JACC: CARDIOVASCULAR IMAGING
VOL. 10, NO. 12, 2017

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER
https://doi.org/10.1016/j.jcmg.2017.11.001

Noninvasive Cardiac Imaging and the Prediction of Heart Failure Progression in Preclinical Stage A/B Subjects

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ABSTRACT

Heart failure (HF) continues to grow as a cause of morbidity and mortality in our community and presents a significant public health problem, predominantly in individuals ≥65 years of age. Early intervention in asymptomatic HF subjects (Stage A/B) at risk of progression to symptomatic HF (Stage C/D) may provide an opportunity to halt this epidemic. The ability of cardiac imaging to assess cardiac structure and function permits early identification of those at increased risk of developing symptomatic HF. Systolic, diastolic, and structural left ventricular parameters each predict symptomatic HF, but no single parameter has sufficient sensitivity for screening to identify individuals with Stage A/B HF who are at increased risk of disease progression. Transthoracic echocardiography (TTE) has the advantage over other imaging modalities in being able to measure systolic, diastolic, and structural left ventricular parameters, and it identified at least 1 abnormal parameter in >50% of individuals with Stage A/B HF ≥65 years of age. Moreover, identification of at least 1 abnormality according to TTE in individuals with Stage A/B HF ≥65 years of age had 72% to 82% sensitivity for detection of those who subsequently developed symptomatic HF. Therefore, a case can be made for cardiac imaging by using TTE for community-dwelling populations with Stage A/B HF ≥65 years of age to identify those with increased risk of symptomatic HF who can be offered preventative therapies. Further studies are required to determine the best strategy for identifying the risk of symptomatic HF in younger individuals. (J Am Coll Cardiol Img 2017;10:1504–19)

Heart failure (HF) is a major cause of premature morbidity and mortality, with approximately 50% of people with symptomatic HF dying within 5 years of diagnosis (1). On the basis of data from the 2011 to 2014 National Health and Nutrition Examination Survey, an estimated 6.5 million Americans ≥20 years of age have HF, with a projected increase to >8 million people ≥18 years of age with HF in 2030 (2,3). In 2012, the total annual cost for HF was estimated to be $30.7 billion and is projected to increase to $69.7 billion in 2030. Great potential, therefore, exists for reductions in premature morbidity and mortality and for cost savings through more effective prevention of HF by the improved identification of individuals at increased HF risk and the prescription of preventative therapies.

HF is a progressive condition. The American College of Cardiology Foundation/American Heart Association describe 4 stages of HF: Stages A and B, which are asymptomatic (**Figure 1**), and Stages C and D, which are symptomatic. At age 45 to 95 years, lifetime risks for HF are 30% to 42% in white male subjects, 20% to 29% in black male subjects, 32% to 39% in white female subjects, and 24% to 46% in black female subjects; these risks are higher for those with higher blood pressure and body mass index at all ages (3). In addition to the risk factors that define Stage A HF, the predominant risk factor is age. In the Framingham Heart Study (1980 to 2003), the annual rates per 1,000 person-years of new HF events for white male subjects were 9.2 for those 65 to 74 years of age, 22.3 for those 75 to 84 years of age, and 43.0 for those ≥85 years of age; for white female subjects in

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Manuscript received November 28, 2016; revised manuscript received October 25, 2017, accepted November 1, 2017.

the same age groups, these rates were 4.7, 14.8, and 30.7, respectively. Thus, any strategy for HF prevention may need to be aimed at older individuals (≥60 years of age) at greatest risk.

HF is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood (1). HF may result from disorders of the pericardium, myocardium, endocardium, heart valves, or great vessels, or metabolic abnormalities; however, most patients with HF have symptoms due to impaired left ventricular (LV) structure or function. Although many cardiac imaging modalities detect systolic and diastolic dysfunction and structural abnormalities that predict HF progression in subjects with preclinical Stage A/B HF, the lower cost and widespread availability of transthoracic echocardiography (TTE) makes this modality the most useful for this purpose. This state-of-the-art paper summarizes the mechanisms of systolic and diastolic dysfunction and structural abnormalities detected by using cardiac imaging and reviews the utility of cardiac imaging for the prediction of HF progression in subjects with preclinical Stage A/B HF. This paper highlights the need for further understanding of the prognostic utility of many commonly used imaging parameters in daily practice and an evaluation of their use in an HF prevention strategy.

MECHANISMS OF SYSTOLIC AND DIASTOLIC DYSFUNCTION AND STRUCTURAL ABNORMALITIES

Systolic, diastolic, and structural abnormalities frequently co-exist (4–6), and the mechanisms of these abnormalities overlap (**Table 1**). These mechanisms result from changes induced by an initial insult, such as ischemia, pressure or volume overload, or inflammation (7,8), and they may result in HF with either preserved (HFpEF) or reduced (HFrEF) ejection fraction. Early post-infarct rat models demonstrated dilatation of both infarcted and noninfarcted segments that initially maintains cardiac output but leads to a decline in left ventricular ejection fraction (LVEF) (9). Pressure and volume overload induce an increase in myocyte diameter and length, respectively, that normalize wall stress (10) and produce concentric and eccentric hypertrophy, respectively (**Figure 2**).

Alterations in extracellular matrix and calcium homeostasis affect both systolic and diastolic function. Collagen synthesis contributes to replacement fibrosis (scar) and reactive fibrosis and contributes to both increased myocardial stiffness and contractile dysfunction (11). Hypertensive rats with subendocardial fibrosis exhibited evidence of both impaired global longitudinal strain (GLS) and diastolic stiffness (12). Hypophosphorylation of titin contributes to myocyte stiffness in animal models (13). These impairments in myocardial relaxation and stiffness are reflected in diastolic parameters of mitral inflow and tissue Doppler indices (**Figure 3**) but also in the consequence of increased LV filling pressures with left atrial dilatation, increased tricuspid regurgitant velocity, and higher LV end-diastolic volumes. Diastolic dysfunction occurs in both HFpEF and HFrEF (4).

Driving these changes are concurrent neurohumoral influences. Hyperadrenergic signaling contributes to myocyte apoptosis and increased matrix metalloproteinase activity, which degrades the extracellular matrix causing LV dilatation (10). Conversely, excess inhibition of matrix metalloproteinase promotes fibrosis (8). Activation of the renin-angiotensin-aldosterone system promotes myocyte hypertrophy, apoptosis, and interstitial fibrosis (10).

Although best characterized in patients with HF, these same mechanisms (**Table 1**) contribute in varying degrees to the systolic and diastolic dysfunction and structural abnormalities of asymptomatic individuals. However, while the diastolic dysfunction of HFpEF (14) and HF (15) in diabetes is associated with fibrosis, the diastolic dysfunction of diabetes, obesity, or aging without HF is not associated with increased myocardial fibrosis (16–18). By contrast, patients with hypertension with diastolic dysfunction may have increased myocardial fibrosis (19).

