardiography. LV mass can also be calculated from planimetered dimensions of 2D images obtained during real-time transthoracic imaging[40] with the area-length or truncated-ellipsoid formulas as noted above. This specific methodology recommended by the American Society of Echocardiography (ASE) for 2D estimation of LV mass has also been validated.[41]

More recently, 3D echocardiography using a polyhedral surface reconstruction algorithm has been used to measure LV mass.[42-44] This has the advantage of reducing dependence on geometric models and reducing error incurred from angulated images. Although this technique holds the promise of less variability and greater accuracy than 2D or 2D-targeted M-mode echocardiography for estimation of LV mass[45] and can measure change in LV mass with therapy in fairly small sample sizes,[46] it has not yet been used in multicenter trials to measure LV mass and sequential change with therapy.

Reproducibility. Reproducibility of echocardiography for measurement of LV volumes and LV mass may vary based on technique, laboratory, and patient population. In an early study of variability of repeated 2D echocardiography of normal subjects

measured by multiple observers,[47] the 95% confidence limits were wall thickness ± 9%, LV diastolic volume ± 11%, and LV mass ± 12%. In a multicenter trial of hypertension treatment,[48] reader agreement for LV mass between cardiologists was 0.83 but varied substantially by center. Another study evaluating an adolescent cohort in an observational study found greater interobserver variability (24 g) than intraobserver variability (19 g) for measurement of LV mass. In a multicenter study that used 2D-targeted M-mode echocardiography, the test-retest reliability for measurement of change in LV mass not due to biological or methodological variability was found to be 59 g. However, when anatomically correct linear measurements directly from 2D were used in a more recent study[49] with newer equipment, the test-retest reliability was 35 g (95% confidence limits), or approximately 18% of the baseline value. An 80% likelihood of true interval change would be predicted by a difference of 17 g on sequential studies. With 3D echocardiography, a 12% interobserver variability for LV mass has been reported,[45] in contrast to that of 8% for magnetic resonance imaging (MRI) and 18% for 2D echocardiography, and correlation with MRI-measured LV mass was higher (r = 0.93, SEE = 9.2 g) than correlation of M-mode echocardiography with MRI (r = 0.73, SEE = 26 g).

LV Systolic Function

Ejection fraction. LV EF is a time-honored standard and a useful measurement in studies of heart failure, in epidemiology studies of coronary artery disease, and in monitoring the effects of drugs on the heart. Methods for echocardiographic measurement were discussed previously. Although visual ("eyeball") estimation of EF is commonly used in clinical practice, it is not suitable in research studies, in which detection of small changes may be highly relevant. The expense and time requirements of 3D reconstruction methods have limited the application of these techniques in clinical trials, but real-time 3D acquisition and measurement may become the future method of choice for measuring LV EF in clinical trials.

Reproducibility. Reproducibility of EF on echocardiography can be as good as about ± 7%,[50] and test-retest reliability is ± 5%.[51] Three-dimensional echocardiography has shown better accuracy (r = 0.94, comparison with MRI) than 2D echocardiography (r = 0.85).[52]

Segmental LV function. The visual semiquantitative evaluation (scoring) of segmental wall motion is based on qualitative assessment of endocardial excursion and the extent and timing of systolic thickening of myocardial segments. It has not yet been successfully supplanted by quantitative methods, although the application of Doppler methods of measurement of regional wall strain[11,12,14,53] may allow this in the future. Strain rate imaging, in contrast to endocardial excursion, is free of tethering by adjacent myocardial segments and may have the potential to improve analysis of segmental LV function.

Tissue Doppler mitral annular systolic velocity. Tissue Doppler techniques, which are simple to perform,[54] record low-velocity Doppler information in the LV walls. Research[55,56] has shown the value of systolic and diastolic measurements of mitral annular velocity using tissue Doppler techniques, which are beginning to be used in multicenter clinical trials.

Midwall fractional shortening/LV systolic stress relationship. Contraction of muscle fibers in the LV midwall may better reflect intrinsic contractility than does contraction of fibers at the endocardium, which is measured by EF or fractional shortening. It is possible to use mathematical models[57,58] that compute midwall fractional shortening from linear measures of cavity size and diastolic and systolic wall thickness. Midwall fractional shortening has been found to be predictive of incident congestive heart failure.[59] Although M-mode measures of LV function are problematic when there are marked regional differences in function, these more sophisticated measures may be useful in clinical trials such as in hypertension,[60] in which symmetrical LV contraction is usually present because of case selection.

Pitfalls in LV Quantitation and Strategies for Obtaining Quantifiable Images

Foreshortening of the LV cavity by the operator is a common source of underestimation of LV end-diastolic and end-systolic volumes.[61,62] EF, which is calculated as the difference between end-diastolic and end-systolic volume divided by end-diastolic volume, is less affected by LV foreshortening because the error is, in part, self-correcting. Intravenous contrast administration and harmonic imaging improve border detection and lessen foreshortening, with improved reproducibility and better correlation of volumes and EF with the standard of cardiac MRI.[61-64] Images can be obtained at held expiration or during quiet respiration, but either approach should be applied consistently. If images are obtained during held expiration, care must be exercised to avoid a Valsalva maneuver, which can degrade image quality and alter cardiac volumes. If beats are selected during quiet respiration, at least 30 beats should be recorded, which should allow selection of at least 3 beats for averaging that display correct anatomic alignment. It is recommended that the LV be displayed in the most magnified presentation, ie, at the shallowest display depth that contains all components of the image that need to be assessed. Use of greater display depths than neces-

sary results in the desired portions of the image being represented by fewer pixels. The resulting lower pictorial information content may increase measurement error. Additionally, frame rates may be slower at deeper display depths, potentially resulting in blurred endocardial definition and reduced temporal resolution.

Recommendations for measurement of LV volumes, EF, segmental wall motion, and LV mass. Because all of these measurements except segmental wall motion are dependent on accurate and reproducible measurement of LV volumes, they share common recommendations for optimal methodology.

LV volumes and EF. The ASE recommends that for most research purposes, EF should be measured from LV volumes rather than estimated by visual inspection,[65] as is common in clinical practice. For volumes, we recommend the method of discs whenever good apical views can be obtained. If poor-resolution apical images do not allow identification of endocardium or are foreshortened, the method of multiple diameters[24] may be used. In individuals without major shape distortions or substantial dilation of the LV, it is acceptable to use linear dimensions that approximate the minor axis in systole and diastole to calculate volumes and EF. Two-dimensional estimation with the single-plane area-length formula is also acceptable. In the case of distorted LV geometry, biplane apical views should be used. In the case of suboptimal visualization of endocardium, even with tissue harmonic imaging, left heart contrast agents should be used to improve accuracy and reproducibility.

Segmental LV function. The ASE recommends that the 17-segment model adopted by many professional societies in 2002, including the ASE,[66] be used to assign the units of analysis of wall motion. Walls should be scored[67] as 1 = normal, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic, and 5 = aneurysmal (diastolically deformed). The ASE also recommends that wall motion be judged by segmental thickening in addition to endocardial motion.

LV mass. In adequately powered clinical trials evaluating participants without substantial dilation, major distortions of LV geometry, or both (eg, most therapeutic trials in hypertension), the ASE recommends that LV mass be measured with the model of a prolate ellipse of revolution, from linear dimensions of septal wall, LV cavity, and posterior wall along the LV minor axis, identified as the largest diameter perpendicular to the septum and posterior wall. These can be obtained by 2D-targeted M-mode or directly from correctly aligned 2D images. Although they are less desirable because of limitations of lateral resolution, apical windows may be used to obtain 2D linear dimensions perpendicular to the septum and lateral wall at the level of the mitral tips. An acceptable alternative is use of the area-length or truncated-ellipsoid formulas. Because of inherent difficulties in reliably identifying the boundaries of the LV free wall from base to apex in apical windows, the Simpson's rule method is not currently recommended.

Diastolic LV Function

Measures of diastolic function are important in clinical trials of heart failure (particularly with preserved systolic function) and hypertension, as well as in epidemiological studies (Table 2). Research has demonstrated the prognostic value of diastolic function measured by echocardiography in several clinical contexts.[59,68-77] At the present time, a multitude of Doppler-derived parameters have been used to evaluate diastolic function. The physiological basis of these measurements is beyond the scope of this document but is detailed in the accompanying references.[78,79] Recommendations on how to record and measure these parameters have been made recently in a publication from the ASE.[54]

Information from mitral inflow, pulmonary vein flow, LV inflow propagation velocity, and mitral annular diastolic velocity can be used to determine 4 patterns of diastolic function that represent stages of relaxation and compliance abnormality. A recent classification proposed that diastolic dysfunction be graded in 4 stages that correlate with diastolic impairment and symptom class.[80] Characterization of diastolic function patterns and estimation of LA pressure are possible in clinical trials.

Mitral inflow velocities. Early peak filling velocity, which represents acceleration of blood across the mitral valve, and atrial peak velocity are traditional but still valid measures when applied carefully. Deceleration time, a measure of LV stiffness, can also be measured from mitral inflow recording of early filling and may be less influenced by loading conditions than some other measures.

Pulmonary venous flow. Measurement of pulmonary venous flow was the first method to differentiate pseudonormal from normal LV filling, and it has been used to estimate mean LA pressure. However, consistent high-quality recordings in clinical trials using transthoracic echocardiography (TTE) may be difficult to obtain and time-consuming. Hence, pulmonary venous flow recording in clinical trials has largely been supplanted by tissue Doppler and color M-mode flow propagation.

