JACC: HEART FAILURE
VOL. 4, NO. 4, 2016

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jchf.2015.09.015

MINI-FOCUS ISSUE: RISK PREDICTION AND PROGNOSIS IN HEART FAILURE

Assessing the Risk of Progression From Asymptomatic Left Ventricular Dysfunction to Overt Heart Failure

A Systematic Overview and Meta-Analysis

Justin B. Echouffo-Tcheugui, MD, PhD,[a,b] Sebhat Erqou, MD, PhD,[c] Javed Butler, MD, MPH,[d] Clyde W. Yancy, MD, MSc,[e] Gregg C. Fonarow, MD[f]

ABSTRACT

OBJECTIVES This study sought to provide estimates of the risk of progression to overt heart failure (HF) from systolic or diastolic asymptomatic left ventricular dysfunction through a systematic review and meta-analysis.

BACKGROUND Precise population-based estimates on the progression from asymptomatic left ventricular dysfunction (or stage B HF) to clinical HF (stage C HF) remain limited, despite its prognostic and clinical implications. Pre-emptive intervention with neurohormonal modulation may attenuate disease progression.

METHODS MEDLINE and EMBASE were systematically searched (until March 2015). Cohort studies reporting on the progression from asymptomatic left ventricular systolic dysfunction (ALVSD) or asymptomatic left ventricular diastolic dysfunction (ALVDD) to overt HF were included. Effect estimates (prevalence, incidence, and relative risk) were pooled using a random-effects model meta-analysis, separately for systolic and diastolic dysfunction, with heterogeneity assessed with the I^2 statistic.

RESULTS Thirteen reports based on 11 distinct studies of progression of ALVSD were included in the meta-analysis assessing a total of 25,369 participants followed for 7.9 years on average. The absolute risks of progression to HF were 8.4 per 100 person-years (95% confidence interval [CI]: 4.0 to 12.8 per 100 person-years) for those with ALVSD, 2.8 per 100 person-years (95% CI: 1.9 to 3.7 per 100 person-years) for those with ALVDD, and 1.04 per 100 person-years (95% CI: 0.0 to 2.2 per 100 person-years) without any ventricular dysfunction evident. The combined maximally adjusted relative risk of HF for ALVSD was 4.6 (95% CI: 2.2 to 9.8), and that of ALVDD was 1.7 (95% CI: 1.3 to 2.2).

CONCLUSIONS ALVSD and ALVDD are each associated with a substantial risk for incident HF indicating an imperative to develop effective intervention at these stages. (J Am Coll Cardiol HF 2016;4:237–48) © 2016 by the American College of Cardiology Foundation.

From the [a]Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; [b]Rollins School of Public Health, Emory University, Atlanta, Georgia; [c]Cardiology Division, Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; [d]Cardiology Division, Department of Medicine, Stony Brook University, Stony Brook, New York; [e]Cardiology Division, Department of Medicine, Northwestern Feinberg School of Medicine, Chicago, Illinois; and the [f]Ahmanson-UCLA Cardiomyopathy Center, Division of Cardiology, Department of Medicine, Ronald Reagan-UCLA Medical Center, Los Angeles, California. Dr. Fonarow has served as a consultant for Novartis (significant) and for Amgen, Bayer, Gambro, Medtronic, and Janssen (modest); holds the Eliot Corday Chair of Cardiovascular Medicine at UCLA; and is supported by the Ahmanson Foundation (Los Angeles, California). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Echouffo-Tchegui and Erqou contributed equally to this work.

Manuscript received May 12, 2015; revised manuscript received August 25, 2015, accepted September 4, 2015.

ABBREVIATIONS AND ACRONYMS

ALVD = asymptomatic left ventricular dysfunction

ALVDD = asymptomatic left ventricular diastolic dysfunction

ALVSD = asymptomatic left ventricular systolic dysfunction

CI = confidence interval

EF = ejection fraction

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

LVD = left ventricular dysfunction

LVDD = left ventricular diastolic dysfunction

LVSD = left ventricular systolic dysfunction

MI = myocardial infarction

RR = relative risk

Heart failure (HF) is increasingly common, affecting 5.7 million American adults, a number projected to increase by 46% by 2030 (1). HF imposes a substantial morbidity, mortality, suffering, and financial burden to patients and the society globally. To favorably affect these adverse trends, more efficient primary and secondary preventative interventions are necessary. Screening for HF is a consideration; however, any approach to such an undertaking must be dictated by the natural history of the condition. Indeed, the American College of Cardiology and American Heart Association HF Guideline Writing Committee has defined HF as a progressive disorder along a continuum with asymptomatic (stages A and B) and symptomatic (stages C or D) stages (2). Failure to adequately consider assessing and implementing effective interventions at the pre-symptomatic stages of risk progression may account for a large part the continuing burden of incident cases of symptomatic HF. Stage B HF (3,4) includes patients with structural heart disease but no current or prior symptoms of HF and at elevated risk for significant morbidity, mortality, and subsequent development of symptomatic HF (4). Indeed, the absolute number of people with left ventricular dysfunction (LVD) in stage B has been estimated to be 3 to 4 × greater than those at stages C and D combined (3,4).

SEE PAGE 249

The structural changes comprising stage B HF are relatively broad, including asymptomatic left ventricular systolic dysfunction (ALVSD) or asymptomatic left ventricular diastolic dysfunction (ALVDD) (2). The exact duration of the lead time from ALVSD and/or ALVDD to symptomatic stage C HF largely remains unknown. Understanding the speed of this transition is of clinical and public health importance, especially in young adults with a lifetime risk of HF as high as 20% (5) who may most benefit from an early intervention. Population-based studies have reported on the risk of progression to overt HF in people with asymptomatic left ventricular dysfunction (ALVD). These studies included a variety of populations, assessed ALVD and HF in different ways, and mainly focused on ALVSD, with entities like ALVDD remaining poorly understood especially in terms of their prognostic significance. We therefore conducted a systematic review of the current published data and provided an estimate of the risk of progression to symptomatic stage C HF among individuals with ALVD, be it systolic or diastolic in nature.

METHODS

DATA SOURCES AND SEARCHES. We searched PubMed and EMBASE from inception until March 31, 2015, using a combination of terms related to ventricular dysfunction and HF (Online Appendix A) without any restriction. Two evaluators (J.B.E.-T. and S.E.) independently identified and screened papers for inclusion (**Figure 1**). Reference lists of identified studies were manually scanned and cited references were screened through the ISI Web of Knowledge database for additional eligible studies.