The division of TTE parameters into those reflecting systolic and diastolic function and structural alterations are an attempt to simplify the complex mechanisms of cardiac dysfunction that lead to the development of HF. Indeed, it has also become customary to subdivide patients with HF into those with HFrEF and HFpEF depending on predominantly systolic and diastolic abnormalities, respectively. General thresholds for abnormality are presented in guidelines, but the impact of sex and age also need to be accounted for (**Table 2**). Many TTE parameters, separately and in combination, predict incident HF in

ABBREVIATIONS AND ACRONYMS

ALVDD = asymptomatic left ventricular diastolic dysfunction

ALVSD = asymptomatic left ventricular systolic dysfunction

BNP = B-type natriuretic peptide

CAC = coronary artery calcium

CMR = cardiac magnetic resonance

GLS = global longitudinal strain

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

HHE = handheld echocardiography

LV = left ventricular

LVD = left ventricular dysfunction

LVEDD = left ventricular end-diastolic dimension

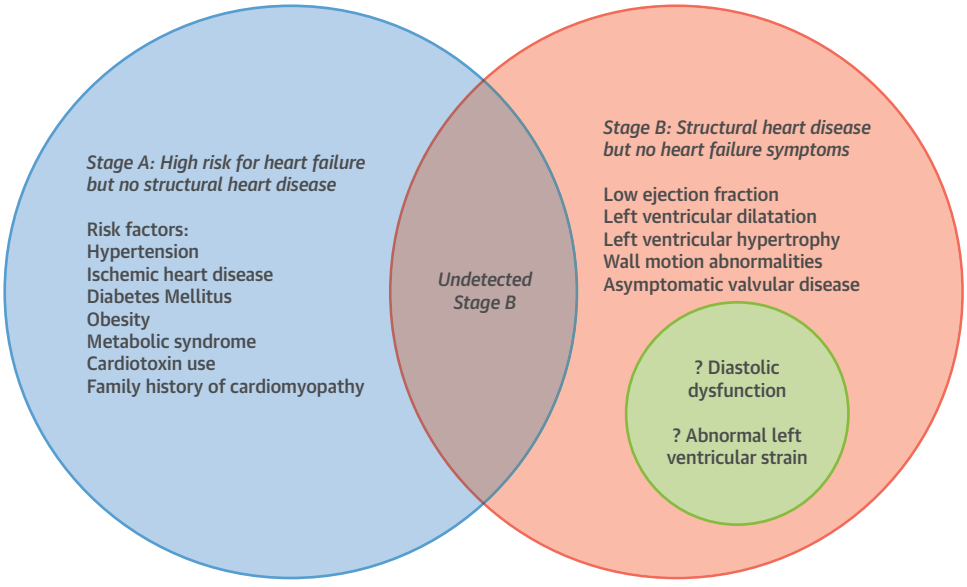
LVEF = left ventricular ejection fraction

LVH = left ventricular hypertrophy

TDI = tissue Doppler imaging

TTE = transthoracic echocardiography

FIGURE 1 ACCF/AHA Stages of Heart Failure A and B



Preclinical stages of heart failure (1) in which risk factors **(blue)** or cardiac structural/functional changes **(pink)** are present in the absence of symptoms and/or signs. A proportion with Stage B heart failure remains undetected without cardiac imaging. Newer measurements may need consideration as important Stage B heart failure markers **(green)**. ACCF/AHA = American College of Cardiology Foundation/American Heart Association.

TABLE 1 Cardiac Functional, Histological, Cellular, and Neurohumoral Alterations Reflected in Echocardiographic Parameters

		Mechanisms
Systolic dysfunction	Impaired cardiomyocyte contractility	Cardiomyocyte injury and cell death resulting from ischemia, infection, autoimmune disease, toxins, drugs, nutritional deficiency
		Impaired ECC due to decreased Ca^{2+} release from the SR
		ß-adrenergic receptor-dependent PKA-mediated hyperphosphorylation of ryanodine channels leading to diastolic calcium leak
		Mitochondrial dysfunction leading to reduced ATP/ADP ratio, increased ROS production, and oxidative stress
		Catecholamine-mediated desensitization and down-regulation of ß-adrenergic receptors
		Genetic causes of impaired contraction and cell death
	LVH	Increased cardiomyocyte width, increased ECM, infiltrative conditions such as amyloidosis
	Increased ECM	Focal/replacement fibrosis; angiotensin II– and aldosterone-induced fibrosis; infiltrative cardiomyopathy due to amyloidosis, sarcoidosis
Diastolic dysfunction	LVH	Increased cardiomyocyte width, increased ECM, infiltrative conditions such as amyloidosis
	Impaired myocyte relaxation	Decreased SERCA2a-mediated transfer of Ca^{2+} from the cytosol to the SR
	Increased cardiomyocyte stiffness	Reduced titin phosphorylation
	Systemic inflammation and coronary microvascular endothelial dysfunction	Macrophage infiltration, increased ROS production, reduced NO production
	Increased ECM	Interstitial/reactive fibrosis; angiotensin II– and aldosterone-induced fibrosis; infiltrative cardiomyopathy due to amyloidosis, sarcoidosis
Structural abnormality	Increased LV wall thickness and LV mass	Increased cardiomyocyte width, increased ECM, infiltrative conditions such as amyloidosis
		Genetic causes of LVH: HCM, infiltrative, and cardiac storage diseases
	Increased LV volumes	Dilated cardiomyopathy due to cardiomyocyte injury and cell death resulting from ischemia, infection, autoimmune disease, toxins, drugs, nutritional deficiency, and genetic causes
		Cardiomyocyte slippage, increased cardiomyocyte length

ATP/ADP = adenosine triphosphate/adenosine diphosphate; ECC = excitation–contraction coupling; ECM = extracellular matrix; HCM = hypertrophic cardiomyopathy; LV = left ventricular; LVH = left ventricular hypertrophy; NO = nitric oxide; PKA = protein kinase A; ROS = reactive oxygen species; SERCA = sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase; SR = sarcoplasmic reticulum.

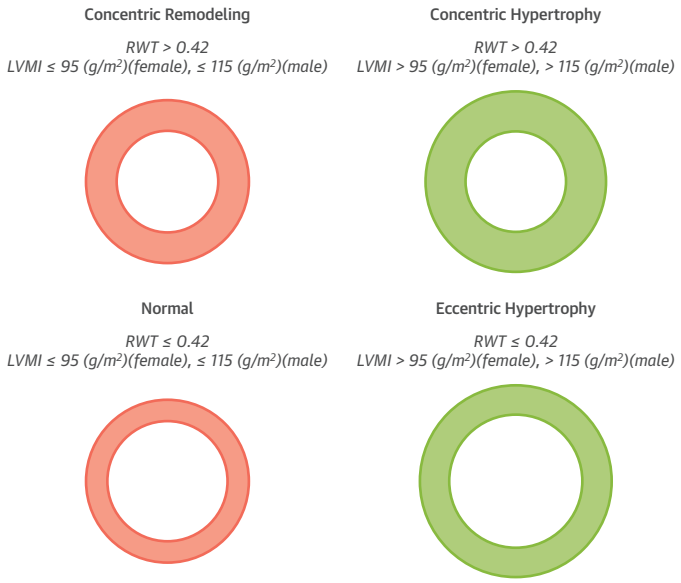
the Stage A/B HF cohort (**Tables 3 to 6**), but further understanding of the optimal method to maximize their prognostic utility is required.

PARAMETERS OF SYSTOLIC FUNCTION THAT PREDICT PROGRESSION OF STAGE A/B HF

LEFT VENTRICULAR EJECTION FRACTION. HF is typically classified according to LVEF, either HFrEF or HFpEF. Fractional shortening was used in older studies as an estimate of global LV function but is of limited accuracy in abnormally shaped ventricles (20). Although 3-dimensional volumetric assessment of LVEF is increasingly used and is more accurate and reproducible, most studies have used 2-dimensional LVEF assessment. Asymptomatic left ventricular systolic dysfunction (ALVSD) is an important predictor of symptomatic HF (**Table 3**). The prevalence of ALVSD depends on the definition of reduced LVEF. In a recent meta-analysis of cohort studies in which the LVEF threshold for ALVSD ranged between 45% and 60%, the prevalence of ALVSD was up to 10% (21), and the combined maximally adjusted relative risk for incident HF was 4.6. Use of lower LVEF thresholds conferred higher relative risks for HF, albeit with lower sensitivity (22–26). Importantly, treatment of ALVSD can reduce the risk of HF. In the SOLVD (Studies of Left Ventricular Dysfunction) Prevention Study, enalapril therapy conferred a 29% risk reduction for incident HF and mortality in asymptomatic individuals with LVEF <35% (27). Similarly, captopril treatment post-myocardial infarction reduced mortality and cardiovascular events in asymptomatic individuals with LVEF ≤40% in the SAVE (Survival and Ventricular Enlargement) trial (28).