Tissue Doppler measurement of mitral annular velocity. Longitudinal velocities within the myocardium can be recorded with pulsed-wave tissue Doppler from the apical window. Velocities at the basilar segments are obtained by placing the sample volume at the junction of the LV wall with the mitral annulus. Most commonly, recordings of septal and lateral anuli are obtained. Early diastolic velocity (Em, also referred to as Ea for annular velocity) has

Table 2 Echocardiographic measures of diastolic function

Measurement location and technique	Measurements	Comments
Mitral inflow: pulsed-wave Doppler (continuous wave can be used for IVRT)	Epk, Apk, E/A ratio, deceleration time, IVRT, A-wave duration	All are preload dependent and may be operator dependent
	Early/late diastolic fractional filling	Less frequently used than previously
Mitral inflow/color flow M-mode	Velocity of LV inflow propagation (Vp)	Measurement may be subject to observer variability and LV cavity dimension
Mitral annulus/tissue Doppler	Peak velocity early filling (Ea) of septal or lateral annulus.	Relatively preload independent. Linear measurement. Values dependent on location of sample volume. Combination of mitral inflow Doppler and tissue Doppler (Epk/Ea ratio) may be useful for estimation of LA mean pressure.
Pulmonary vein Doppler (pulsed wave)	Systolic/diastolic velocities, A-wave duration and depth.	May be technically problematic in large-scale, multicenter trials. Useful in separating normal from pseudonormal patterns.
LA area (4ch)/volume	Area/volume; fractional area/volume changes	Correlates well with Doppler diastolic function measures. Possibly reflects chronic effects of increased LA pressure.
Inferior vena cava size	Linear dimension (diameter)	Related to right atrial mean pressure. Usually affected by respiration.

Apk, Peak velocity of A wave; *Ea,* mitral annular peak velocity of early filling, measured by tissue Doppler; *Epk,* peak velocity of E wave; *IVRT,* isovolumic relaxation time; *LA,* left atrium; *pk,* peak velocity; *4ch,* four chamber view.

been shown to relate inversely to the time constant of early relaxation, tau. Like flow propagation velocity (Vp), Em has been shown to be fairly insensitive to preload when myocardial relaxation is impaired, and thus, it can be used to assess LV relaxation independently of the influence of LA pressure in individuals with diastolic dysfunction. At least one clinical trial of treatment of diastolic heart failure (iPRESERVE) is using measurements of mitral annular velocity and velocity of color flow propagation as Doppler surrogates for LA pressure. Em measurement is simple to perform, and because it yields a linear rather than a biphasic measure, it could supplant the E/A ratio as the most commonly used measure of diastolic function in the future.

Color M-mode flow propagation velocity. Propagation velocity (Vp) is a measure of the rate of propagation of blood flowing from the mitral valve tips to the LV apex. It is derived from the early mitral inflow velocity by color M-mode echocardiography in the apical 4-chamber view and is inversely associated with tau measured with high-fidelity micromanometer-tipped catheters.[81] Importantly, Vp has been shown to be fairly insensitive to changes in preload.[82,83]

Reproducibility. Intraobserver and interobserver correlations of peak mitral inflow velocities have been reported at ≥0.89[84]; however, test-retest reliability of mitral inflow velocities has been noted to be modest,[51] with intraclass coefficients (rho) of correlations for early diastolic filling velocity (E), late filling velocity (A), and E/A ratio of 0.64, 0.65, and 0.12, respectively, possibly due to biological variability. Reproducibility of inflow velocity is better when measured at the tips than at the mitral annulus. Test-retest reliability of Vp and lateral mitral annular velocities is excellent, with an intraclass coefficient of correlation (rho) of 0.90, although reliability for isovolumic relaxation time and deceleration time is less robust (rho 0.72 and 0.60, respectively).

Recommendations for assessment of diastolic function. In hypertension trials, or trials of so-called diastolic heart failure, in which ejection fraction is generally normal, we recommend using Em for the assessment of relaxation. If the available echocardiography machine is not capable of recording tissue annular velocities, Vp may be a useful alternative. However, in hypertrophic hearts with small LV cavities, Vp may provide falsely high values.

Measurements derived from pulmonary vein velocity may not add significant information when the above parameters are available, and they are more difficult to obtain. For assessment of LA filling pressure, the ratio between early diastolic mitral inflow velocity and either mitral annular velocity (E/Em) or Vp (E/Vp) should be measured. Mitral annular velocity appears to be less subject to observer variability than color M-mode flow propagation. In clinical trials of participants with dilated cardiomyopathy and depressed LV EF (<40%), the mitral E/A ratio, isovolumic relaxation time, deceleration time, and measurements from pulmonary vein velocity are excellent indicators of filling pressures and are relatively simple to use.

In the presence of atrial fibrillation, it will not be possible to measure atrial velocity of mitral inflow or

the atrial contributions to pulmonary venous flow or annular velocity.

Right Ventricular Mass, Function, and Pressure

Right ventricular (RV) structure and function are affected importantly in systemic diseases that involve the LV, including hypertension, myocardial infarction, and congestive heart failure, as well as pulmonary vascular and parenchymal diseases. However, for technical and anatomic reasons, standardized and accepted measures of RV mass and EF by echocardiography have not been developed. RV systolic function has been evaluated visually or by area change determined from the apical 4-chamber view. Assessment of RV function may be enhanced in the future with the development of 3D echocardiography techniques. RV systolic pressure is a useful measure of pulmonary hypertension, and can be estimated from even small tricuspid regurgitant (TR) jets, which are commonly present, from the modified Bernoulli equation ($4V^2$ + RAP), where V is peak velocity of the TR jet, and RA is estimated or assumed right atrial pressure.

Left Atrial Size, Volume, and Function

The left atrium enlarges in response to impaired LV filling and with mitral regurgitation and atrial fibrillation. LA size is therefore a useful adjunct in the assessment of diastolic function.[85] LA size can be assessed by measuring a single dimension (eg, 2D-targeted M-mode measurement of anteroposterior dimension). However, the LA enlarges in 3 planes, and a single dimension may fail to accurately represent LA volume.[86] LA volume estimates from the planimetered LA area in the apical 4-chamber view correlate well with volumes obtained by biplane methods,[87] previously validated by cine computerized tomography,[88] and are superior to linear representations of LA size. Moreover, LA volume in a population-based study has been shown to reflect the presence and predict the incidence of cardiovascular disease.[89] Nonetheless, even linear measurements of LA size have been of utility in clinical and epidemiological studies.[85,90-94] LA passive and active emptying volumes can be obtained by measuring LV volume before atrial contraction, at LV end diastole, and at LV end systole.[95]

Reproducibility. Interobserver variability for M-mode, apical 4-chamber, and biplane estimations of LA volume has been reported to be 5 ± 5, 6 ± 6, and 8 ± 9 mL, respectively.[87] The test-retest reliability of 2D-targeted LA anteroposterior dimension is 5.5 mm, with an intraclass coefficient of correlation (rho) of 0.72.[51]

Recommendations for measurement of LA size. The ASE recommends planimetry of the LA area from the apical 4-chamber view as a practical approach. Volume calculations from orthogonal linear measurements or biplane LA areas may also be useful.[96]

IV. VALVULAR STRUCTURE AND FUNCTION

Identification and qualitative assessment[97] of valvular regurgitation are relatively simple with 2D echocardiography and color flow imaging. Such assessments are routinely used in clinical practice[98] and are well described in standard texts[99-101] and ASE guidelines.[54] Measurement of color flow jet areas is operator and machine dependent, however, requiring careful attention to uniform image acquisition. Assessment of change in the magnitude of valvular regurgitation should utilize quantitative methods whenever possible. Volumetric assessments of regurgitation obtained by subtracting forward volume flow from total flow obtained from LV measurements sum the errors of chamber-volume estimations and are of limited utility. However, substantial experience has been obtained with the proximal isovelocity surface area (PISA) method with color flow Doppler for quantitation of mitral regurgitation.[102-105] Effective regurgitation orifice area can be calculated as $6.28 \times (R)^2 \times$ aliasing velocity/peak regurgitation velocity. Although they are quantitative, these techniques may be subject to acquisition and observer variability. Timing of velocity and PISA radius should be the same at mid systole to minimize variability. This technique is used primarily in mitral regurgitation and is more difficult to perform in other valvular regurgitant lesions. For studies that primarily assess valvular regurgitation as a covariate in evaluations of other echocardiographic end points, such as LV mass or systolic/diastolic function, traditional qualitative methods are adequate. In general, clinical trials of valvular stenosis have been evaluations of prosthetic valves, discussed below.

Reproducibility. Interobserver variability for measurement of PISA radius has been reported at 0.1 ± 13.8%,[106] and a 2.7-mm or greater change would have to occur to achieve 95% confidence of true change in severity of mitral regurgitation.

Recommendations for assessment of valvular structure and function. The ASE recommends that when qualitative assessment of valvular regurgitation, stenosis, and structure is performed, firm definitions should be established in advance as part of the study design. Quantitation of valvular thickness is limited by the technical characteristics of ultrasound and can be a problematic end point in clinical research. Leaflet mobility can be assessed qualitatively or by quantitative measurements of leaflet excursion.