STUDY SELECTION. Papers that reported data on individuals with ALVD were sought from either epidemiologic cohort studies or control groups of randomized controlled trials. Studies were included if they: 1) followed ambulatory participants for at least 1 year; 2) reported data from people with ALVD defined by imaging (echocardiography or magnetic resonance imaging); and 3) reported on the future progression to clinically overt HF. Studies were excluded if they assembled the initial cohort from acutely ill individuals (e.g., those with myocardial infarction [MI]) or focused on specific populations, such as those with valvular heart disease, or on pre- or post-operative populations.

To avoid double counting of a cohort, we tried to use 1 set of results when multiple publications were available for the same cohort. For the meta-analysis, the priority was given to the study with the longest follow-up with the largest number of incident HF cases. In some instances we used more than 1 report from the same cohort, because these may have reported on different types of structural disease (left ventricular diastolic dysfunction [LVDD] vs. left ventricular systolic dysfunction [LVSD]), and thus, a single report would not always contain the totality of the information needed. For example, 2 reports on LVD and risk of HF were based on the Framingham Study data, with one focusing on LVSD (6) and the other examining both forms of LVD (7). In this case, we used the report with a large number of HF cases for the association analyses (7), but we also retained the second report because it provided information on incidence rate of HF (6). Similarly, there were 2 reports for the Cardiovascular Health Study (8,9), one addressing both LVSD and LVDD and the other only LVDD with a larger number of HF events (9).

We retained both reports, using the larger study for our LVSD analyses and the smaller one for our LVDD analyses.

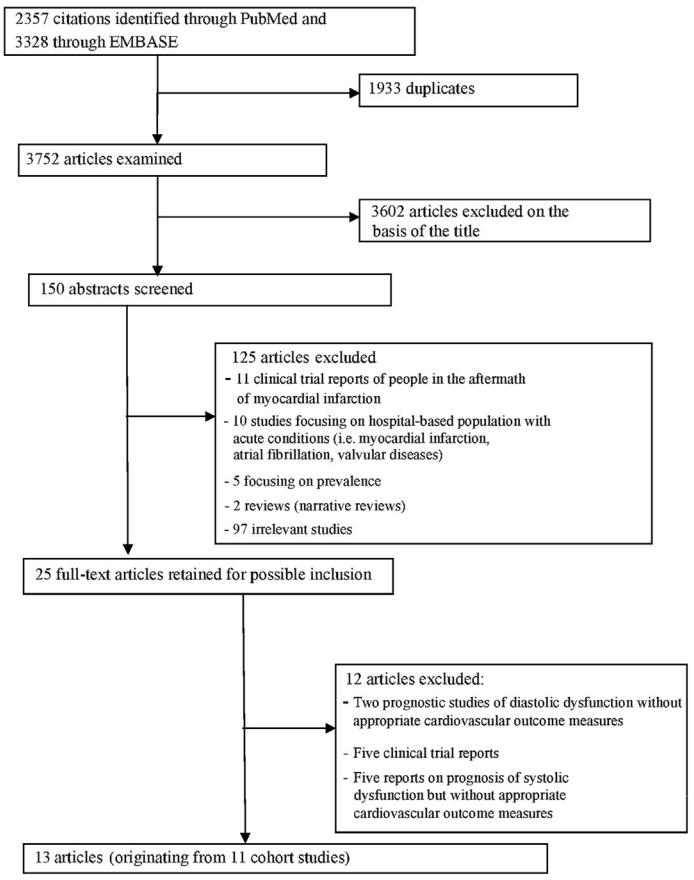
DATA EXTRACTION AND QUALITY ASSESSMENT. Two investigators (J.B.E.-T. and S.E.) independently abstracted data from eligible studies and conducted quality assessment. Discrepancies were resolved by discussion with a third investigator (G.C.F.). Data were extracted on study characteristics (setting, period, design), participant characteristics (demographics [e.g., age, sex, ethnicity], medical history [e.g., history of hypertension, diabetes, or cardiovascular disease], and clinical data [e.g., blood pressure, body mass index]), echocardiographic parameters (e.g., left ventricular hypertrophy, E/E′ ratio), type and prevalence of ALVSD at baseline (i.e., systolic or diastolic), degree of LVD (e.g., ejection fraction [EF] cutoff, diastolic dysfunction class), duration of follow-up, definition of incident HF, incidence rate of HF, and relative risk (RR) of HF among those with ALVD (along with 95% confidence intervals [CIs] or standard errors). Where available, we extracted information on the maximally adjusted RR estimates along with information on degree of adjustment. We categorized the degree covariate adjustment as follows: – no adjustment, + age and sex, ++ adjustment for additional clinical variables (e.g., blood pressure or race), and +++ further adjustment for echocardiographic variables (e.g., left ventricular hypertrophy).

We assessed the quality of studies on the basis of the criteria developed by the United States Preventive Services Task Force as good, fair, or poor (10). Studies were grouped according to the type of ALVD (i.e., systolic or diastolic) mainly assessed by echocardiography except for 1 study that used magnetic resonance imaging indexes for assessing ventricular dysfunction (11). When a study assessed diastolic or systolic dysfunction with different indexes, we chose indexes used in the assessment of the risk of HF. Some studies used continuous measures of ventricular dysfunction to assess the risk of progression (**Table 1**) and others used categorical definition of ventricular dysfunction (**Table 2**).

STATISTICAL ANALYSES. Data abstracted from the included studies were used to calculate the measures of risk. For randomized trials that were restricted to people with LVD, raw data from the placebo arm were used to estimate the incidence rates; RR could not be estimated because there was no "nonexposed" group. To limit potential biases arising from between-study differences with regard to method of LVD assessment and baseline risk of HF, we performed all analyses using only within-study comparisons. We derived the 95% CI for prevalence of baseline ALVD using a binomial distribution. Where available information allowed, we calculated the person-years of follow-up by multiplying the mean follow-up period by the number of individuals included in the study. We estimated HF incidence rates (per 100 person-years) and the corresponding 95% CIs using a Poisson distribution. For studies reporting RRs per a unit change in a measure of ALVD (e.g., EF), we calculated the corresponding risk estimate for 1-SD change to undertake comparisons across studies; we assumed the presence of a log-linear association between the exposure and disease risk in making these conversions.