LV LONGITUDINAL FUNCTION. The subendocardium of the heart is more susceptible to injury because it is farthest from epicardial coronary blood flow, experiences large fluctuations in blood pressure, and is prone to structural alterations such as myocardial fibrosis (29). Long-axis function largely reflects subendocardial function because myocardial fibers are roughly longitudinal in this layer. The mitral annular plane systolic excursion and mitral annular systolic velocity (S′) are 2 parameters for assessing longitudinal function that correlate well with LVEF (30). In addition, decreased mitral annular plane systolic excursion values have been recorded in individuals with HFpEF (31). However, data regarding the prognostic value of these parameters for incident HF in an asymptomatic population are scarce. One study reported a 26% increased risk of incident HF with every 1 cm/s reduction in S′ (32). These parameters are easily obtained, and further consideration of their potential as an HF risk marker is warranted.

FIGURE 2 Left Ventricular Hypertrophy

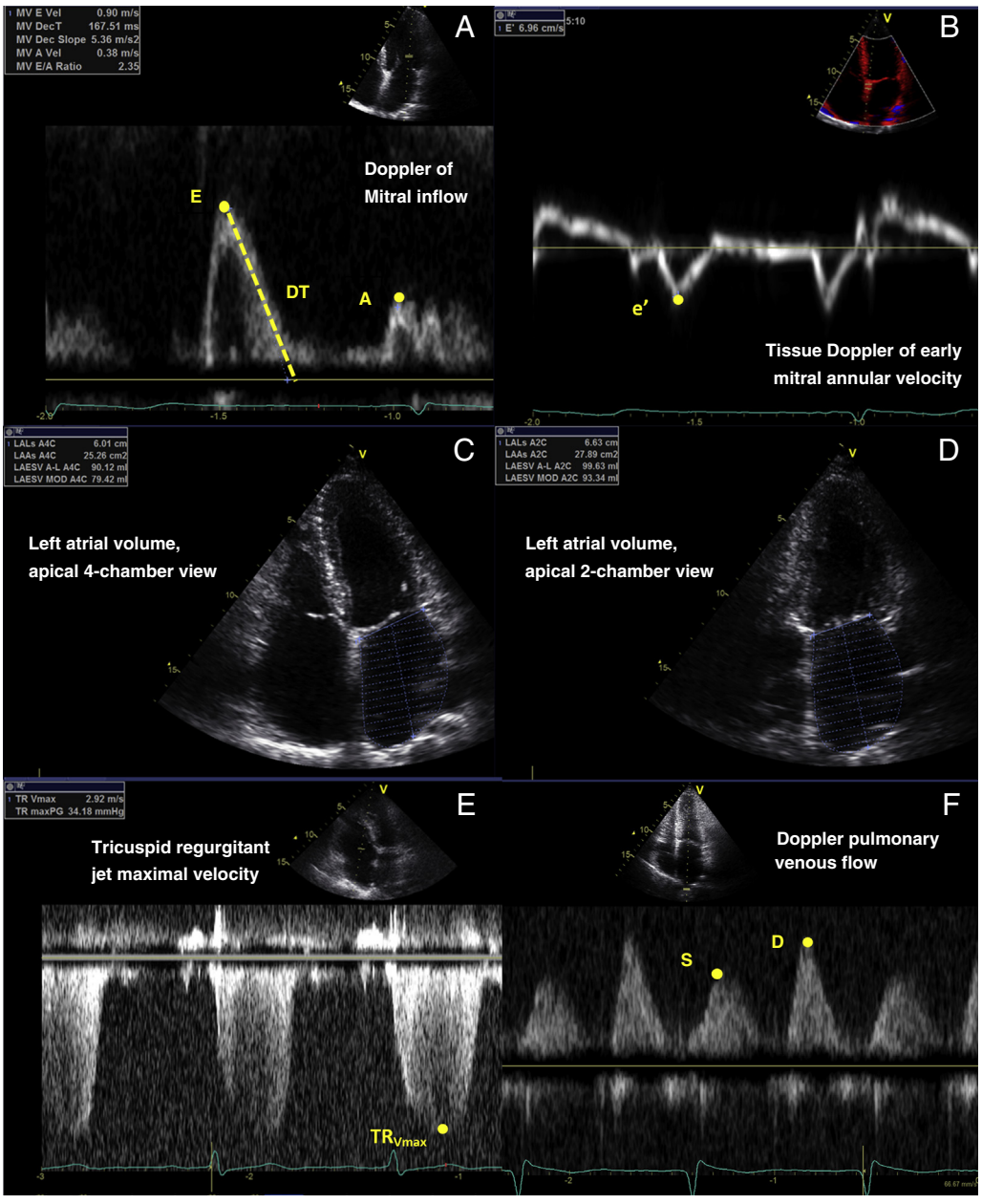


Combining regional wall thickness (RWT) and left ventricular mass index (LVMI) parameters to reflect patterns of left ventricular remodeling (20).

STRAIN. Although LVEF is the most frequently used parameter to define LV systolic function, it is operator dependent, requires geometric assumptions, and has high inter-reader variability. Measurement of strain was developed as an alternative, less subjective approach to the assessment of LV function (33). Strain describes deformation, or the shortening and lengthening, of the myocardium in a longitudinal, circumferential, or radial direction (**Figure 4**). GLS is expressed as a negative value because it represents shortening of the myocardium relative to the original length, with impaired GLS reflected by a value closer to zero.

Impaired GLS can detect subtle LV systolic dysfunction in many situations in which LVEF remains preserved, such as coronary disease, valvular heart disease, aging, diabetes, obesity, amyloidosis, hypertrophic cardiomyopathy, and Friedreich's ataxia (6,33). GLS is also impaired in patients with hypertension and preserved LVEF, either with coexisting left ventricular hypertrophy (LVH) with or without diastolic dysfunction (34), or without LVH in younger patients with hypertension (35).

FIGURE 3 Guideline-Directed Assessment of Diastolic Function



Guideline-directed assessment of diastolic function (4) includes **(A)** elevated E/A ratio 2.35 and short DT, **(B)** low e′ and normal E/e′ ratio 12.9, **(C and D)** increased left atrial volume index 42.1 ml/m^2, **(E)** elevated peak tricuspid regurgitant velocity (TRV_{max}), 2.9 m/s, consistent with restrictive filling (grade III diastolic dysfunction). **(F)** Supplemental measurement of pulmonary venous systolic (S) and diastolic (D) velocity with S < D (4).

Impaired GLS is associated with adverse outcomes. In a prospective study of 230 asymptomatic patients with type 2 diabetes and LVEF ≥50%, 45% had abnormal GLS at study entry, and GLS was independently associated with subsequent all-cause mortality and hospitalization (36). GLS also predicted survival in unselected patients referred for echocardiography (37) and in patients with systemic amyloidosis (38), and it predicted cardiovascular outcomes, including HF hospitalizations in cardiac sarcoidosis (39). Moreover, GLS detected subclinical left ventricular dysfunction (LVD) before a reduction in LVEF (40)

and predicted subsequent reduction in LVEF, symptomatic HF, and mortality after chemotherapy (41,42). GLS also predicted HF in individuals with Stage A/B HF ≥65 years of age (**Table 3**) (43,44) and in a community population aged 20 to 93 years (45). Importantly, there is evidence that impaired GLS is reversible, with improvements in GLS reported in obese patients after weight reduction (46).