Quantitation of valvular regurgitation is desirable and recommended when feasible or in stud-

Table 3 Recommendations for echocardiography in clinical trials of hypertension

Principal investigator; director of core laboratory	Coordinate and participate in echo protocol, site selection, training, reading, analysis, manuscripts.
Participate in study design	Avoid partition values of LV mass for entry, or assess for regression to the mean.
Select sites with capability and interest in research echocardiography	Sites submit sample echocardiogram for prequalification. Try to obtain sites capable of meeting recruitment goals and doing high-quality research echocardiography.
Sonographer training	Central meeting with participant demonstration; instructional videotape; Webcast.
Sonographer premeasurement	Sonographer measurements (not used for data) assist in critical assessment of echo quality before participant leaves the laboratory.
LV mass measurement (ellipsoid model, linear LV cavity, wall thickness)	Linear dimensions: targeted M-mode if eccentricity of parasternal short axis <1.1, or 2D images with correctly aligned linear dimensions.
Record systolic posterior wall thickness and LV dimension	Allows calculation of end-systolic stress.
Biplane LV EF	"Eyeball" EF as an alternative, but subject to challenge.
Diastolic function assessment	LA area (apical 4 channel), question LA volumes (ellipsoid model), Epk, Apk, tissue Doppler annular velocity, other as practical.
Core laboratory reading	Fewer readers better than many (limits variability). Batch reading at end of study avoids temporal variability from drift in reading styles but limits ability to monitor study quality and is impractical in large, long-term studies. Alternative: periodic rereads of aliquot of test echocardiograms to measure reader drift. Question statistical correction of data as necessary.
Quality assessment/improvement	Acquisition: quality grades, communication, online recommendations for improvement as needed. Core laboratory; interobserver, intraobserver variability. Measure test-retest reliability and temporal drift in reading style.

Apk, peak mitral inflow velocity of atrial contraction measured by Doppler; *EF,* ejection fraction; *LA,* left atrium; *LV,* left ventricle.

ies primarily assessing valvular disease or heart failure. However, quantitation is subject to sources of variability in acquisition and interpretation similar to those with qualitative assessments. Therefore, the severity of valvular regurgitation should be determined by a combination of semiquantitative methods and more quantitative methods, such as PISA, depending on the objectives and size of the study. For recommendations regarding quantitation of valve areas, see below ("Prosthetic Valves").

V. RELATED TECHNIQUES IN CARDIOVASCULAR RESEARCH

Echocardiography research laboratories, and echocardiographers, have increasingly extended their activities from cardiac imaging to evaluation of anatomic and functional cardiovascular end points not usually evaluated in clinical echocardiography laboratories. Principally, these include assessment of endothelial function by measurement of flow-mediated brachial vasodilation (see below) and assessment of atherosclerotic burden by measurement of carotid artery intima-media thickness or identification of discrete carotid plaque. Additionally, cardiovascular ultrasound now involves partnerships with invasive cardiologists and radiologists in research applications of ultrasound imaging of coronary and peripheral arteries. Epidemiological studies and studies of therapeutic interventions in hypertension and dyslipidemia that evaluate mechanistic end points require assessment of not just LV mass and function but also endothelial function and atherosclerosis. Hence, it is reasonable to incorporate these cardiovascular ultrasound assessments within the same site and core laboratories as traditionally used for echocardiographic research.

Intravascular and Intracoronary Ultrasound (Table 3[2])

Because intravascular ultrasound (IVUS) and intracoronary ultrasound (ICUS) are invasive techniques, their use in clinical trials will be essentially limited to participants with a clinical requirement for cardiac catheterization or as part of an interventional (stent) trial. Accordingly, ICUS and IVUS data are usually obtained by invasive cardiologists, not echocardiographers. Nevertheless, there are important diagnostic applications of ultrasound for assessment of artery and stent diameters, as well as presence and composition of atherosclerotic plaque and its change with therapy.

Reproducibility. Interobserver differences in lumen, vessel, and plaque volume have been reported[107] to be $\leq$0.4%, with coefficients of variation of $\leq$1.7% and test-retest differences of $\leq$2.6% (coefficients of variation $\leq$8.6%).

Recommendations for performance of IVUS and ICUS. IVUS/ICUS should be limited to those laboratories that use the technology regularly (in general,

≥5 times per week). In addition to the general recommendations presented later (VIII. Summary and Recommendations), equipment between sites should be standardized. The interpretation methods and nomenclature used in a clinical trial should be consistent with those set forth by the American College of Cardiology's Task Force on Clinical Expert Consensus Documents.[108] As with all other core laboratory analyses, intrareader and interreader variability should be assessed, and there should be documentation of the images analyzed and the measurements made.

Flow-Mediated Brachial Arterial Dilation Assessment of Endothelial Function

Endothelial dysfunction is a key step in atherogenesis that contributes to the initiation, propagation, and clinical manifestations of atherosclerosis. Abnormal endothelial function has been implicated both in early atherogenesis and in hypertension[109,110] and has been demonstrated in humans before the appearance of intimal thickening by ICUS111 or other evidence of atherosclerosis.[112] Lipid-lowering and other therapies have been shown to improve endothelial function.[113-115] Hence, there is great potential for use of noninvasive measurement of endothelial function in clinical trials of hypertension and dyslipidemia, as well as in epidemiology studies..

Brachial artery ultrasound is a safe and noninvasive technique for detecting endothelial dysfunction and for following longitudinal changes in vascular reactivity in response to interventions. Normally, increased blood flow raises shear stress on endothelial cells, which leads to production of vasodilators and arterial dilation, which is mediated by nitric oxide produced by endothelial cells. This arterial dilation can be measured by 2D echocardiography.

The diameter of the brachial artery is measured at baseline and in response to increased forearm blood flow, induced by occlusion of the arteries in the arm or forearm for approximately 5 minutes, the release of which leads to reactive hyperemia. The maximum change in brachial artery diameter from baseline in response to hyperemia, adjusted for the baseline diameter, defines flow-mediated dilation (FMD). Administration of nitroglycerin provides a control intervention to assess non–endothelium-dependent vasodilation. The techniques for assessing FMD have been reviewed in detail elsewhere.[116]

Although most reported studies have been single-center studies, multicenter studies have been reported and are under way, including the Multi-Ethnic Study of Atherosclerosis (MESA), the Cardiovascular Health Study (CHS), and the Framingham Heart Study. FMD frequently is used to assess the effect of interventions (eg, lipid lowering) on endothelial function. Crossover and parallel-group trial designs have been used.

Reproducibility. The interobserver variability (mean ± standard deviation) is approximately 1.2 ± 0.4% when the average FMD is 7 ± 1%.[117] In experienced laboratories with excellent reproducibility, a 2% to 3% improvement in FMD can be detected in crossover trials with about 15 to 30 subjects and in parallel-group trials with about 25 to 45 subjects per treatment arm.[116,117]

Recommendations for assessment of FMD with brachial ultrasound. Brachial artery ultrasound studies of FMD should be performed in the morning in the fasting state, to eliminate circadian and postprandial variability in arterial diameters, and in a temperature-controlled room. Subjects who regularly use tobacco-containing products must refrain from such use for 12 hours. Because it is more comfortable and permits continuous arterial imaging, the ASE suggests the use of forearm occlusion in preference to upper-arm occlusion in multicenter clinical trial environments.

These studies are technically challenging, and both technicians and readers have a steep learning curve. Because baseline brachial artery diameters typically are approximately 4 mm (less in children and women) and the observed change may only be 2% to 4%, changes in diameter of 0.12 to 0.16 mm must be detected. Therefore, the ASE suggests that experienced sonographers perform a minimum of 20 supervised scans and experienced readers review 5 to 10 high-quality scans by the specific study protocol before beginning unsupervised scanning. Ongoing scanning, at least 3 studies per month and 36 studies per year, should be performed, with at least semiannual review by an experienced reader to ensure maintenance of quality and adherence to the research protocol. Changes in FMD in response to interventions should be described in terms of absolute and percent change. Apparent changes in FMD oftentimes are attributable to changes in baseline brachial artery diameter, which may change with temperature, sympathetic tone, the postprandial state, and other physiological factors. Statistically, between-group comparisons should adjust for baseline artery diameters to minimize this effect.

Carotid Artery Imaging in Cardiovascular Clinical Trials—Measurement of Intima-Media Thickness (Table 4)

Carotid atherosclerosis has proved to be a useful surrogate for coronary atherosclerosis in epidemiological and prospective interventional trials of antiatherosclerotic agents. Ultrasonography permits noninvasive detection and quantification of abnormalities of carotid arterial structure, including wall thickening, plaque formation, and lumen enlargement. High-resolution B-mode ultrasound

Table 4 Summary of selected trials with ultrasound measurement of carotid intima-media thickness as a surrogate for atherosclerosis