We pooled studies that assessed LVSD and LVDD separately, to minimize heterogeneity and also

FIGURE 1 Study Selection Process



Flowchart showing search strategy for published data and selection process for inclusion of studies in the systematic review.

because from mechanistic, structural, and clinical viewpoints these 2 entities are different. Furthermore, we performed subgroup analysis within categories of systolic or diastolic dysfunction; we pooled studies that reported association per unit change in a measure of ventricular dysfunction (converted to 1-SD change) separately from those studies that reported association using dichotomous comparison (e.g., EF <50% vs. >50%, or presence vs. absence of diastolic dysfunction).

We pooled the study-specific measures (i.e., prevalence, incidence, RR) using random-effects model meta-analysis to provide a single summary estimate. Random-effects model meta-analysis makes an allowance for between-study heterogeneity. We provided pooled estimates along with their 95% CIs. We assessed heterogeneity between studies using Q and I^2 statistics. The I^2 statistic, recommended by the Cochrane collaboration (www.cochrane-handbook.org), estimates the percentage of total variation across studies caused by a true difference rather than chance (12). In general, I^2 values ≤25%, 50%, and ≥75% represent low, moderate, and high levels of heterogeneity, respectively.

Given that we had already grouped by type of ventricular dysfunction (systolic vs. diastolic) and type of metric used to express LVD (dichotomous vs. per unit change), there were too few studies remaining within each category of meta-analysis to enable further meaningful subgroup analyses. We assessed publication bias using Egger regression test p value for funnel-plot asymmetry. Statistical tests were 2-sided and used a significance level of $p < 0.05$. Analyses were conducted with Stata 13 (Stata Corp LP, College Station, Texas).

RESULTS

Figure 1 illustrates the study selection; 25 studies were included. Of the papers that met the inclusion and exclusion criteria, 13 papers reported data on ALVD from 10 observational cohort studies and 1 randomized trial (13).

CHARACTERISTICS OF STUDIES. The included studies involved data from 25,369 unique individuals and 3,034 incident HF cases from 11 distinct cohorts (13 reports). The study characteristics are shown in Tables 1 and 2. Additional study design characteristics, including incident HF definition, case ascertainment method, and list of covariates adjusted for in regression models are shown in Online Table 1.

Two of the included studies were retrospective cohorts (14,15), 1 was a randomized controlled trial (13), and the rest were cohort studies. The studies were almost exclusively conducted in the United States,

TABLE 1 Characteristics of Cohort Studies of the Association of Asymptomatic Left Ventricular Dysfunction and Incident Heart Failure

First Author, Year (Ref.#)	Study/Country	Baseline Year	Study Design	Study Population	N	Cases (n)	Male (%)	White (%)	Black (%)	Average Age (yrs)	Mean bl. EF	Follow-Up (yrs)
Nicklas et al., 1992 (13)	SOLVD/U.S., Canada, Belgium	1990	RCT	Low EF (<35%)*	2,117	518	89	87	10	59	0.28	1.5
Aurigemma et al., 2001 (8)	CHS/U.S.	1989–1993	Cohort	General	2,671	170	37	94	6	72	–	5.2
Wang et al., 2003 (6)	Framingham/U.S.	1987–1995	Cohort	General	4,257	175	86	99	1	61	–	5
Verdecchia et al., 2005 (16)	PUMA/Italy	1986	Cohort	Hypertensive	2,384	24	54	99	1	50	0.67	6
Ren et al., 2007 (18)	HSS/U.S.	2000–2002	Cohort	IHD	693	33	81	60	32	67	0.65	3
Bibbins-Domingo et al., 2009 (17)	CARDIA/U.S.	1985	Cohort	General	5,115	27	55	48	52	25	0.63	15
Correa de Sa et al., 2010 (14)	NR/U.S.	2005	Retrospective cohort	Diastolic dysfunction	82	2	33	99	1	69	0.66	2
From et al., 2010 (15)	Olmsted/U.S.	2001–2007	Retrospective cohort	Diabetic	1,760	379	49	99	1	60	0.62	2.9
Lam et al., 2011 (7)	FHS/U.S.	1987–1990	Cohort	General	1,038	248	39	99	1	76	–	11
Pandhi et al., 2011 (9)	CHS/U.S.	1989–1993	Cohort	General	5,649	1559	42	87	13	73	–	10.9
Kane et al., 2012 (20)	Olmsted/U.S.	1997–2000	Cohort	General	1,402	81	49	99	1	61	0.66	6.3
Vogel et al., 2012 (19)	REP/U.S.	2004–2005	Cohort	Diastolic dysfunction	388	51	43	99	1	67	0.64	3.9
Yeboah et al., 2012 (11)	MESA/U.S.	2000	Cohort	General	5,004	112	47	39	25	62	0.69	7.5

*Asymptomatic low EF.

CARDIA = Coronary Artery Risk Development in Young Adults; CHS = Cardiovascular Health Study; EF = ejection fraction; FHS = Framingham Heart Study; Framingham = Framingham and Framingham Offspring; HSS = Heart and Soul Study; IHD = ischemic heart disease; MESA = Multi-Ethnic Study of Atherosclerosis; Olmsted = Olmsted Country Study; NR = not reported; PUMA = Progetto Ipertensione Umbria Monitoraggio Ambulatoriale; RCT = randomized controlled trial; REP = Rochester Epidemiology Project; SOLVD = Studies of Left Ventricular Dysfunction.

except for the SOLVD (Studies of Left Ventricular Dysfunction) clinical trial, which also involved Canada and Belgium (13), and the PUMA (Progetto Ipertensione Umbria Monitoraggio Ambulatoriale) study conducted in Italy (16). The U.S.-based studies included multiethnic populations, but overall the proportion of whites in these studies was generally >50% (**Table 1**). All studies enrolled both sexes with the proportion of males ranging between 33% and 89% (weighted average, 56%), with an average age of participants ranging from 25 to 76 years (weighted average, 58 years).

Five studies reported on LVSD (6,11,13,16,17), 3 on diastolic dysfunction (14,18,19), and 4 reported both systolic and diastolic dysfunction (7,8,15,20). Assessment of LVD was conducted by echocardiography, except for 1 study that used magnetic resonance imaging (full) (11), using various definitions of ALVSD and ALVDD shown in Online Table 1. The definition of ALVSD was mostly based on the EF (with a cutoff varying from 30% to 50%), and the mean EF among 9 studies that reported this information ranged between 28% and 69% (weighted average, 61%). Assessment of diastolic dysfunction rested on the Doppler transmitral inflow velocity in early diastole (E wave) and in late diastole during atrial contraction (A wave), and deriving the E/A ratio; or on the E/E′ ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (E′) on tissue Doppler imaging.