There are currently no guideline-recommended thresholds for abnormal strain, as it is dependent on the equipment and software used (20). Due to lack of standardization of strain measurements between vendors, it is essential that each institution defines its own normal range for strain and ensures a high degree of reproducibility. Serial evaluations should be performed with similar equipment and algorithms for calculating strain (47).

PARAMETERS OF DIASTOLIC FUNCTION THAT PREDICT PROGRESSION OF STAGE A/B HF

DIASTOLIC FUNCTION. Diastolic function was initially assessed noninvasively using mitral inflow parameters on TTE (**Figure 3**). The relationship between E/A ratio and incident HF is nonlinear, and both E/A >1.5 and <0.7 are associated with incident HF (**Table 4**) (48). Subsequent incorporation of TDI parameters has helped to further characterize diastolic function. A low e′ indicates impaired myocardial relaxation, and an elevated E/e′ indicates elevated LV filling pressures (4,49). Left atrial dilatation and elevated tricuspid regurgitant jet velocity may also reflect elevated LV filling pressures and, together with mitral inflow patterns and TDI, combine to form the current assessment of diastolic function (**Figure 3**) (4).

The growing prevalence of HFpEF has highlighted the importance of assessment of diastolic function and, in particular, the importance of asymptomatic left ventricular diastolic dysfunction (ALVDD). In a cross-sectional study, approximately 28% of a general adult community with a mean age of 68 years had some degree of diastolic dysfunction (50). Studies of ALVDD have used various definitions for diastolic dysfunction, with varying sensitivities for prediction of HF (**Table 4**). Two-year probabilities of incident HF vary from 1.9% to 5.7% depending on the definition of HF and the degree of ALVDD (21). Moderate and severe ALVDD with pseudo-normal and restrictive diastolic filling patterns, respectively, confer the highest risk of HF (51,52). There are as yet no reports of the prediction of HF by the current guideline-based algorithm for assessing diastolic function (4).

Although we currently have no therapies that improve the prognosis of HFpEF, several strategies have been shown to improve diastolic function and may therefore prevent HFpEF. Hypertension is an important risk factor for diastolic dysfunction and subsequent HF. Although trials correlating improvement in diastolic function with clinical outcome are lacking, trials of blood pressure-lowering therapies have shown significant reductions in all-cause and cardiovascular mortality, nonfatal myocardial infarction, stroke, and HF (53–56),

TABLE 2 Threshold Values That Define Abnormal Echocardiographic Imaging Parameters

	ASE/EACVI Guidelines		Population Studies	
	Women	Men	Women	Men
Parameters of systolic function				
LVEF, % (Simpson's biplane)	<54 (20)	<52 (20)	<57.4% (43)	<59.0 (43)
$FS_{endocardium}$ (M mode)	<0.27 (93)	<0.25 (93)		
FS (2-dimensional)	<0.18 (93)			
MAPSE, mm			<11 (94)	<13 (94)
S′ septal, cm/s			<6.0* (95)	
S′ lateral, cm/s			<6.7* (95)	
S′ average, cm/s			<8.1† (96)	
GLS, %‡	>-18		>-15.2 (43) >-18 (44)	>-14.7 (43) >-18 (44)
Parameters of diastolic function				
E/A	≤0.8 or ≥2 (4)		≤0.75 or >1.5 (48,50,52)	
DT, ms			<140 (50)	
Septal e′, cm/s	<7 (4)		<4.1 (43)	<4.3 (43)
Lateral e′, cm/s	<10 (4)			
Septal E/e′	>15 (4)		>17.4 (43)	>14.8 (43)
Lateral E/e′	>13 (4)			
Average E/e′	>14 (4)		>13 (44) >15 (96) ≥10 (50)	
TRV_{max}, m/s	>2.8 (4)			
LAVI, ml/m^2§	>34 (4,20)		>32.4 (43)	>34.2 (43)
Structural parameters				
LVEDD, mm	>52.2 (20)	>58.4 (20)		
LVESD, mm	>34.8 (20)	>39.8 (20)		
LVEDVI, ml/m^2§	>61 (20)	>74 (20)	>51.9 (43)	>60.2 (43)
LVESVI, ml/m^2§	>24 (20)	>31 (20)		
LVMI, g/m^2 (2-dimensional)§	>88 (20)	>102 (20)		
LVMI, g/m^2 (linear method)§	>95 (20)	>115 (20)		
LVMI, g/$m^{2.7}$ (linear method)‖	>44 (93)	>48 (93)	>41.5 (43)	>45 (43)

*Age 35 to 75 years. †Age >60 years. ‡Vendor specific. §Indexed to body surface area. ‖Indexed to height.

ASE/EACVI = American Society of Echocardiography/European Association of Cardiovascular Imaging; DT = mitral E wave deceleration time; E/A = mitral E/A ratio; FS = fractional shortening; GLS = global longitudinal strain; Lateral e′ = lateral mitral annular early diastolic velocity; LAVI = left atrial volume index; LVEDD = left ventricular end-diastolic dimension; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic dimension; LVESVI = left ventricular end-systolic volume index; LVMI = left ventricular mass index; MAPSE = mitral annular plane systolic excursion; S′ average = average mitral annular systolic velocity; S′ lateral = lateral mitral annular systolic velocity; S′ septal = septal mitral annular systolic velocity; Septal e′ = septal mitral annular early diastolic velocity; TRV_{max} = peak tricuspid regurgitant velocity.

TABLE 3 Prediction of Symptomatic HF According to LV Systolic Dysfunction

First Author (Ref. #)	Study/ Country	Study Population	Age (yrs)	Follow-Up (Mean Years)	Imaging Modality	Definition of LV Systolic Dysfunction	Definition of HF	N	HF Cases	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Gottdiener et al. (22)	CHS/U.S.	General	65–100	5.2	TTE	LVEF <45%*	Physician	4,932	553	9	97	27	90
Aurigemma et al. (48)	CHS/U.S.	General†	65–100	5.2	TTE	$FS_{endocardium}$ <25%	Physician	2,671	170	13	95	15	94
	CHS/U.S.	General†	65–100	5.2	TTE	$FS_{midwall}$ <14%	Physician	2,671	170	11	94	11	94
Wang et al. (24)	FHS/U.S.	General	40–95	5	TTE	LVEF ≤50%	FHS criteria	4,257	175	19	98	26	97
Verdecchia et al. (25)	PIUMA/Italy	Essential hypertension‡		6	TTE	LVEF ≤50%	HF hospitalization	2,384	24	33	97	9	99
Pandhi et al. (23)	CHS/U.S.	General	≥65	11.7 (median)	TTE	LVEF <55%	Record review	5,386	1,559	17	96	66	74
Yeboah et al. (26)	MESA/U.S.	General§	45–84	7.5	MRI	LVEF <50%	Physician	5,004	112	14	99	19	98
Yang et al. (44)	Australia	Stage A/B HF‖	≥65	1.2	TTE	GLS >-18	Physician	410	51	49	70	19	91

*Qualitative assessment of LVEF. †Participants with myocardial infarction, angina, heart failure (HF), or atrial fibrillation were excluded. ‡Participants without secondary causes of hypertension or previous cardiovascular disease. §Participants without known cardiovascular disease at baseline. ‖Patients with known coronary disease, more than moderate valve disease, LVEF <40%, or atrial fibrillation were excluded.