Reference Number	Trial	Treatment	Length, y	Subjects, n	Sites	Mean/Maximum	Findings
Lipid-lowering trials							
215	CLAS	Colestipol-niacin vs placebo	2	146	CCA	Mean (1)	Less progression with colestipol-niacin
124	ACAPS	Lovastatin vs placebo	3	919	CCA, bulb, ICA	Mean max (12)	Less progression with lovastatin
216	ARBITER	Atorvastatin vs pravastatin	1	161	Far wall CCA	Mean (2)	More regression with atorvastatin
217	FAST	Probucol vs pravastatin vs diet	2	246	CCA	Mean (6)	Less progression with probucol or pravastatin than with diet
218	PLAC-II	Pravastatin	3	151	CCA, bulb, ICA	Mean max (12)	Less progression with pravastatin
219	ASAP	Atorvastatin vs simvastatin	2	325	CCA, bulb, ICA	Mean (6)	Less progression with atorvastatin
220	LIPID	Pravastatin	4	522	CCA	Mean (1)	Less progression with pravastatin than placebo
221	BCAPS	Metoprolol CR/XL and fluvastatin vs placebo	3	793	CCA, bulb, ICA	Mean (3)	Less progression with metoprolol XL, less progression with fluvastatin than with placebo
222	KAPS	Pravastatin	3	447	CCA, bulb	Max (4)	Less progression with pravastatin than placebo
223	REGRESS	Pravastatin	2	885	CCA, bulb, ICA	Mean (12)	Less progression with pravastatin than placebo
224	CAIUS	Pravastatin	3	305	CCA, bulb, ICA	Mean max (12)	Less progression with pravastatin than placebo
225	MARS	Lovastatin	4	188	CCA	Mean (2)	Less progression with lovastatin than placebo
Antihypertension trials							
125	ELSA	Lacidipine vs atenolol	4	2334	CCA, bulb	Max (4)	Less progression with lacidipine
221	BCAPS	Metoprolol CR/XL and fluvastatin vs placebo	3	793	CCA, bulb, ICA	Mean (3)	Less progression with metoprolol XL, less progression with fluvastatin than with placebo
226	PREVENT	Amlodipine	3	825	CCA, bulb, ICA	Mean max (12)	Less progression with amlodipine than placebo
227	MIDAS	Isradipine vs hydrochloro-thiazide	3	883	CCA, bulb, ICA	Mean max (12)	No difference in atherosclerosis progression, IMT difference favored isradipine
228	VHAS	Verapamil vs chlorthali-done	4	498	CCA, bulb, ICA	Mean max (6)	No difference in atherosclerosis progression, verapamil greater after correcting for initial IMT

Table 4 Continued

Reference Number	Trial	Treatment	Length, y	Subjects, n	Sites	Mean/Maximum	Findings
229	INSIGHT	Nifedipine vs hydrochlorothiazide/amilo-ride	4	439	CCA	Mean (1)	Less progression with nifedipine
230	SECURE	Ramipril vs vitamin E vs placebo	4.5	732	CCA, bulb, ICA	Mean max (12)	Less progression with ramipril than placebo, no vitamin E effect

CCA, Common carotid artery; *ICA*, internal carotid artery; *IMT*, intima-media thickness; *max*, maximum.

permits accurate and reproducible identification and measurement of the combined thickness of the intimal and medial layers of the carotid artery. Several large epidemiological studies have shown significant associations between carotid intima-media thickness (CIMT) and both prevalent and incident coronary and cerebrovascular disease.[118-121] Accordingly, measurement of CIMT has been a mainstay of cardiovascular epidemiological research for more than 2 decades. When scanning and reading are performed carefully, the reproducibility and reliability of CIMT measurement can be excellent.[122,123]

Cross-sectional analyses suggest that age-related increases in mean CIMT average approximately 0.010 mm per year for women and 0.014 mm per year for men in the internal carotid artery and 0.010 mm per year for both sexes in the common carotid artery.[124] Similar values have been observed in prospective studies.[215,225,226] Because the magnitude of clinically relevant differences in percentiles of CIMT and the progression rates are close to the resolution of vascular ultrasound transducers, highly standardized protocols are needed for performing and interpreting studies, which underscores the importance of high-quality, detailed image-acquisition protocols and highly skilled and trained ultrasonographers.

Reproducibility. In highly trained centers, average reproducibility rates of 0.01 mm (standard error of the mean 0.01 mm) have been obtained on blinded repeat scans at 4-week intervals.[122] With highly standardized protocols in populations with atherosclerosis, CIMT can be used as a continuous variable with sufficient reliability to detect annual changes in CIMT progression of approximately 0.01 mm relative to placebo, with a sample size between 100 and 200 subjects. Intrareader and interreader reliability have been reported at 0.915 and 0.872, respectively.[123,125]

Recommendations for measurement of CIMT. Scans should be obtained from multiple angles (circumferential scanning), and the near and far walls of multiple segments should be measured. For epidemiological and cross-sectional assessment, mean values of CIMT are sufficient. For longitudinal assessments, as in interventional trials, the use of mean maximal values from multiple sites provides the greatest sensitivity for detection of interval change. Measurements of carotid wall thickness can be made by manual tracing of wall interfaces or automated border-detection programs.[126-128] It is important to monitor observer reproducibility throughout the study for each method of measurement; reproducibility differs between manual and automated techniques.

VI. APPLICATIONS OF ECHOCARDIOGRAPHY IN CLINICAL TRIALS

The use of echocardiography in clinical trials was preceded by early investigations designed to define normative values for M-mode echocardiographic measurements of the LV, LA, aortic root dimension, and mitral valve.[129-132] These initial studies were important in documenting the relationships of cardiac structural measurements to age and body size, as well as their accuracy and reproducibility.

Epidemiological and Observational Studies

The Framingham Heart Study was the first epidemiological study to use echocardiographic measurements, particularly of LV mass and geometry, to examine its cohort (1993-1998).[34,133-137] Importantly, Framingham first demonstrated LV mass to be an independent predictor of cardiovascular events in a population-based sample. These and other normative and prognostic echocardiographic observations continue to be important as a basis for the current and future use of this technique in epidemiological studies and clinical trials (Table 5). Subsequently, other epidemiological studies, including the Cardiovascular Health Study, the Coronary Artery Risk Development in Young Adults (CARDIA) Study, the Olmstead County Heart Study, and the Helsinki Heart Study, have provided important cross-sectional and longitudinal information on relationships between cardiac structure and func-

Table 5 Echocardiography in epidemiological studies

Study	No. of participants	No. of Echo sites	Echo frequency	Population; follow-up	Year echo performed	Study aims
Framingham[231]	4950+	1	Per examination cycle	Population-based CVD, original cohort and descendants; >20 years	1981-present	Assessment of LV mass, function, chamber size
Cornell-Worksite Studies[232]	409	1	Up to 4 examinations over 10 years	Normotensive and hypertensive adults from employed population samples	1985-1998	Relations of LV structure and function to ambulatory blood pressure; longitudinal change
Olmstead County (Mayo)[233]	2042	1	Twice	3.5 years	1997, 2002	Population-based assessment of systolic and diastolic dysfunction
Cardiovascular Health Study (CHS)[234]	5888	4	Twice; 5-year interval	Elderly >65 years; 14-year follow-up	1990, 1995	Population-based assessment of LV mass, systolic and diastolic function, chamber size. Comparison with wide array of clinical and biomedical variables.
CARDIA[235]	1189	4	Twice; 5-year interval	Age 23-35 years; approximately 14-year follow-up	1990, 1995	Population-based per above; comparison with wide array of clinical and biomedical variables
Baltimore Longitudinal Aging Study[129]	1100+	1	Multiple	Age 21-90+ years	—	Population-based aging study begun in 1940s
Helsinki Aging Study[236]	577	1	Once	Random sample of Helsinki residents born 1904, 1909, or 1914	1989	LV mass calculable in 87% of subjects
Strong Heart Study[237]	3501	3	Once: 2nd Strong Heart Study exam	American Indian, CV events after exam	1993-1995	Cardiac disease and outcome in population with high rates of overweight and diabetes
HyperGEN[238]	2966	4	Once: 1st HyperGEN exam	White & African-American hypertensive adults from population-based sources	1996-1999	Heritability and genetic linkage of LV hypertrophy and dysfunction
Strong Heart Family Study[239]	3600+	3	Once: 4th Strong Heart Study exam/ Strong Heart Family Study (some Strong Heart Study participants reexamined)	American Indians in large 3-generation families, CV events after examination	2001-2003	Heritability and genetic linkage of LV hypertrophy and dysfunction; LV-arterial relations (with carotid ultrasound)

Table 5 Continued

Study	No. of participants	No. of Echo sites	Echo frequency	Population; follow-up	Year echo performed	Study aims
HyperGEN II	1000	4	Once: 2nd HyperGEN exam	Relatives of white and black hypertensive adults from population-based sources	2001-2003	Heritability and genetic linkage of LV hypertrophy and dysfunction
Family Blood Pressure Program	6000	5	Once: 2nd Family Blood Pressure Program examination	African-American, Hispanic, and Japanese-American adults from population-based samples	2001-2003	Heritability and genetic linkage of LV hypertrophy and dysfunction

CVD, Cardiovascular disease; *CV*, cardiovascular; *LV*, left ventricular.

tion, determined echocardiographically, with clinical expressions of disease and with clinical outcome. Importantly, in aging populations in which health becomes the outcome variable and disease status is the normative state, echocardiography may help define the phenotype of healthy aging. Epidemiological studies have additionally defined vascular phenotype and the presence and burden of atherosclerosis by measurement of carotid intima-medial thickening.

Hypertension

Evaluation of treatment effects on LV mass. Although the application of echocardiographic methods to trials of antihypertensive therapy has been shown to reduce LV mass and LV hypertrophy,[138,139] some studies[140-145] indicate that not all drugs are equally effective in reducing LV mass, even with comparable reduction of blood pressure. Table 3 summarizes the echocardiographic findings of several multicenter trials of antihypertensive treatment that used core laboratories and blinded readings. In appropriately designed studies, which are well powered and have sufficient duration of events ascertainment, important mechanistic information can be generated on relationships between clinical outcome and selection of therapy, based on its impact on cardiac function and structure. For example, in the LIFE (Losartan Intervention for Endpoint Reduction) study,[146] not only was the experimental therapeutic limb associated with greater LV mass reduction, but LV mass reduction was also associated with improved clinical outcome independent of blood pressure lowering or treatment selection. Echocardiography has also been of use in demonstrating sustained reduction in LV mass in patients with hypertrophic obstructive cardiomyopathy after nonsurgical septal reduction therapy with intracoronary ethanol.[147]

Effects of treatment on systolic and diastolic LV function. Clinical studies that have evaluated ejection phase indices and diastolic filling with echocardiography[148-158] have not demonstrated adverse effects of LV mass reduction on systolic or diastolic function during or after antihypertensive therapy. In fact, improvement may actually occur,[159] particularly in diastolic performance, which may be an important therapeutic end point.