The ascertainment of HF was based on hospital or death records, with no distinction by types of HF with reduced EF or heart failure with preserved ejection fraction (HFpEF). The degree of covariate adjustment varied across studies (**Table 1**, **Figures 4** and **5**), with only 2 studies accounting for intermediate states, such as coronary heart disease (9,15). The included studies were at low risk for bias of participation or study attrition. However, the included studies had different quality profiles for other domains, such as definition of ventricular function and confounding adjustment. All of the selected studies were graded as fair to good by the criteria developed by the United States Preventive Services Task Force (10).

PREVALENCE OF LVSD. Among the 6 studies that did not select their participants based on presence of LVD (6,8,11,16,17,20) the prevalence of LVSD (defined as EF <50% in 4 studies, <55% in 1 study, and <60% in 1 study) ranged between 1.7% (95% CI: 1.3% to 2.1%) and 9.9% (95% CI: 9.1% to 10.7%), with a random-effect model pooled estimate of 4.7% (95% CI: 2.3% to 7.1%) (**Figure 2**).

ASSOCIATION BETWEEN LVD AND INCIDENT HF. The participants were followed for an average of 1.5 to 15 years (weighted average, 7.9 years). The incidence of HF ranged between 1.2 and 3.7 per 100 person-years for individuals with baseline ALVDD, between 1.5 and 16.3 per 100 person-years for those with

TABLE 2 Additional Characteristics of Cohort Studies of the Association of Asymptomatic Left Ventricular Dysfunction and Incident Heart Failure

First Author, Year (Ref.#)	Study	LVSD (%)	LVDD Class	DM (%)	HTN (%)	CAD (%)	LVH (%)	Smoker (%)	Average BMI (kg/m^2)	Average SBP (mm Hg)	ACEI/ARB (%)	BB (%)
Nicklas et al., 1992 (13)	SOLVD	100	N/A	15.1	37.3	83	–	24	–	126	0	23.1
Aurigemma et al., 2001 (8)	CHS	5.8	N/A	5.4	29	0	8.7	12	–	–	–	–
Wang et al., 2003 (6)	Framingham	3	N/A	8	43	>50	1	–	–	131	8	–
Verdecchia et al., 2005 (16)	PUMA	3.6	N/A	5	100	0	37	24.5	27	157	50	22
Ren et al., 2007 (18)	HSS	0	II/III	24	71	100	50	18	29	134	46	57
Bibbins-Domingo et al., 2009 (17)	CARDIA	9.9	N/A	1.6	2.6	–	5.6	31	24.5	110	–	–
Correa de Sa et al., 2010 (14)	N/A	–	II/III	12	76	29	10	45	–	–	40	59
From et al., 2010 (15)	Olmsted	–	EE′ >15	100	86	36	–	–	33	–	–	–
Pandhi et al., 2011 (9)	CHS	7.6	NA	15.6	43.7	18.6	4.4	11.7	26.6	136	6.7	12.7
Lam et al., 2011 (7)	FHS	5	N/A	10	77	>9	–	–	–	147	–	–
Kane et al., 2012 (20)	Olmsted	2.4	Any degree	10.3	42.4	16.7	–	–	28.3	126	17.9	21.6
Vogel et al., 2012 (19)	REP	0	II/III/IV	30	87	52	–	–	29	–	–	–
Yeboah et al., 2012 (11)	MESA	1.7	N/A	10.2	–	0	–	13	28	125	10.8	8.6

*Asymptomatic low ejection fraction.

ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptors blockers; BB = beta-blockers; BMI = body mass index; CAD = coronary artery disease; DM = diabetes mellitus; EE′ = EE′ ratio; HTN = hypertension; LVDD = left ventricular diastolic dysfunction; LVH = left ventricular hypertrophy; LVSD = left ventricular systolic dysfunction; N/A = not applicable; SBP = systolic blood pressure; other abbreviations as in Table 1.

ALVSD, and between 0.1 and 2.4 per 100 person-years for control subjects. The corresponding random-effects model pooled incidence estimates were 2.8 per 100 person-years (95% CI: 1.9 to 3.7 per 100 person-years), 8.4 per 100 person-years (95% CI: 4.0 to 12.8 per 100 person years), and 1.0 per 100 person-years (95% CI: 0.0 to 2.2 per 100 person-years), respectively (**Figure 3**). The main predictors of progression investigated in the various studies included age, sex, blood pressure, diabetes, and body mass index.