CHS = Cardiovascular Health Study; FHS = Framingham Heart Study; FS = fractional shortening; MESA = Multi-Ethnic Study of Atherosclerosis; MRI = magnetic resonance imaging; NPV = negative predictive value; PIUMA = Progetto Ipertensione Umbria Monitoaggio Ambulatoriale Study; PPV = positive predictive value; TTE = transthoracic echocardiography; other abbreviations as in Tables 1 and 2.

and it is likely that a proportion of HF prevented was HFpEF. Antihypertensive treatment leads to a small but significant improvement in e′, LV wall thickness, and regression in left ventricular mass (55,57), and an increase in the proportion of subjects with normal diastolic function, while decreasing the proportion with grade I and II diastolic dysfunction (58). However, some contrary data have been reported in which no improvement in diastolic dysfunction (using E/e′ as a marker) was found despite LVH regression with antihypertensive therapy (59). Patients with hypertension with diastolic dysfunction have increased myocardial fibrosis (19), and lisinopril therapy in this group induced regression of myocardial fibrosis in association with improvements in diastolic function.

Caloric restriction for 12 months was also shown to improve diastolic function in nonobese individuals with diastolic dysfunction (60), and long-term caloric restriction for 3 to 15 years ameliorated the age-associated decline in diastolic function (61). In addition, weight reduction in obesity improved diastolic dysfunction (46,62) and reduced the incidence of HF (63).

TABLE 4 Prediction of Symptomatic HF According to LV Diastolic Dysfunction

First Author (Ref. #)	Study/ Country	Study Population	Age (yrs)	Follow-Up (Mean Years)	Imaging Modality	Definition of Diastolic Dysfunction	Definition of HF	N	HF Cases	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Aurigemma et al. (48)	CHS/U.S.	General*	65–100	5.2	TTE	E/A >1.5 or <0.7	Physician	2,671	170	40	83	14	95
Ren et al. (52)	Heart & Soul/U.S.	CHD†	65 (mean)	3	TTE	E/A ≤0.75 & systolic dominant PV flow	HF hospitalization	621	25	48	74	7	97
						E/A 0.75-1.5 & diastolic dominant PV flow or E/A >1.5 & diastolic dominant PV flow	HF hospitalization	693	33	24	90	11	96
Kane et al. (51)	Olmsted/ U.S.	General	>45	4	TTE	Diastolic grade‡	FHS criteria	1,295	6	83	76	1.6	99.9
Yang et al. (44)	Australia	Stage A/B HF§	≥65	1.2	TTE	E/e′ >13	Physician	410	51	24	89	24	89
						LAVI >34 ml/m^2	Physician	410	51	51	71	20	91

*Participants with myocardial infarction, angina, HF, or atrial fibrillation were excluded. †Participants with LVEF <50%, heart rate >100 beats/min, or severe mitral disease were excluded. ‡Mild: E/A <0.75; moderate: E/A 0.75 to 1.5 and deceleration time >140 ms plus 2 other Doppler indices of elevated end-diastolic filling pressure; severe: E/A >1.5 and deceleration time <140 ms, plus Doppler indices of elevated end-diastolic filling pressure. §Patients with known coronary disease, >moderate valve disease, LVEF <40%, or atrial fibrillation were excluded.

CHD = coronary heart disease; E/A = mitral early to late diastolic velocity ratio; other abbreviations as in Tables 2 and 3.

TABLE 5 Prediction of Symptomatic HF According to LV Structural Abnormality

First Author (Ref. #)	Study/ Country	Study Population	Age (yrs)	Follow-Up (Mean Years)	Imaging Modality	Definition of Left Ventricular Structural Abnormality	Definition of HF	N	HF Cases	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Aurigemma et al. (48)	CHS/U.S.	General*	65–100	5.2	TTE	LVMI† >95% of reference range	Physician	2,671	170	24	92	18	95
Yang et al. (44)	Australia	Stage A/B HF‡	≥65	1.2	TTE	LVMI >95 g/m^2 (women), >115 g/m^2 (men)	Physician	410	51	20	87	18	88
Yeboah et al. (97)	MESA/U.S.	General‡	45–84	9.4	MRI	LVEDD >52 mm	Physician	4,974	177	21	90	7	97

*Participants with myocardial infarction, angina, HF, or atrial fibrillation were excluded. †Indexed to height. ‡Patients with known coronary disease, >moderate valve disease, LVEF <40%, or atrial fibrillation were excluded.

Abbreviations as in Tables 1, 2, and 3.

STRUCTURAL PARAMETERS THAT PREDICT PROGRESSION OF STAGE A/B HF

LV CHAMBER DIMENSION. Left ventricular end-diastolic dimension (LVEDD) predicts HF (Table 5). The Framingham Heart Study showed that each SD increase in LV end-diastolic and end-systolic dimensions increased the risk of incident HF by 47% and 43%, respectively (64), and individuals in the Cardiovascular Health Study with LVEDD in the highest quartile had a 2-fold higher risk of HF than individuals with LVEDD in the lowest quartile (65). Furthermore, angiotensin-converting enzyme inhibitors reversed this dilatation (66,67), a key process of reverse remodeling. There would seem to be a strong argument for including LV chamber dimension as a Stage B abnormality.

LEFT VENTRICULAR HYPERTROPHY. LVH and increased LV mass predict risk for incident HF (Table 5) (25,65). This relationship holds true regardless of whether LVH is adjusted for height or for body surface area (68). The patterns of LVH are also predictive, with eccentric hypertrophy associated with the development of HFrEF and concentric hypertrophy associated with the development of HFpEF (69). As previously mentioned, antihypertensive therapy reduces LV mass (55,57) and the risk of future cardiac events, including HF (53–56), and LVH should therefore be viewed as a modifiable risk factor in the prevention of incident HF.

VALVULAR HEART DISEASE. Valvular heart disease can lead to HF, and guidelines describe "at risk" and "progressive" categories of asymptomatic individuals with valvular heart disease based on resting TTE parameters who require their own monitoring pathways (70). Stress echocardiography can assist the assessment of asymptomatic severe valvular disease when resting parameters and symptoms are discordant. In

TABLE 6 Prediction of Symptomatic HF According to Any of a Composite of Imaging Parameters for LVD

First Author (Ref. #)	Study/ Country	Study Population	Age (yrs)	Follow-Up (Mean Years)	Imaging	Definition of LVD	Definition of HF	N	Cases	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Yang et al. (44)	Australia	Stage A/B HF*	≥65	1.2	TTE	LVM (>95 g/m^2 in women, >115 g/m^2 in men) *OR* GLS >–18 *OR* E/e′ >13 *OR* LA enlargement (LAVI >34 ml/m^2)	Physician	410	51	82	41	17	94
Shah et al. (43)	ARIC/U.S.	Stage A/B HF	67–91	1.7 (median)	TTE	Structural, systolic, or diastolic abnormality†	Death/HF hospitalization	4,693	149	72	48	4	98

*Patients with known coronary disease, >moderate valve disease, LVEF <40%, or atrial fibrillation were excluded. †Structural abnormality defined as per Table 2.

ARIC = Atherosclerosis Risk in Communities; LA = left atrial; LVD = left ventricular dysfunction; other abbreviations as in Tables 2 and 3.

aortic stenosis, an exercise-induced increase in mean aortic pressure gradient >20 mm Hg predicted increased risk for cardiovascular death and need for intervention driven by HF symptoms (71); lack of contractile reserve with exercise or dobutamine infusion were markers of poor prognosis (72). An absence of contractile reserve assessed by GLS during exercise stress echocardiography was associated with higher rates of cardiovascular mortality, need for mitral valve surgery, and HF hospitalizations in asymptomatic moderate to severe mitral regurgitation (73). Less information is available, however, regarding the prognostic significance of poor contractile reserve with exercise stress echocardiography in asymptomatic severe aortic regurgitation (72).