Intercenter differences in acquisition quality. In previous large echocardiography trials, major differences in echocardiography quality have existed between field centers.[160] For example, in one trial of antihypertensive monotherapy, the percent of readable echocardiograms for LV mass varied among centers from approximately 30% to 85%, probably owing to variation in technical performance. Importantly, extensive previous clinical experience in echocardiography was no guarantee of high-quality echocardiograms for quantitative research.

Recommendations for echocardiography in hypertension clinical trials (Table 6). Sonographer training is important to obtain reproducible images that are anatomically correctly oriented. Some of the flexibility in clinical examination techniques may be counterproductive to obtaining high-quality research studies. Specific training and monitoring of study quality as outlined in Section VIII is helpful.

Given the large confidence intervals that may exist for measurement of LV mass, it could be argued that treatment trials should recruit participants with markedly increased LV mass. However, selection of participants with values for LV mass values substantially above (or below) the population mean can result in subsequent tests that reflect regression to the mean. Therefore, higher than "true" values for LV mass on an initial determination will tend to decrease on subsequent measurement. It is recommended that if possible, partition values

Table 6 Selected multicenter treatment trials in hypertension with echocardiography

Study	References	Echo participants	Echo sites	Echo Frequency	Length, y	Study aims	Principal findings
VA Cooperative Studies: Monotherapy in Hypertension	[144] [94]	587	15	Baseline, 1, 2 years	1	LV mass reduction in participants on competing single-drug assignments for mild-moderate hypertension	Diuretic effective for decreasing LV mass and LA size; diuretic, captopril, atenolol for LV mass
TOMHS (Treatment of Mild Hypertension Study)	[240]	902	4	Baseline, annually for 4 years	4	LV mass reduction with monotherapy vs dietary-hygienic control	All treatments associated with decrease in LV mass. Diuretic greater than other drugs at 1 year
Isradipine vs hydrochlorothiazide	[145]	134	18	Baseline, 6 mo, 12 mo, 2 weeks after drug withdrawal	.5	Isradipine vs hydrochlorothiazide monotherapy for LV mass and LA dimension reduction	Decreased LV mass and LA size with hydrochlorothiazide, not with isradipine.
LIFE (Losartan Intervention for Endpoint Reduction in Hypertension)	[241]	754	47	Baseline, 1, 2, 3, 4, and 5 years	4.8	Losartan vs atenolol for LV mass reduction; prognostic significance of LV mass reduction	Greater LV mass reduction with losartan than with atenolol. Strong predictive value of lower on-treatment LV mass for outcome.
PRESERVE (Prospective Randomized Enalapril Study Evaluating Regression of Ventricular Enlargement)	[242]	303	28	Baseline, 6 and 12 mo	1	Nifedipine vs enalapril for LV mass reduction. Added medication as needed for blood pressure control.	No between-group difference in LV mass reduction or mitral inflow filling velocities
SANDS (Stop Atherosclerosis in Native Diabetics)	*	488	4	Baseline, 18 and 36 mo	3	Intensive treatment (LDL ≤75 mg/dl, BP ≤115/75 mmHg will reduce carotid IMT and LV mass more than standard treatment	In progress

BP, Blood pressure; *IMT,* intima-media thickness; *LDL,* low-density lipoprotein; *LV,* left ventricular.
*Personal communication from Dr Richard Devereux.

for LV mass not be used as requirements for entry into the study. If such values are used, then batch reading at completion of the study (with continuous monitoring of studies for acquisition quality) should be done. This may not be practical in long-term studies. Additionally, over time, there may be changes in reading style that can systematically bias the interpretation of studies and lead to type I error. Periodic rereading of sample test echocardiograms will allow quantification of regression to the mean and of temporal reader drift.

Heart Failure (Table 7)

Given the central role of alterations of cardiac function and structure in this important disorder, echocardiography is well-suited to the evaluation of patients with congestive heart failure in that it provides rapid assessment of systolic and diastolic LV (and RV) function, as well as comorbid valvular, myocardial, and pericardial abnormalities. Echocardiography is the most commonly used initial imaging test for patients with heart failure.[161,162]

Table 7 Echocardiography in clinical trials of congestive heart failure

Trial	Treatment	No. of participants	Echo #	Prot.	Core lab	Echo role	Echo variables	Echo findings
SAVE[243]	Captopril	2231	512	M, S	Y	O	A, EF	Echo predicts outcome
SOLVD[26]	Enalapril	2569	301	M, S	Y	O	F, V, M	ACE-inhibitor attenuates adverse LV remodeling
V-HeFT I & II[244]	Vasodilators	1466	1466	M, S	Y	O	D, W	Echo variables feasible in multicenter trial, predict mortality
V-HeFT III[168]	Felodipine	450	260	M, S	Y	S, O	D, V, EF, F, M, E	Echo had good reproducibility, predicted mortality, hemodynamics
CIBIS-II[245]	Bisoprolol	2647	Most	M, S	Y	S	EF	
Hall et al[246]	Metoprolol	26	26	M, S	Y	O	V, EF, M	Time course of EF improvement with beta-blocker treatments
Doughty et al[247]	Carvedilol	123	123	M, S	Y	S, O	V, EF	Improvement in EF and LV remodeling in ischemic CHF
Tang et al[248]	Carvedilol	256	256	M	Y	O	D, EF	Baseline echo did not predict EF improvement
Arcensio et al[249]	Ibopamine	18	18	M, S	Y	S, O	D, R	Improvement in LV function
Capucci et al[170]	Pacing	38	38	M, S	Y	S, O	D, R	Best atrioventricular interval with pacing for optimization of hemodynamics
MIRACLE[169]	Pacing	453	453	M	Y	S, O	D, EF, R	Diastolic dimension, severity of mitral regurgitation, EF
Jette et al[250]	Aerobic exercise	39	39	M, S	Y	S, O	D, EF	No change with training
Pu et al[251]	Resistance exercise	96	96	M, S	Y	S, O	D, EF, R	No change with training
PRAISE-2[252]	Amlodipine	1600	93	C, B	Y	S, O	D, EF, R	EF and mitral regurgitation predicted mortality
PEP-CHF[167]	Perindopril	1000	1000	M, S	Y	S, O	D, EF, R	Ongoing
CHARM[253]	Candesartan	6500	TBA	TBA	TBA	TBA	TBA	Ongoing trial of diastolic and systolic heart failure
I-PRESERVE, echo substudy*	Irbesartan	3600	500	M	Y	S, O	D, M, EF, F	Ongoing trial of treatment of diastolic heart failure. Diastolic function measures include tissue Doppler

Treatment, Intervention; tested; *Pts,* participants; *Echo#,* number of participants in echocardiographic substudy (*S,* participant selection, *O,* outcome measurement); *Prot.,* capture protocol (*C,* casual, *M,* mandated by protocol, *B,* baseline only, *S,* serial); *Y,* yes; *N,* no; *A,* LV areas; *F,* diastolic filling; *V,* LV volume; *E,* end systolic; *M,* LV mass; *D,* LV dimensions; *W,* wall thicknesses; *R,* regurgitation; *ACE,* angiotensin converting enzyme; *CHF,* congestive heart failure; *LV,* left ventricular; *EF,* ejection fraction.
*Personal communication from Dr J. Gottdiener.

Despite the many multicenter trials involving large numbers of participants over the past 3 decades, until recently, cardiac imaging was used almost solely for participant selection and screening.[163] Commonly, heart failure trials centered on participants with signs and symptoms of heart failure in the presence of decreased LV EF and LV dilation, and echocardiography or other imaging techniques, often abstracted from clinical records, were used primarily for entry criteria, to ensure a reduced LV EF and/or dilated chamber. This significant heterogeneity and lack of attempt at quality control of a pivotal entry criterion (EF) reduced costs but likely contributed to the variability of results.

More recently, echocardiography has been used in a careful and systematic fashion in large, multicenter trials.[164-167] The Veterans Cooperative Trials group (V-HeFT I, II, and III and Val-HeFT) pursued the development of echocardiographic methods for multicenter heart failure trials through a series of substudies nested within large trials. V-HeFT-I and II were exploratory in nature.[165] In V-HeFT-III, quantitative measurements were made at local sites, although quality control and oversight were provided by a central core laboratory.[168] PEP-CHF, a pioneering trial in diastolic heart failure, declared Doppler echocardiographic outcomes to be particularly important.[167] Mitral regurgitation has been shown to be an important prognostic factor in patients with heart failure, and several potential mechanisms for mitral regurgitation have been proposed. There are several clinical trials to attempt to improve participants' heart failure status and their survival by reducing the amount of mitral regurgitation by a surgical or percutaneous device. In these trials, it will be important to use several semiquantitative and quantitative methods for evaluating the severity and mechanism of mitral regurgitation.