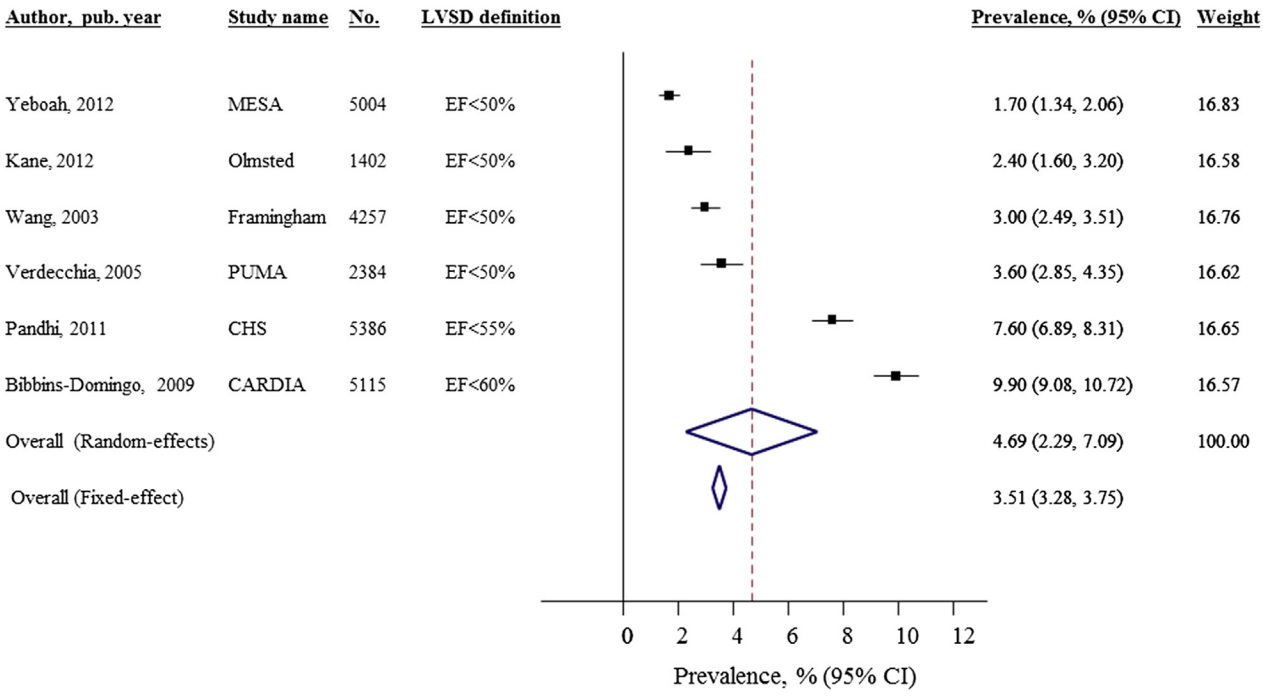
Based on random-effects model meta-analysis, the combined maximally adjusted RR of HF for individuals with systolic dysfunction across 6 studies was 4.6 (95% CI: 2.2 to 9.8) (**Figure 4**). The corresponding estimate in a fixed-effect model meta-analysis was 2.1 (95% CI: 1.8 to 2.4). For 4 studies that reported HF risk per unit change in EF, the combined maximally adjusted RR of HF per 1-SD lower EF ratio was 1.4 (95% CI: 1.1 to 1.7) (**Figure 4**). The corresponding estimate in fixed-effect model meta-analysis was 1.3 (95% CI: 1.2 to 1.4).

The overall maximally adjusted RR of HF for individuals with ALVDD across 5 studies was 1.71 (95% CI: 1.3 to 2.2) (**Figure 5**). The corresponding RR estimate in a fixed-effect model meta-analysis was 1.6 (95% CI: 1.4 to 1.9). For 3 studies that reported HF risk per unit change in E/E′ ratio, the combined maximally adjusted RR of HF per SD higher E/E′ ratio was 1.20 (95% CI: 1.1 to 1.3) (**Figure 5**). The corresponding estimate in fixed-effect model meta-analysis was 1.2 (95% CI: 1.1 to 1.3). The combined RRs of HF based on unadjusted (minimally adjusted) estimates were somewhat stronger than the corresponding maximally adjusted RRs (Online Figures 1 and 2). There was low heterogeneity across the LVDD studies I^2: 23% and 42%; $p > 0.05$), whereas the LVSD studies had substantial heterogeneity between them (I^2: 88% and 91%; $p < 0.001$), largely because of a modest RR estimate by the large report from the Cardiovascular Health Study (9). The Egger test for bias did not show strong evidence of publication bias for most of the comparisons (Online Figure 3).

DISCUSSION

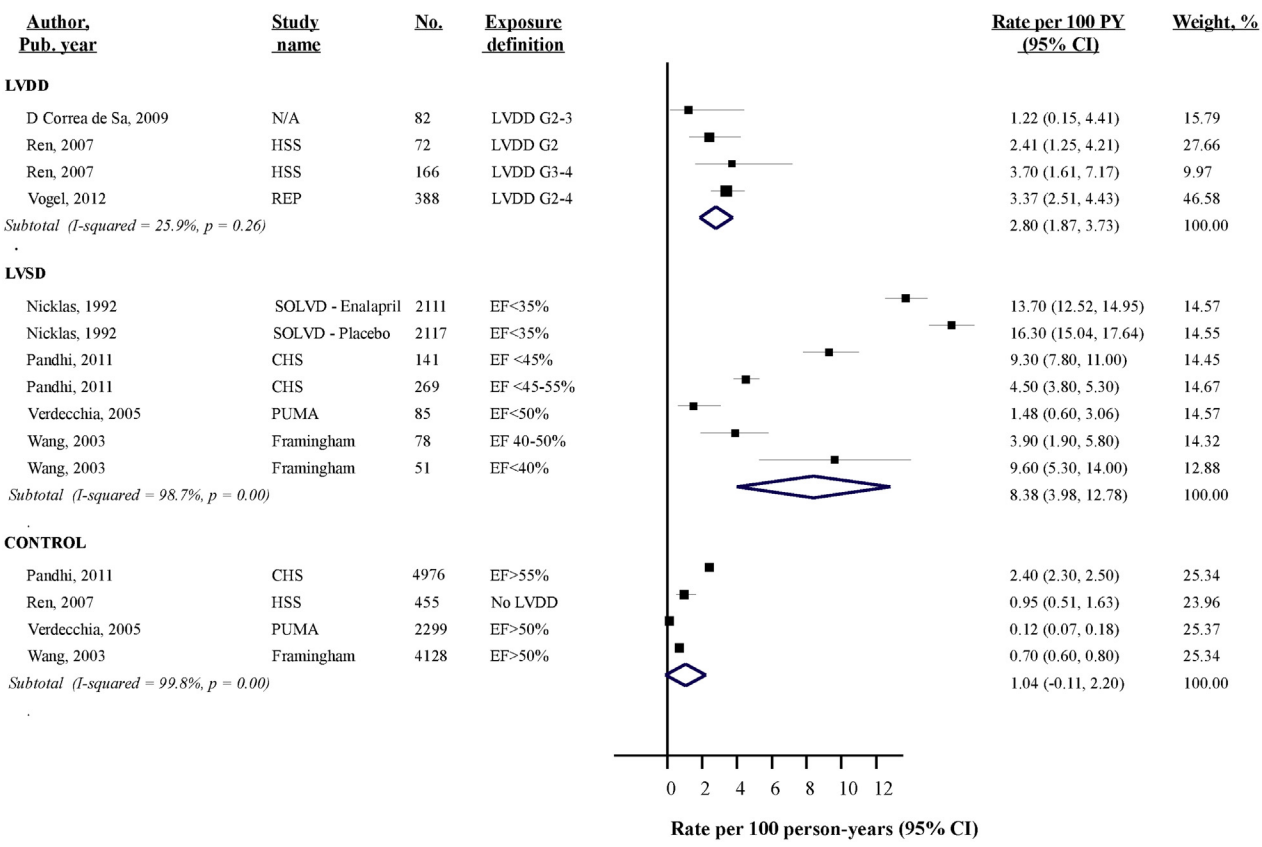
Overall, the present study demonstrates that ALVD (systolic or diastolic) is associated with a significantly higher absolute risk and RR of developing HF

FIGURE 2 Meta-Analysis: Prevalence of LVSD in 6 Cohorts



Forest plot showing the overall estimate of the prevalence of left ventricular systolic dysfunction (LVSD) in 6 cohorts included in meta-analysis. CI = confidence interval; EF = ejection fraction.