PREDICTION OF HF BY MULTIPLE IMAGING PARAMETERS

Individuals with Stage A/B HF may exhibit a range of abnormal cardiac imaging parameters, and no single parameter identifies all individuals at increased risk of symptomatic HF (**Tables 2 to 4**). Sensitivities for prediction of symptomatic HF by using systolic and structural parameters were <50%, with GLS the best predictor with a sensitivity of 49%. Diastolic parameters predicted symptomatic HF with higher sensitivities. However, the 83% sensitivity for prediction of symptomatic HF according to diastolic grade reported by Kane et al. (51) was based on only 6 of 12 patients who developed HF and had gradable diastolic function. The highest sensitivity for prediction of symptomatic HF was provided by a composite of TTE imaging parameters (**Table 5**), consistent with the multiple overlapping mechanisms of HF pathogenesis (**Table 1**).

PRE-SCREENING STRATEGIES TO SELECT INDIVIDUALS FOR NONINVASIVE IMAGING

Most information for the prediction of HF according to noninvasive imaging was obtained for individuals ≥65 years of age (**Tables 3 to 6**), which is the age group at highest risk and for which the prevalence of any echocardiographic abnormality was 53% to 59% of Stage A/B HF community participants (43,44). We currently lack data for the use of cardiac imaging to predict HF risk in younger individuals who have a much lower incidence of HF and much lower prevalence of abnormal imaging parameters, and for which a low-cost pre-screening strategy may be required to select who to image. Possible pre-screening strategies include the measurement of B-type natriuretic peptides (BNP) levels and the use of handheld echocardiography (HHE).

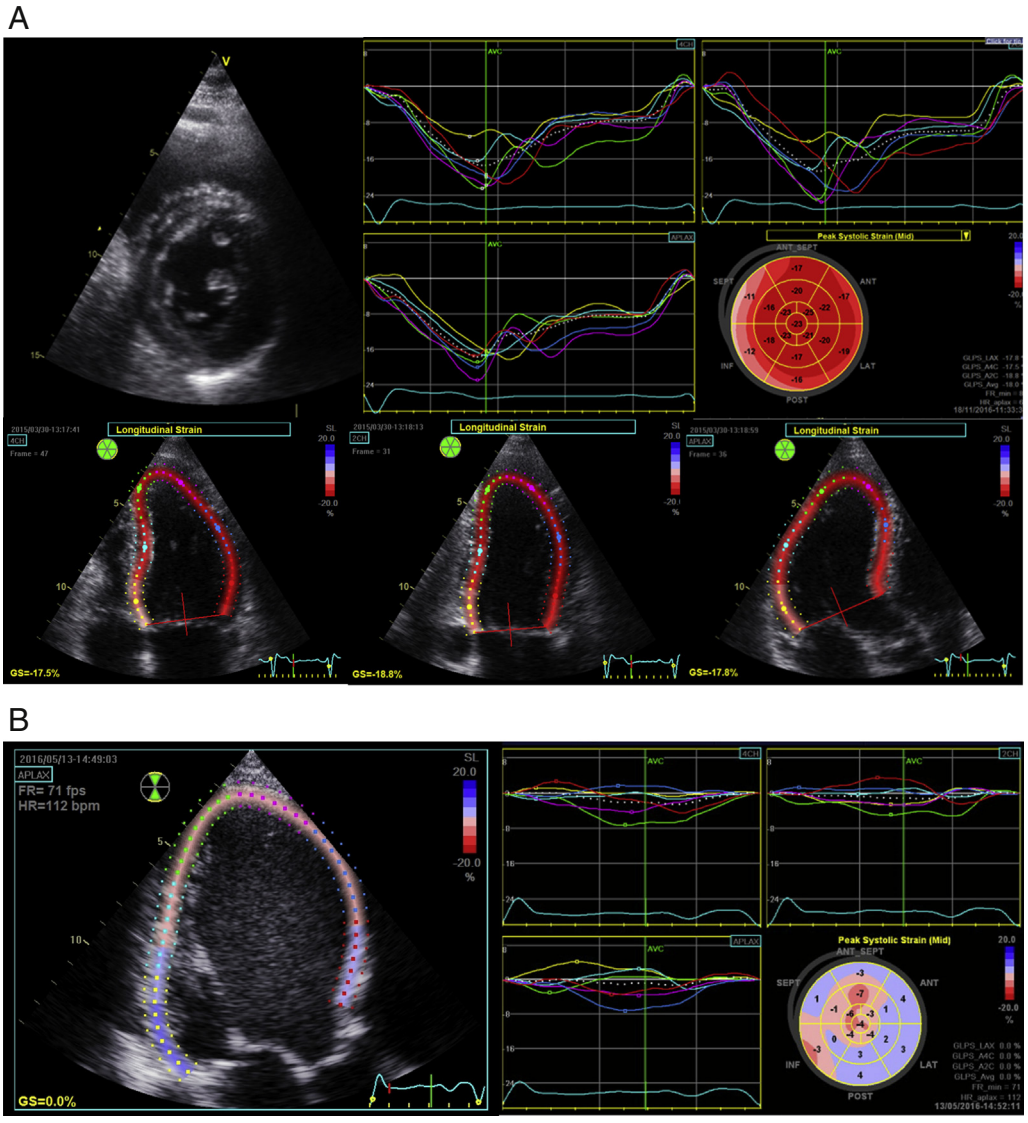
Prediction of LVD according to BNP levels in asymptomatic populations depends on both the study population and the definition of LVD (**Table 7**). Higher sensitivities are achieved for ALVSD (LVEF <50%) and moderate to severe ALVDD, separately and in combination, than for mild ALVDD (74). Moreover, lower sensitivities are achieved for individuals in the general population than for "high-risk" individuals with ≥2 cardiovascular risk factors (75). Further study is required to define how best to use BNP levels for predicting HF progression in Stage A/B HF subjects before it can be considered for pre-screening purposes.

HHE offers another pre-screening option, and its technology continues to evolve. Image analysis on HHE achieves reasonable accuracy compared with TTE for measurements of LV size, thickness, wall motion, and systolic function; however, grading of valvular lesions is more variable due to the lack of spectral Doppler imaging (76–80). Interobserver variability is also higher when less-experienced operators are performing and interpreting scans (81). Pre-screening with HHE has shown significant cost savings when used as a gatekeeper procedure compared with performing TTE in all subjects referred, without adverse impact on long-term outcomes (77,82). However, studies have not yet been performed addressing the use of either individual or composite HHE-measured parameters in predicting HF in Stage A/B HF. Importantly, based on the current data, it seems that diastolic parameters and GLS are likely to be crucial to improving the sensitivity of predicting HF progression in Stage A/B HF individuals, and current HHE technology does not allow the assessment of either, which may limit its application.

OTHER CARDIAC IMAGING MODALITIES

TTE has many advantages for the noninvasive cardiac imaging assessment of risk of progression of Stage A/B HF; its key advantage is that it can measure all of the parameters that have been shown to predict progression. Despite its operator dependency, requirement for geometric assumptions, and inter-reader variability, TTE's portability and availability place it at the forefront of any HF prevention strategy. Other imaging modalities have limitations for use in screening: cardiac magnetic resonance (CMR) is not as widely available and is more expensive, coronary computed tomography angiography requires radiation, and both are less well studied in the Stage A/B HF population. However, these early studies are promising, and further investigation into

FIGURE 4 Echocardiographic Assessment of Strain



(A) Concentric hypertrophy with preserved left ventricular ejection fraction (56%) but mildly impaired global longitudinal strain (GLS) –18%. **(B)** Severely impaired GLS 0% in idiopathic dilated cardiomyopathy.

how best to use the complementary information they provide in a Stage A/B HF cohort will hopefully be forthcoming.