Resynchronization/biventricular pacing studies in heart failure. Resynchronization of ventricular contraction with biventricular pacing has been

Table 8 Commonly used echocardiography measures in heart failure trials

Most commonly used measures	LV EF and volumes (2D quantitative recommended)
Covariates of interest	A. Practical in large, multicenter trials: LV regional wall-motion abnormality, LV mass and wall thickness, qualitative or quantitative assessment of mitral regurgitation, carotid intima-media thickness, aortic distensibility/compliance, RV pressure, severity of tricuspid regurgitation.[12] B. May be more practical in smaller studies: LV end-systolic stress, tissue strain rate imaging, LV midwall fractional shortening ("myocardial" function), aortic systolic velocity integral (estimate of stroke volume). C. Pertinent to biventricular pacing/resynchrony studies: LV electromechanical delay (time interval from onset of QRS to beginning of aortic flow recorded by pulsed- or continuous-wave Doppler), RV electromechanical delay (time interval from onset of QRS to beginning of pulmonary flow recorded by pulsed- or continuous-wave Doppler), interventricular conduction delay (difference between LV and RV electromechanical delay), septal to posterior wall-motion delay (shortest time interval from maximum excursion of ventricular septum and maximum excursion of posterior wall).
Diastolic function	A. Practical in large, multicenter trials: LA size (2D area/volume), Doppler E and A peak velocities, deceleration time, tissue Doppler mitral annular velocity. B. May be more practical in smaller studies: pulmonary vein velocities, color M-mode velocity of inflow propagation, isovolumic relaxation time; estimation of PA diastolic pressure from PR jet when present.
Echo to identify confounding nonmyocardial causes of heart failure	Screening for clinically significant aortic valve stenosis and regurgitation, evidence of constrictive pericarditis, pericardial effusion with tamponade, cardiac tumors, vegetations

A, Mitral inflow velocity of atrial contraction measured by Doppler; *E,* early diastolic mitral inflow velocity measured by Doppler; *LA,* left atrium; *LV,* left ventricle; *PR,* pulmonary regurgitation; *PA,* pulmonary artery; *RV,* right ventricle.

shown to improve symptoms of patients with dilated/ischemic cardiomyopathy and left bundle-branch block.[169,170] With pacing, echocardiography studies have shown that the LV becomes smaller and systolic function improves after 3 to 6 months. However, not all patients with dilated cardiomyopathy and left bundle-branch block benefit from biventricular pacing. The degree of asynchrony between the right and left ventricles has been shown to correlate with the degree of reverse remodeling. The duration of QRS on an electrocardiogram does not predict the degree of ventricular dyssynchrony. However, echocardiographic parameters of ventricular dyssynchrony measured with M-mode, 2D, Doppler, and tissue Doppler identify participant populations that may benefit the most from resynchronization therapy and enable the monitoring of therapeutic response.[169,171-173] Moreover, echocardiography can also determine surrogate end points of successful therapy, such as improvement in systolic function, mitral regurgitation, diastolic filling, and pulmonary hypertension.

What to measure with echocardiography in heart failure trials. Heart failure is a clinical syndrome that overlies complex alterations in cardiac structure and physiology and in peripheral vasculature and neuroendocrine responses. Hence, there is no simple set of echocardiographic measures that is diagnostic of heart failure per se. However, in that echocardiography readily provides a rich array of information on virtually every cardiac abnormality (and some peripheral vascular abnormalities as well) that underlies heart failure, it is singularly well suited for heart failure trials. Table 8 is a list of echocardiographic measures, grouped by commonality and purpose of usage, that are reasonable for use in heart failure trials; it is not intended to be comprehensive. In trials of biventricular pacing, additional echocardiographic parameters to evaluate ventricular dyssynchrony are useful.

Although the flexibility of echocardiography provides a great deal of information pertinent to heart failure, that very flexibility can lead to measurement variability. A recent report indicates that even with careful site selection, a specified protocol, and exclusion of participants with poor acoustic windows, the variability of basic outcome measures by echocardiography is greater than with alternative techniques such as radionuclide angiography and MRI,[174] although echocardiography is considerably less expensive and more accessible. Moreover, harmonic imaging, contrast agents, and 3D echocardi-

ography all have the potential to improve the applicability and reproducibility of echocardiography. Use of contrast agents may have the largest potential for improving data yield and quality in clinical trials.[63]

Recommendations for echocardiography in heart failure studies. The successful application of echocardiography in clinical heart failure trials depends on attention to quality control, including careful protocol design targeted to ensuring an adequate number of echocardiographic assessments without producing undue participant and sonographer burden; site training and monitoring; and echocardiographic coordination and interpretation by an experienced and competent core laboratory. Recommendations for assessment of echocardiography parameters used in heart failure trials are provided elsewhere in this document.

Myocardial Infarction

LV remodeling after acute myocardial infarction is a well-known pathological process that results in progressive dilatation (remodeling) and distortion of the LV. It is determined by the size, location, and extent of myocardial infarction, as well as the reperfusion status of the infarct-related artery. This process produces many echocardiographically recognizable changes, such as an increase in LV size and volume, mitral valve regurgitation, altered LV geometry, diastolic dysfunction, and other hemodynamic changes. It has been shown that LV volume is one of the most prognostic parameters after acute myocardial infarction. Optimal treatment of acute myocardial infarction minimizes the extent of LV remodeling and hence those echocardiographic changes associated with LV remodeling. Therefore, clinical trials to identify beneficial management modalities for participants with acute myocardial infarction should utilize the hemodynamic, structural, and functional changes related to LV remodeling as their end points. This requires accurate sequential assessment of LV size and volume, LV sphericity, and LV segmental function and quantitative assessment of mitral regurgitation, pulmonary artery pressure, and diastolic filling patterns. These assessments are discussed elsewhere in this document.

Clinical Trials With TEE: Stroke, Atrial Fibrillation, and Guidance of Interventional Procedures

Stroke is the third-leading cause of death in the United States,[175] and approximately 15% of strokes are considered to have a cardioembolic source.[176] The causes of cardioembolism include nonvalvular atrial fibrillation in 45% of patients, LV dysfunction in 25%, rheumatic heart disease in 10%, prosthetic valves in 10%, and other miscellaneous causes, such as endocarditis and cardiac tumors, in 10%.177 Echocardiography has been important in clinical trials[178,179] in identifying sources of cardioembolism.[177]

In suspected cerebral embolism, TTE is of use in identifying the presence of LV thrombus and cardiac comorbidity such as LV hypertrophy or LV dysfunction. However, the yield is low for identifying and characterizing potential sources of cardioembolism such as PFO, atrial septal aneurysm, thoracic aortic atheromas, and clot in the LA appendage. TEE is of greater utility than TTE in these circumstances,[180-183] as well as for measurement of LA appendage velocity, itself a predictor of thrombus and stroke.[184,185]

There have been several stroke and atrial fibrillation trials in which echocardiography has played a major role (Table 9), including the SPAF III trial[186] and the ACUTE multicenter trial.[178] In SPAF III, TEE was useful in defining stroke risks of atrial fibrillation on the basis of LA abnormalities (LA appendage thrombus, dense spontaneous echocardiography contrast, or LA appendage flow <20 cm/s) and complex atheroma plaque.[187] In the WARSS trial[188] of participants with stroke, which compared the value of warfarin with that of aspirin for prevention of recurrent stroke, all participants had TEE at randomization. In a substudy, TEE was used to determine the relationship between PFO and recurrent stroke.[183] With warfarin or aspirin therapy, the presence of PFO in those with stroke did not increase the chance of adverse events regardless of PFO size or the presence of atrial septal aneurysm.

Clinical trials in atrial fibrillation: TEE-Guided Cardioversion. TEE with short-term anticoagulation has been proposed as an alternative strategy in patients with atrial fibrillation who undergo electrical cardioversion. TEE involves greater logistic complexity than TTE. However, in the ACUTE study,[189] TEE was shown to be feasible in a large multicenter study. With the use of uniform acquisition and interpretation criteria for identification of LA thrombus, it was found that the time to cardioversion and the composite rate of major and minor bleeding complications over an 8-week period were reduced with TEE-guided therapy.

LA appendage closure devices. There are ongoing trials using TEE to assess the efficacy of percutaneous excluding devices of the LA appendage to decrease the risk of stroke.[190] TEE and intracardiac echocardiography are also involved in the evaluation of pulmonary vein stenosis after radiofrequency ablation for atrial fibrillation.[191,192]

PFO closure devices. Recently, there has been increased interest in surgical and percutaneous catheter-based methods to close PFOs.[193] With FDA approval of the Amplatzer and Cardioseal devices to close PFO, there is increasing interest in the use of TEE and intracardiac echocardiography[194] to guide the closures.

Table 9 Echocardiography in clinical trials of stroke

Ref. no.	Trial	Treatment	No. of participants	Outcome	Echo role	Findings
186	SPAF III	Low-dose warfarin or ASA vs adjusted dose of warfarin in participants with stroke	382	Stroke	TEE	High-risk group with LA abnormality and complex atheroma had stroke rate of 21% per year; adjusted dose of warfarin reduced rate of stroke
178	ACUTE I	TEE guided vs conventional therapy in participants undergoing DCC	1227	Stroke, TIA, peripheral embolus	TEE	No difference in stroke/TIA; lowered bleeding in TEE arm
254	ACUTE II	Low-molecular-weight heparin vs IV heparin in participants undergoing TEE-guided cardioversion	200	Stroke, bleeding, increased cost	TEE	Ongoing
188	WARSS	Warfarin or ASA in participants with stroke	2206	Recurrent embolic events or death	TTE	No difference in recurrent stroke or death
183	PICSS	Warfarin or ASA in participants with PFO	630	Recurrent stroke or death	TEE	No difference between warfarin or ASA in participants with PFO
255	WARCEF	Warfarin or ASA in participants with low EF	2860	Recurrent stroke, death, or intracerebral bleed	TTE	Ongoing
255	WATCH	Warfarin, ASA, clopidogrel in participants with CHF and low EF	4500	Stroke, death, or MI	TTE	Ongoing

ASA, Aspirin; *CHF,* congestive heart failure; *DCC,* direct current cardioversion; *EF,* ejection fraction; *IV,* intravenous; *MI,* myocardial infarction; *PFO,* patent foramen ovale; *TIA,* transient ischemic attack; *TEE,* transesophageal echocardiography.