FIGURE 3 Incident Congestive Heart Failure Event Rates Among Individuals With LVSD or LVDD and Control Subjects



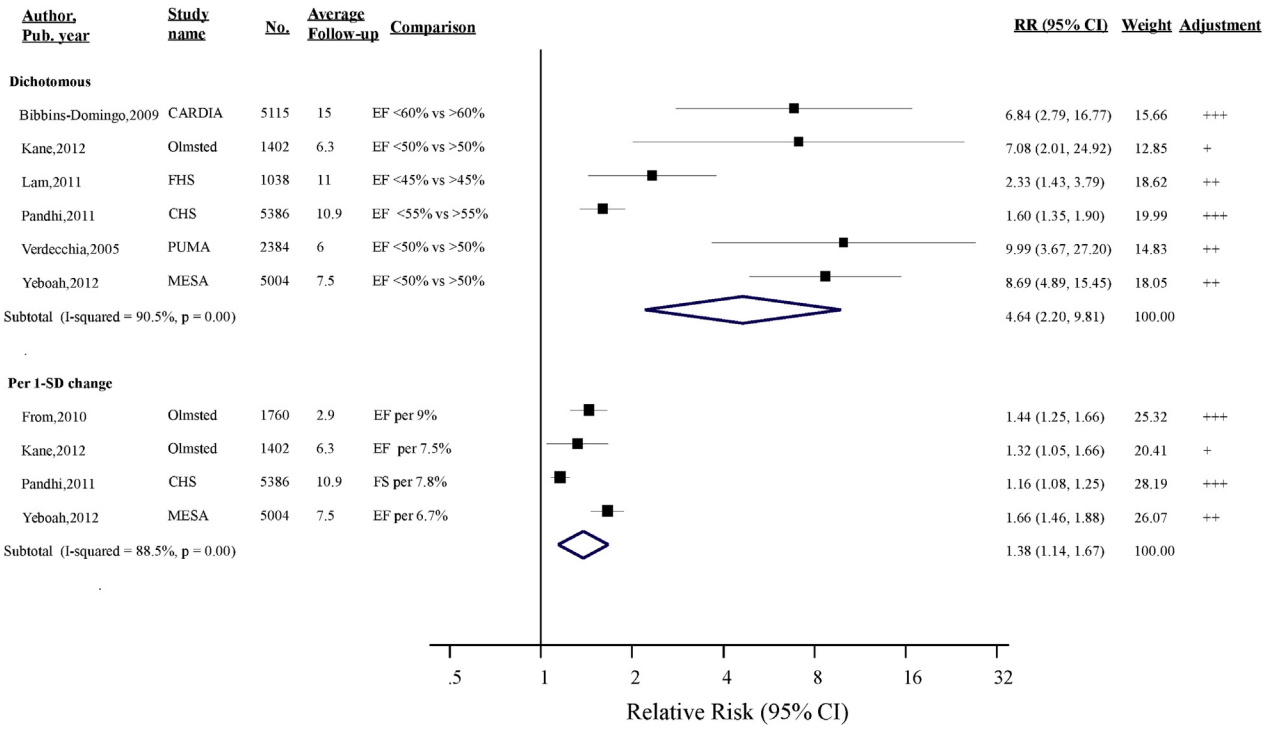
LVDD = left ventricular diastolic dysfunction; PY = person-year; other abbreviations as in Figure 2.

compared with those without ventricular dysfunction, with a variable rate of progression. The risk for developing symptomatic HF was higher in absolute and relative terms for patients with ALVSD compared with those with ALVDD. Importantly, the risk of progressing to HF from ALVSD is nearly 500% higher than in control subjects, and for those with ALVDD there is a 70% increased risk of progressing to HF. These observations represent an extraordinary opportunity to modify the natural history of HF and should serve to better inform efforts at HF prevention.

To the best of our knowledge, this is the first meta-analysis to evaluate the relationship between ALVD and HF, accounting for both systolic and diastolic dysfunction. The results are important because they reinforce the importance of ALVSD as a potential screening and therapeutic target, but also drive attention to ALVDD. Indeed, current recommendations are still unclear on how to clinically handle these intermediate stages of HF in terms of management and surveillance interval (2,21). Our data argue for focused clinical trials intended to interrupt the natural history for ALVSD and ALVDD. These additional studies are needed because events associated with ALVD extend beyond incident HF. In many of the studies included in our meta-analysis, ALVD was also associated with reduced survival (6,9,11,15,17–19), as well as in other studies, such as the Mayo Olmsted County study. The latter study found a marked difference in survival for American College of Cardiology/American Heart Association stage A/B HF versus stage C1/C2/D HF (5-year survival was 99% in stage 0, 97% in stage A, 96% in stage B, 75% in stage C, and 20% in stage D) (3).

MECHANISMS OF PROGRESSION TO HF. Our data indicate a relatively accelerated transition from ALVSD to overt symptomatic HF that correlates with the extent of EF lowering. The events that underlie this transition are not completely understood (22–24).