CMR IMAGING. A major advantage of CMR over TTE is the ability for tissue characterization. Late gadolinium enhancement was initially used to detect focal replacement myocardial fibrosis. The presence of late gadolinium enhancement in asymptomatic individuals with ischemic heart disease was associated with increased risk of future cardiovascular events (83,84). Diffuse myocardial fibrosis can be detected with the use of more recently developed T_1-mapping techniques, and a shortened post-contrast T_1 time is associated with combined HF hospitalizations and cardiovascular mortality in HFpEF (85). There is also early evidence of an association between shortened post-contrast T_1 time and adverse prognosis in other cardiomyopathies and the possibility of detecting subclinical disease with this method (86). Moreover, cardiac iron deposition, detected with a shortened T_2* relaxation

TABLE 7 BNPs for Detecting Asymptomatic LVD

First Author (Ref. #)	N	Population	Age (yrs)	BNP	Definition of LVD	Cutoff (pg/ml)	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
Betti et al. (98)	1,012	Primary care	36–88	NT-proBNP	Moderate–severe LVDD	125	80	98	99.8	24
					LVEF ≤50% and moderate–severe LVDD	125	98	80	99.8	29
Macabasco-O'Connell et al. (99)	53	Ambulatory care	≥30	BNP	LVEF <45% or any LVDD	50	88	67	-	-
Luers et al. (74)	542	Primary care	63 ± 11 (mean)	Log NT-proBNP	LVEF <50%	5.94	65	88	98	19
					Severe LVDD	5.67	67	83	99	10
					LVEF <50% or severe LVDD	5.94	63	89	97	30
Costello-Boerrigter et al. (100)	1,869	General	45–96	NT-proBNP	LVEF ≤40%	228	87	86	-	-
					LVEF ≤50%	129	74	74	-	-
					Moderate–severe DD and LVEF ≤40%	124	73.4	73.4	-	-
					Moderate–severe DD and LVEF ≤50%	111	70.6	70.6	-	-
				BNP	LVEF ≤40%	66	81	81	-	-
					LVEF ≤50%	40	69	69	-	-
					Moderate–severe DD and LVEF ≤40%	44	72.7	72.4	-	-
					Moderate–severe DD and LVEF ≤50%	39	69.6	69.6	-	-
Mureddu et al. (75)	1,452	General	65–84	NT-proBNP	LVSD <50%	278	64	89	8	99
					Moderate–severe DD		35	90	19	96
					Stage B HF		14	9	79	37
		High-risk (≥2 cardiovascular risk factors)			LVEF <50%		100	81	7	100
					Moderate–severe DD		57	83	24	95
					Stage B HF		23	89	87	25
Vasan et al. (101)	3,177	General	58 ± 10 (mean)	BNP	Increase LV mass (men)	46	27	95	92	38
					Increase LV mass (women)	47	13	95	91	22
					Any LVSD* (men)	45	29	95	93	38
					Any LVSD* (women)	50	14	95	98	7
					Moderate–severe LVSD* (men)	51	33	95	97	22
					Moderate–severe LVSD* (women)	50	40	95	96	5

*Left ventricular systolic dysfunction (LVSD) using fractional shortening <29%.

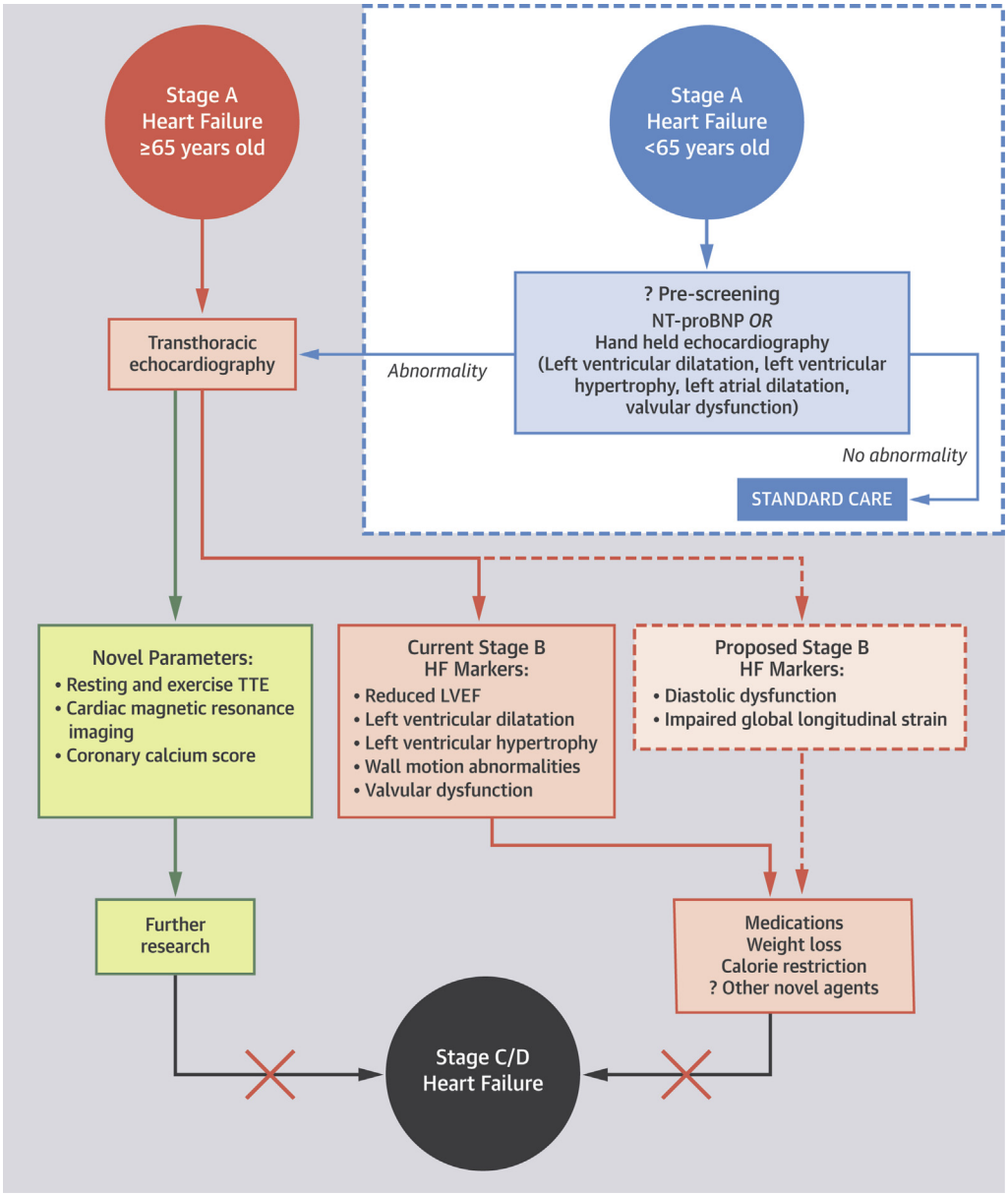
BNP = B-type natriuretic peptide; DD = diastolic dysfunction; LVDD = left ventricular diastolic dysfunction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; other abbreviations in Tables 1, 2, 3, and 6.

time, predicts cardiomyopathy and HF in patients with transfusion-dependent anemias (87).

CORONARY ARTERY CALCIUM. Coronary computed tomography angiography allows the evaluation of coronary artery calcium (CAC). The Rotterdam Study (88) reported that a CAC score >400 was associated with an approximately 4-fold increased risk of incident HF in asymptomatic adults without known HF. Compared with a CAC score of 0 to 9, a CAC score >400 was associated with almost double the risk of diastolic dysfunction in patients >55 years of age suspected of having coronary artery disease (89). Although CAC scores are predictive of coronary events, their use in predicting HF and LVD is not established and requires investigation.