Recommendations for TEE-guided clinical trials. As with other multicenter trials, the ASE recommends use of standardized acquisition protocols and core laboratory measurement of TEE parameters. However, onsite qualitative and quantitative assessments, even though not used as study findings, can be useful tools to optimize the technical quality of studies.

Inherently, both TTE and TEE may have significant variability in the detection of source of emboli in clinical trials. It is imperative that exact definitions of the sources of emboli be noted in the standard operating procedures manual, with illustrations (cine loops). Core laboratories should be used to verify the accuracy of the site data, ie, LA appendage thrombus, PFO, and atrial septal aneurysm. It is important to differentiate LA appendage thrombus from pectinate muscles, pulmonary vein limbus artifact, severe smoke, and sludge.

In general, both TTE and TEE are useful in clinical trials involving cardioembolic stroke. The best yield is with TEE with the finding of LA appendage thrombus, spontaneous echocardiography contrast, aortic atheroma, and PFO.

Prosthetic Valves

Manufacturers of prosthetic valves rely on Doppler echocardiographic measurements of valvular hemodynamics in vivo to fulfill FDA requirements[195] for new device applications. Because most prosthetic valves are inherently stenotic, spectral Doppler can be used to evaluate valve performance in a manner analogous to native valve stenosis.[54,196-202] The general principles for evaluating prosthetic valve function are similar to those of native valve stenosis. The velocity across the valve reflects the pressure gradient. Velocities and gradients through prosthetic valves depend on valve type and size, flow, and heart rate.[198,200] Overall, Doppler pressure gradients correlate well with gradients by catheter.[203] However, in certain valve prostheses, specifically smaller bileaflet valves, overestimation of gradients by

Doppler has been demonstrated and related to the "pressure-recovery" phenomenon.[203,204] In newer stentless biological valves used for the aortic position, the valve orifice size is close to that of native valves, and consequently, Doppler velocities are near normal or, at most, slightly increased.[205] However, stented biological and mechanical valves have smaller effective orifice areas than corresponding normal native valves, which results in higher velocities and therefore higher pressure gradients derived with the $4V^2$ equation.

Evaluating prosthetic aortic and pulmonic valves. The following parameters are recommended when evaluating an aortic prosthesis: peak transvalvular velocity (peakV), mean transvalvular gradient, peak LV outflow velocity, the ratio of peak LV outflow velocity to peakV (known as the Doppler velocity index or dimensionless index), and the effective orifice valve area, derived with the continuity equation. Details on the technical aspects of recording and measuring velocities from Doppler recordings are to be found in the "Recommendations for Quantification of Doppler Echocardiography" document from the ASE.[54]

Use of the continuity equation to measure prosthetic aortic valves requires calculation of the cross-sectional area of LV outflow, commonly derived by use of the diameter of the LV outflow tract. When the diameter cannot be visualized reliably, the sewing ring diameter of the prosthesis can be used.[200,203] Doppler-derived effective valve areas have been reported for few prostheses and appear to be related to valve size. In contrast, the Doppler velocity index is less dependent on valve size and is therefore quite useful when the valve size is not known at the time of the study.[200,206]

Prosthetic aortic valve regurgitation can be detected readily with transthoracic Doppler echocardiography. Color Doppler is quite sensitive, so that even the "built-in" functional regurgitation associated with some of the mechanical valves can be visualized.[202,207] Whenever one finds more than trivial insufficiency by Doppler, it is recommended that the following parameters be used to assess severity: (1) the width of the regurgitant jet in the LV outflow tract relative to the LV outflow diameter, (2) the pressure half-time of the regurgitant jet recorded with continuous-wave Doppler, and (3) the magnitude and duration of the retrograde diastolic velocity in the upper descending aorta or the abdominal aorta, recorded with pulsed-wave Doppler.

Pulmonic prosthetic valves are implanted infrequently, and thus fewer data are available on their evaluation. Because of the dynamics of RV ejection in native pulmonic stenosis, the peak instantaneous transvalvular gradient derived from the peak velocity is similar to the peak-to-peak gradient at catheterization.

Evaluating prosthetic mitral and tricuspid valves. The following parameters are recommended when evaluating a mitral prosthesis: (1) peak transvalvular velocity, (2) VTI of the transvalvular velocity, (3) mean transvalvular gradient, (3) pressure-half time (p 1/2t), and (4) effective mitral valve area (MVA). With valve obstruction, the peak velocity, VTI, mean gradient, and pressure half-time are generally increased, whereas mitral valve area is decreased (Table 2). Although the formula MVA = 220 ÷ p 1/2t, validated in native mitral stenosis, has been applied to prosthetic mitral valves, it has never been properly validated.[208] Nevertheless, most significantly obstructed mitral prostheses have a valve area derived by p 1/2t of 1.0 cm^2 or less. However, as with native valves, the P 1/2t method can underestimate or overestimate mitral valve area in patients with significant aortic insufficiency, restrictive LV filling, severe relaxation abnormalities, arrhythmias, or sinus tachycardia. In these situations, the continuity equation may be applied using the LV outflow to determine stroke volume if there is no significant prosthetic valve regurgitation.[209] No data are available for the application of the continuity equation in tricuspid valves.

Detection and evaluation of prosthetic mitral valve regurgitation with TTE is hampered by ultrasound shadowing and Doppler flow masking that occurs when the sound waves are reflected by the prosthesis. This problem is more severe in mechanical valves than in bioprosthetic valves, which limits the sensitivity of transthoracic color and spectral Doppler for detection of prosthetic mitral valve regurgitation.[210,211] Therefore, we recommend the use of a nonimaging continuous-wave transducer in all participants with prosthetic mitral valves, because its lower frequency provides better penetration and can often record a regurgitant jet that has been missed by the imaging transducer. TEE is often needed to confirm this lesion and assess the severity of regurgitation. For the most part, prosthetic tricuspid valve regurgitation is easier to detect than prosthetic mitral regurgitation.

Recommendations for echocardiography in the assessment of prosthetic valves. It is recognized that the FDA guidelines for echocardiographic evaluation of prosthetic valves in clinical trials are an exhaustive compendium of Doppler measurements and flow data derived from 2D-estimated cardiac volumes. The potential for contradictory and confusing data is therefore large. Although comprehensive data acquisition is necessary to meet FDA guidelines, the echocardiography core laboratory principal investigator, in collaboration with the study sponsors, should specify which echocardio-

graphic measures are of primary interest (ie, most reliable) in contrast to those measures required for comprehensive evaluation but believed to be of lesser reliability.

Because Doppler measurements may be heart rate dependent, heart rate at the time of recording should be reported. Measurements should be averaged over 3 to 5 cardiac cycles in sinus rhythm and 5 to 10 cycles in atrial fibrillation. When serial evaluations are made, particularly in clinical trials, it is recommended that the same instrument be used and the same sonographer perform the examination. A note should be made in the participant's file as to the window that provided the best recording of the transvalvular velocity.

Echocardiographic Assessments of Cardiac Toxicity: Opportunity and Challenge

Echocardiography has been used extensively to assess potential cardiac toxicity from pharmacological agents. However, issues of potential cardiac toxicity may mandate rapid initiation and completion of clinical trials. This may make training, standardization, and quality assurance more difficult. Regardless of the difficult circumstances, it is the investigators' responsibility to perform and interpret the echocardiographic studies using the same standards employed in other clinical trials.

Recommendations. Whenever possible, a blinded control group should be used to determine whether the treatment group has developed cardiac toxicity. Arbitrary cutpoints should not be used to determine toxicity versus no toxicity because these cutpoints may introduce bias. For example, an EF less than a predetermined value should not be a cutpoint; rather, a statistically significantly lower EF in the treatment group than in the control group would indicate toxicity.

A large study conducted in a short time may require substantial support, such as from a clinical research organization. Regardless of the support network for the study, the investigator responsible for the echocardiograms should write the echocardiography acquisition protocol and determine the interpretation methodology. The interpretation methodology must be determined before review of the echocardiograms. An analysis plan for the echocardiographic data pertinent to the hypotheses of the study should be developed with substantial input from the investigator responsible for the echocardiograms before the study begins. The investigator must have access to all of the echocardiographic data. The sponsor or a clinical research organization may support data analysis, but an investigator should be allowed to perform independent analysis to verify accuracy.

Commercial vs Noncommercial Studies: Influence on Trial Design, Data Interpretation, and Publication

Echocardiographer-investigators should be integrally involved in the design of the echocardiographic examinations in clinical trials. This is important because echocardiographers, especially those who have had experience in the management of core laboratories, are aware of the quality-control issues involved in processing large number of studies, including appropriate training and monitoring of interreader and intrareader measurement variability, test-retest reliability, and temporal drift, as well as the practical requirements of ensuring smooth operation of the laboratory. Readers must also be blinded as to treatment group, demographics, and other key characteristics of participants whose echocardiograms they are interpreting. Important statistical issues include enrolling a sufficient number of subjects to ensure adequate power to test the hypotheses of greatest interest. In addition, the potential of regression to the mean is an important statistical consideration. Enrolling subjects with high (or low) partition values for a given parameter (eg, LV mass) may be attractive to the sponsor as a way to increase the likelihood of demonstrating a positive effect of a treatment. In the absence of a placebo control group, this can result in an erroneous interpretation treatment effect for all treatment arms because of regression to the mean, although with highly experienced core laboratories, this may not occur.[38] Possible solutions to this problem include averaging measurements from multiple studies performed in close temporal proximity in the same subject and inclusion of a placebo group in the context of a randomized, controlled clinical trial.