FIGURE 4 Meta-Analysis: Association of Asymptomatic LVSD and Incident Clinically Overt Heart Failure (Maximal Adjustment)

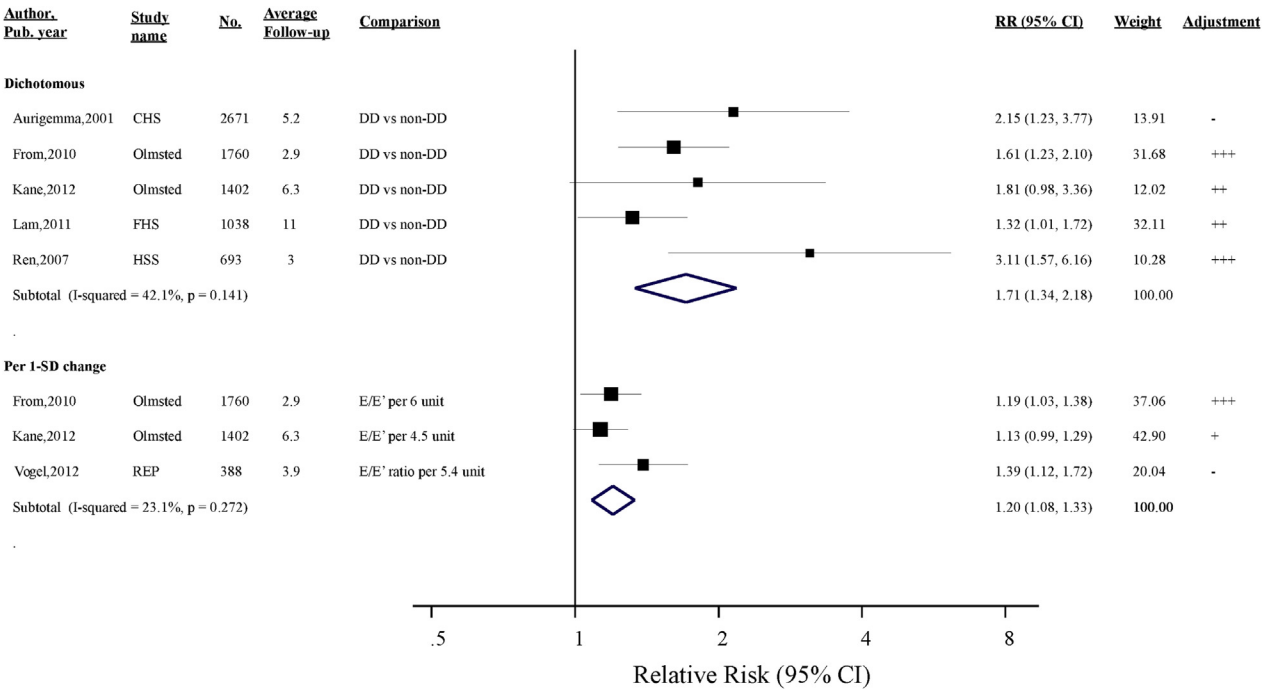


Forest plot showing the overall maximally adjusted estimate of the association of asymptomatic LVSD and incident clinically overt heart failure. RR = relative risk; other abbreviations as in Figure 2.

It is unknown if this progression is linear, logarithmic, or abrupt based on intercurrent events. However, intercurrent MI occurs in less than one-third of HF cases (22–24), with clinically overt HF occurring in only 2% to 20% of cases in the aftermath of MI (within the first 4 weeks) depending on the extent of the acute injury (22–24). The initial loss of cardiac function results in an activation of compensatory mechanisms, including peripheral vasoconstriction, salt and water retention, or enhanced inotropy, to maintain systemic blood flow and pressure. The ensuing structural remodeling results in LV dilation and hypertrophy, and is accompanied by myocardial fibrosis. The change in LV shape toward a more spherical, less efficient chamber results in increased end-diastolic volume, reduced systolic function, and a decrease in ventricular compliance (22–24). Thus, mild LVSD may progress to moderate or severe dysfunction before developing symptomatic HF, with the possibility of death from cardiovascular causes without passing through a symptomatic phase of HF. A high rate of sudden death has been demonstrated in patients with severe systolic dysfunction after MI for which an implantable cardioverter-defibrillator represents a primary prevention strategy that should be deployed (25).

Our study also provides useful data on the natural history of ALVDD, namely the transition rate to symptomatic HF. However, the pathophysiological and molecular specifics of this relationship remain largely unknown. Although ALVDD tends to worsen with time (26), and may progress from ALVDD to HFpEF (27), it is conceivable that ALVDD may progress to HF with reduced EF or may revert to a pre-clinical state if certain causal factors (e.g., hypertension) are better controlled (27). A significant proportion of those with ALVDD would develop HFpEF; however, not all people with ALVDD progress (27). The exact factors that preside over the progress of ALVDD to overt HF are poorly understood, but recent evidence suggests that changes in collagen deposition and titin may be responsible for changes in LV compliance, the sine qua non for diastolic

FIGURE 5 Meta-Analysis: Association of Asymptomatic LVDD and Incident Clinically Overt Heart Failure (Maximal Adjustment)



Forest plot showing the overall maximally adjusted estimate of the association of asymptomatic LVDD and incident clinically overt heart failure. Abbreviations as in Figures 2 and 3.

dysfunction (28). Other factors that may accelerate this progression include aging and comorbidities (27). The risk of progression to symptomatic HFpEF seems to also depend on comorbidities. The impairment in cardiovascular, pulmonary, and renal reserve in response to systemic insult may be a central key in differentiating between those with ALVDD that progress to develop HFpEF and those that remain asymptomatic.

STUDY IMPLICATIONS. Our investigation has significant implications for HF prevention, the management of patients with ALVD, and for the evaluation of community-based screening strategies. Hitherto, the prognosis of ALVSD had mainly been based on the experience of participants in randomized-controlled trials (4), which have seldom included people with an EF >35%, thus not capturing the whole spectrum of risk represented by ALVSD. In view of the exceptionally high absolute and RR of progression of ALVSD to HF, and more particularly given the fact that any drop in EF from baseline confers a non-negligible degree of HF risk, it is imperative to consider screening for this condition. Our results point to the need for testing current and novel agents that may reverse the defect and reduce the risk of future overt HF (stopping disease progression) through inclusion of people with ALSVD in clinical trials and establishing a screening/surveillance frequency (i.e., the interval for rescreening).

It is not unreasonable to infer from extant trial data that the earliest possible identification of patients enabling early treatment of ALVSD could confer the highest benefit. Evidence from the SOLVD trial indicates that angiotensin-converting enzyme inhibitors (and probably also angiotensin receptor blockers) would prevent or delay the occurrence of overt HF (13). Although extant data suggest that beta-blockers (29,30) or mineralocorticoid receptor antagonists may have significant benefits, their exact role in the management of stage B HF still needs to be clarified. Clinical trials testing various medications among people with ALVD, similar to the STOP-HF (Screening to Prevent Heart Failure) trial, are needed. The STOP-HF trial showed that it is possible to modify the natural history

of HF using renin-angiotensin-aldosterone system modifying therapies among individual at high risk of HF selected using B-type natriuretic peptide and early echocardiography. In this trial, there was a reduction in the incidence of ALVD by at least 40% (30% for ALVSD and 42% for ALVDD) and of HF by 48% (31).