STRESS ECHOCARDIOGRAPHY. Despite continual revision of the algorithms for the diagnosis of HFpEF, resting TTE assessment often produced an indeterminate diastolic assessment and failed to identify diastolic dysfunction in >60% of individuals with chronic dyspnea who were subsequently confirmed to have HFpEF via invasive assessment (90). However, exercise E/e′ >14 confirmed a diagnosis of HFpEF in individuals who could not be classified on the basis of

CENTRAL ILLUSTRATION Strategy for the Application of Imaging to Predict HF



Gong, F.F. et al. J Am Coll Cardiol Img. 2017;10(12):1504–19.

Individuals with Stage A heart failure (HF) ≥65 years of age undergo transthoracic echocardiography (TTE) to detect current markers of Stage B HF **(orange)**. These abnormalities may be amenable to reversal or stabilization with intervention, reducing future HF events. Other abnormal parameters also confer HF risk **(orange dashed)** and should be considered for inclusion in Stage B HF; further research is required to evaluate the effect of their treatment on HF outcomes. Individuals with Stage A HF <65 years of age have a lower prevalence of cardiac abnormalities, and the optimal approach to screening is unclear. Pre-screening with biomarkers or handheld echocardiography before formal TTE may reduce costs and increase the yield of subsequent abnormalities detected **(blue)**, but it currently lacks robust outcomes data. Other cardiac imaging parameters may indicate future HF risk and deserve ongoing research; these include right ventricular parameters, left and right atrial size, other Doppler and tissue Doppler parameters on resting and exercise stress TTE, calcium score on coronary computed tomography angiography, and tissue characterization on cardiac magnetic resonance **(yellow)**. LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

TABLE 8 Future Directions for HF Risk Prediction in Stage A/B HF

Consider broadening the definition of Stage B HF • Consider the addition of proposed markers of diastolic dysfunction and GLS
Confirm utility of TTE screening in individuals ≥65 yrs of age • Using current Stage B HF markers • Using proposed Stage B HF markers • Assess impact on clinical outcomes (including HF and other cardiovascular disease) with intervention • Assess cost-effectiveness
Further research in Stage A/B HF individuals <65 yrs of age • Stage A individuals: assess the ability of BNP, NT-proBNP, and HHE as pre-screening strategies to detect Stage B HF markers, and impact on cost-effectiveness and clinical outcomes • Investigate the performance of using a combination of TTE parameters to identify risk for progression of HF (as already performed for individuals ≥65 yrs of age) and its impact on cost-effectiveness and outcomes • Consider the frequency of repeat screening if no abnormalities detected on index assessment
Future intervention trials • Assess the impact of therapy (e.g., antihypertensive agents, caloric restriction, weight loss) on the evolution of cardiac structural and functional changes • Assess the impact of therapy on incidence of HF and other cardiovascular outcomes
Investigate the role of other cardiac imaging modalities • Cardiac MRI • Coronary CTA • Nuclear imaging

CTA = computed tomography angiography; HHE = handheld echocardiography; other abbreviations as in Tables 1, 2, 3, and 7.

resting criteria; the addition of exercise E/e′ to resting diastolic parameters improved the sensitivity for HFpEF diagnosis from 34% to 90%. Moreover, exercise E/e′ independently predicted combined coronary ischemia and HF events (91). Exercise stress echocardiography may similarly assist in the demonstration of diastolic dysfunction and the identification of risk of symptomatic HF in Stage A/B HF subjects. Although individuals with chronic dyspnea are not asymptomatic, their lack of diagnostic diastolic abnormalities on resting TTE still only affords them a classification of Stage A HF and may significantly underrepresent their HF risk. The use of stress echocardiography in risk-stratifying Stage A/B HF subjects deserves further investigation.

APPLICATION OF IMAGING TO THE PREDICTION OF HF

The objective of performing noninvasive cardiac imaging in subjects with Stage A/B HF is to identify those individuals with asymptomatic LV dysfunction that predicts HF progression and who might benefit from therapy to prevent HF. The SOLVD (27) and SAVE (28) trials showed that treatment of individuals with ALVSD prevents HFrEF. Moreover, antihypertensive therapies, weight reduction, and caloric restriction may prevent HFpEF by reducing LVH and improving parameters of strain and diastolic dysfunction (46,55,57,58,62).

An ideal strategy to predict progression of Stage A/B HF would separate those destined to progress from those not at risk. However, the risk of progression increases continuously with age. Available data provide an estimate of risk based on studies with a limited period of observation, and individuals who do not progress during the observation period remain at risk. Thus, the main objective should be a strategy with high sensitivity that identifies most individuals at risk, as predicted by current studies, and hopefully includes most individuals at risk of later development of symptomatic HF.

Available evidence suggests that differing strategies may be required for individuals ≥65 years and <65 years of age (**Central Illustration**). For Stage A/B HF individuals ≥65 years of age, the high prevalence of any of a composite of structural or functional abnormalities and their sensitivity for predicting symptomatic HF (**Table 6**) suggests that performing a TTE in everyone ≥65 years of age is a possible strategy. Indeed, 1 recent study has gone further and attempted to address the efficacy of such a strategy on clinical outcomes, providing medical therapy to elderly individuals with Stage A HF with a composite of impaired GLS and/or diastolic dysfunction (92). Although low medication adherence likely affected the negative study outcomes, it is encouraging to see these studies finally being attempted. Further research is required to define the best strategy for identification of the risk of progression in individuals <65 years of age with Stage A/B HF. A pre-screening strategy may allow more cost-effective detection of younger individuals at highest risk according to TTE. Further research is required to define the utility of BNP measurement and HHE as part of a pre-screening strategy.

Any strategy for the prediction of HF progression in subjects with Stage A/B HF will require an analysis of cost-effectiveness. In conducting such an analysis, it will be important to consider that any strategy to identify Stage A/B HF subjects at increased HF risk and to institute preventative therapy will affect the incidence of not only symptomatic HF but also ischemic heart disease, cerebrovascular disease, peripheral vascular disease, and complications of diabetes and obesity.

FUTURE DIRECTIONS

Many abnormal imaging parameters predict progression of Stage A/B HF. Importantly, diastolic dysfunction and strain are not included in the

definition of Stage B HF despite the prediction of incident HF and mortality by these parameters (**Tables 3 and 4**). As emphasized by current guidelines (20) and investigators (43), it is important that age-specific thresholds for the identification of abnormal imaging parameters and their utility in the prediction of symptomatic HF be defined.

Although most of the available data are based on 2-dimensional TTE, the role of 3-dimensional TTE and other cardiac imaging methods in the Stage A/B HF cohort should not be neglected. CMR offers more accurate assessment of cardiac structure and function. However, given its limited access and greater cost, how much CMR improves our screening strategies above and beyond TTE is unknown. Insufficient data are available to support the widespread use of CMR for tissue characterization in this preclinical group. The place of coronary computed tomography angiography for HF risk assessment also continues to evolve as radiation doses decline.

Future research should build on the current strong evidence base (**Table 8**). Individuals with Stage A/B HF <65 years of age will likely require pre-screening strategies before TTE, whereas use of TTE in all Stage A/B HF individuals ≥65 years of age may be an effective approach. These strategies will require analysis of cost-effectiveness and efficacy. Future outcome studies will better define the role of cardiac imaging in the prevention of progression in preclinical Stage A/B HF subjects. The aim should be to produce a reliable and widely applicable method for targeted population-based screening, in the hope that risk factor modification and appropriate medical therapy in the highest risk group can curtail their progression to symptomatic HF.

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KEY WORDS cardiac biomarkers, cardiac imaging, heart failure, heart failure prevention, risk prediction