Patients give their consent to participate in clinical trials and provide consent with regard to the associated risks, discomforts, and demands on their time with the implicit understanding that the information obtained will be used to advance our understanding of disease and its treatment. Pharmaceutical or other industry sponsors of clinical trials have a responsibility to determine the safety and efficacy of their product and to present the information to the FDA in a timely and cost-effective way. These 2 goals of clinical trials may not always overlap completely, and it is the responsibility of the echocardiographer-investigator working with the industry sponsor to ensure that the clinical trial data are analyzed fully and completely and that the results of those analyses are presented for publication even if considered negative.

Recommendations for echocardiographer-investigator participation in clinical trials. Ivestigators must minimize actual or perceived conflicts of interest and disclose any financial support received from commercial sponsors. In commercially sponsored

Table 10 Recommendations for use of all cardiac ultrasound techniques in multicenter clinical trials

1. **Echocardiography principal investigator (PI) should be named.**
   Level III ASE, experienced in clinical trials methodology and research applications of cardiovascular ultrasound
2. **Use echocardiography central reading laboratory**-under direction of echo PI
   a. Minimize number of readers
   b. Periodic joint reading sessions with echo PI to maintain parallel reading styles
   c. Monitor reader variability
   d. Rapid communication with study sites on study quality and opportunities for optimization
   e. Maintain communications with study sponsor on work throughput and quality issues
3. **Standardized "hands-on" training of sonographers and readers** onsite or at centralized meeting. When hands-on training not feasible, alternatives include instructional videotapes, Webcasts, etc.
4. **Monitoring of sonographers for technical quality;** encode study quality in database.
5. **Record selective measurements and assessments** by sonographer (or physician performing the echocardiogram) on transmittal sheet to encourage critical evaluation of echocardiogram before sending to core laboratory.
6. **Appoint clinical site echo PI to oversee local acquisition quality**
7. **Late-model quality echocardiographic instrumentation, less than 5 years old**
   a. Periodic calibration as needed with appropriate phantoms
   b. Digital recording and review when possible
8. **Reading strategies**
   a. *Batch read when possible to minimize systematic temporal drifts.* If studies are batch read at end of recruitment and after completion of intervention, continuous reading still needed for quality monitoring.
   Alternative to batch reading is periodic rereads of sample aliquot to measure trends in systematic temporal bias. Introduce corrective measures as needed. Other alternative is to reread initial studies at the same time as follow-up studies:
   b. *Average multiple beats* (minimum of 3 in regular rhythm, 5 in atrial fibrillation.)
   c. *Single reader preferable.* If duplicate independent reads of same studies, adjudicate differences with consensus reads. If multiple readers used for different studies, establish and adjust for interreader differences. Train for parallel reading styles in joint reading sessions.
9. **Establish acquisition and reader variability**
   a. Test-retest of small sample of participants, ie, same participant repeated over small interval, same machine, same sonographer, same reader.
   b. Blind duplicates for interreader and intrareader variability assessment.
10. **Scientific participation of echocardiography PI** and investigators in data analysis, presentations, publications.

studies, issues of particular importance include blinding of readers (for example, to demographics and treatment group), ensuring access of the investigators to all relevant echocardiographic and nonechocardiographic data, and maintaining editorial control of the preliminary and final publications.

VII. HOW TO EVALUATE AND CONTROL ECHO VARIABILITY IN CLINICAL TRIALS: METHODS FOR QUALITY CONTROL

Methods to Limit Measurement Variability

There are many ways to identify and control acquisition and measurement variability. Table 10 outlines approaches for decreasing variability that are generally applicable to measurement of LV mass and all other echocardiographic parameters. As part of all core laboratory practice, intrareader and interreader variability should be measured, with documentation of the images analyzed and measurements made. A potentially difficult problem is found in the changes in reading style that may occur over time and which may systematically bias the interpretation of studies and lead to type I error. Periodic rereading of sample test echocardiograms will allow quantification of temporal reader drift and regression to the mean. Alternatively, batch reading of echoes at the completion of the study can be done, although this is likely to be logistically problematic, particularly in large clinical trials or epidemiological studies. A minimum number of readers should be used to limit the effects of interreader variability.

Equipment. Contemporary (less than 5 years old) echocardiographic machines should be used in clinical trials. All machines should undergo regular maintenance by a qualified technician and have yearly evaluations of their internal electronic calibration. Internal calibration avoids the need to use ultrasound phantoms.

Site training. Site training is a crucial step in ensuring high-quality, consistent study data. The physician lead investigator and the lead sonographer typically perform site training. Both the physician and sonographer selected to fulfill these responsibilities should have extensive research experience with image acquisition, measurements and calculations, and protocol training. In addition, they should have recently demonstrated a high level of personal expertise acquiring

and measuring the echocardiographic data described in the study protocol.

The lead investigator of the study, with assistance from the lead sonographer, should coordinate the initiation training for all participating sites at a group training session. This meeting should include not only all investigators but also the participating sonographers and nurses, if possible. The suggested agenda for the initiation meeting should emphasize a review of the study goals and protocol, live demonstration of the image-acquisition protocol using a test subject, and presentation of the protocol measurements and calculations (even if these will be performed by the core laboratory). If possible, each site should acquire images from the same test participant to ensure consistent imaging techniques for all sites. If the individual sites are performing any of the measurements and calculations, these should be performed using the same images from the test participant. To minimize interoperator variability, specific guidelines should be included in the protocol regarding backup sonographer coverage and training/initiation requirements for the backup sonographers. The core laboratory should provide each site with an image-acquisition protocol, training or reference videotape, and a core laboratory contact list for questions or problems that may arise at the site. Additional responsibilities for the lead investigator and/or the lead sonographer include training replacement sonographers, if necessary, and providing follow-up information to the individual sites based on regular reviews of each site's images and measurements.

Training can be facilitated by specially prepared videotapes, CDs, internet Webcasts, or in-person investigator meetings. Careful and timely monitoring, especially at the start of the study, is important in allowing rapid feedback and correction of technical errors in image acquisition. For some studies, site submission of validation cases before the study begins will be useful to ensure compliance with the acquisition protocol and the ability to perform the aims of the echocardiography protocol properly.

Core laboratory. Research has shown the value of core laboratories in multicenter clinical trials.[212,213] A core laboratory is necessary to ensure standardization of data collection throughout the study and to provide centralized training and certification of all sonographers, who should have participated in a standardized training program. It is important to monitor changes in performance of personnel and equipment. To minimize reader variability, a practical minimum number of readers should be used, and interreader variability should be monitored. Training sets of echocardiograms should be interpreted jointly by all readers to encourage a parallel reading style, and interreader and intrareader variability should be assessed periodically. Measurement reading drift between readers must be identified and corrected as it occurs. The core reading laboratory should encourage and assist in timely transmission of studies from study sites to the core laboratory and should notify study sites promptly of deficiencies in technical quality. The core laboratory must also cooperate fully with regulations regarding confidentiality of participant data and privacy and must be fully compliant with federal and industry standards for data integrity.

The core laboratory should be involved in the study design. This is particularly important in estimations of sample size. The variability of echocardiography measurements can be mitigated by ensuring that a sufficiently large sample size is used to determine whether the treatment is associated with a change of a given magnitude in the echocardiography end point. If the study goals require determination of individual patient responses to therapy, then high test-retest reliability must be established.

Sonographer training. A cardiac sonographer is an allied health professional who performs cardiac ultrasound examinations. The role of these individuals in clinical research is critical. The primary responsibility of the sonographer is to attain high-quality, diagnostically correct ultrasound images and Doppler data. Echocardiography is operator dependent, requiring skill and experience in obtaining and integrating accurate diagnostic information. The educational requirements to reach this level of competence must incorporate detailed, structured, and comprehensive curricula.[214] In clinical trials, particularly those in which multiple sites participate, sonographers should complete a standardized qualification process to ensure standardization of data acquisition.

VIII. SUMMARY AND RECOMMENDATIONS FOR USE OF CARDIOVASCULAR ULTRASOUND IN CLINICAL TRIALS

Echocardiography has been and remains a valuable tool for evaluating the effects of disease and its treatment on cardiac anatomy and physiology. The value of echocardiography has been extended by related vascular ultrasound techniques, which can be performed with the same personnel and essentially the same instrumentation and which permit assessment of vascular atherosclerosis and endothelial function. Because of its near-universal availability, noninvasive nature, acceptance by participants, and relatively low cost, as well as the wealth of worldwide experience with echocardiography for more than 30 years, cardiac ultrasound is well suited for use in large clinical trials and epidemiological studies. However, the technical flexibility and large quantity of data obtainable with echocardiography can result in study variability and loss of focus in capturing the desired information. Optimal deploy-

ment of cardiac ultrasound in clinical trials and epidemiological studies requires particular care beyond that used for patient care.

Accordingly, the ASE has developed guidelines that we hope will assist in the design and implementation of protocols for clinical trials. These guidelines are based on the combined experience of the Committee, guided by an extensive literature on echocardiography in clinical investigations. Basic to these recommendations is the utilization of an ASE level 3 physician echocardiographer with experience in clinical trial methodology to guide protocol development, training of site sonographers, and interpretation of ultrasound data, preferably at a central reading (core) laboratory under the direction of the principal echocardiography investigator. Quality-control measures to assess and minimize acquisition and reading variability must be implemented as described above.

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