Regarding ALVDD, its risk of progression to HF seems to be much less rapid than that of ALVSD. However, many would progress from ALVDD to HFpEF, and given the potential public significance of this pre-clinical group at the population level, there is an imperative to consider early detection of ALVDD as well. Indeed, in the community, more than one-half of patients with HF have preserved EF, isolated diastolic dysfunction is present in more than 40% of HF cases, and the mortality rate related to HFpEF is comparable with that of HF with reduced EF (32,33). Reducing or eliminating the factors that influence progression of ALVDD seems to be a clinical and research challenge, because there are currently no specific therapeutic approaches proven to influence clinical outcomes and decrease mortality in patients with ALVDD, or even with HFpEF.

Additional data examining the conversion of any form of ALVD to HF are needed to reflect potential differences in the risk of progression by ethnicity, sex, or comorbidities, such as diabetes or chronic kidney disease. Furthermore, the effect of the combined presence of ALVSD and ALVDD on the incidence of overt HF has not been assessed. Also, it is appropriate to investigate the ideal screening frequency (based on the rate of progression), which could be done in cost-effectiveness studies because the rescreening interval would determine the extent of resource uses. This may further underscore the need for including imaging at an early stage of a potential HF screening process, because structural changes are key prognostic features (34). The challenge to clinicians and public health practitioners is not only to develop strategies to identify patients at risk, but also to apply those evidence-based therapies that improve outcomes in those with ALVSD and identify effective therapies for those with ALVDD.

Overall identification of pre-clinical HF in the community can possibly be improved by supplementing imaging findings with appropriate biomarkers. Such an approach is conceivable. Not everyone who develops HF would necessarily have obviously identifiable echographic changes before manifesting the condition. However, there is variability of the diagnostic imaging cutoffs used for ALVSD and ALVDD, with possibly some degree of misclassification. In the Cardiovascular Health Study, adding N-terminal pro–B-type natriuretic peptide levels to a composite echographic score was shown to improve reclassification of those at intermediate risk of HF to the high-risk category (35).

STUDY LIMITATIONS. Various categorical echocardiographic indexes were used to define LVSD or LVDD with the limitations inherent to the use of a categorical versus a continuous variable. A misclassification bias may have occurred because the classification of LVSD and LVDD has evolved with time. The reproducibility of a single test/echocardiography is operator-dependent and adds uncertainty to the precision of estimates of progression derived from small studies. It is also possible that some cases of ALVDD were missed because of the lack of assessment after exercise in conducted studies, because some people with a substrate for LVDD would have apparently normal markers of LV relaxation and no echocardiographic markers of elevated LV filling pressure at rest, which may be unmasked by evaluation after exercise (36). Also, the use of EF for estimating LV systolic function has some limitations. For example, the 3-dimensional echographic estimation of EF rests on several geometric assumptions for LV volume calculations, which are made regarding of the shape of the heart. These assumptions may be problematic in case of ischemic cardiomyopathy and focal wall motion abnormalities, or may not hold in the setting of dilated cardiomyopathy because as the heart dilates the LV becomes more spherical and the relationship between length and diameter is altered (37).

The extent of adjustment for confounders varied across studies. Differing criteria for a diagnosis of HF were used in the various studies, which may account for some of the variation in HF incidence and estimate of risk. There were limited data on nonwhite populations. The number and design of the studies included in the meta-analysis limited our ability to conduct subanalyses, such as stratification by race/ethnicity, sex, and comorbidities. Last, we had no access to individual patient-level data to conduct subgroup analyses and consistent adjustment across studies.

CONCLUSIONS

Overall, our data show a significantly and alarmingly high absolute risk and RR of progression from ALVD to overt HF, much higher for systolic than for diastolic dysfunction. Sustained efforts are needed

to further clarify the progression rate across various subpopulations, especially racial/ethnic minorities; the sequence of progression; and the types of HF to which these entities progress. Our findings point to the need for a more aggressive pharmacological and lifestyle management of patients with ALVD and for defining viable screening strategies, as well as testing and implementation of pre-emptive cost-effective interventions to reduce the burden of HF burden in our communities.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Justin B. Echouffo-Tcheugui, Brigham and Women's Hospital, 221 Longwood Avenue, Boston, Massachusetts 02115. E-mail: jechouffotcheugui@partners.org.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The community-based prevalence of asymptomatic systolic or diastolic left ventricular dysfunction (stage B heart failure) is high, and its risk of progression to overt heart failure (stage C) is increased by 70% to 500%, thus the need to intervene early in the natural history of the disease.

TRANSLATIONAL OUTLOOK: Clinical trials to test the effects of therapies, neurohormonal modulators, on the progression of asymptomatic systolic or diastolic dysfunction are needed to quantify the extent of the benefits that could be derived from early intervention in the course of heart failure.

REFERENCES

1. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. Circulation 2014;131:e29–322.

2. Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation. J Am Coll Cardiol 2005;46:e1–82.

3. Ammar KA, Jacobsen SJ, Mahoney DW, et al. Prevalence and prognostic significance of heart failure stages: application of the American College of Cardiology/American Heart Association heart failure staging criteria in the community. Circulation 2007;115:1563–70.

4. Wang TJ, Levy D, Benjamin EJ, Vasan RS. The epidemiology of "asymptomatic" left ventricular systolic dysfunction: implications for screening. Ann Intern Med 2003;138:907–16.

5. Lloyd-Jones DM. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. Circulation 2002:3068–72.

6. Wang TJ, Evans JC, Benjamin EJ, Levy D, LeRoy EC, Vasan RS. Natural history of asymptomatic left ventricular systolic dysfunction in the community. Circulation 2003;108:977–82.

7. Lam CSP, Lyass A, Kraigher-Krainer E, et al. Cardiac dysfunction and noncardiac dysfunction as precursors of heart failure with reduced and preserved ejection fraction in the community. Circulation 2011;124:24–30.

8. Aurigemma GP, Gottdiener JS, Shemanski L, Gardin J, Kitzman D. Predictive value of systolic and diastolic function for incident congestive heart failure in the elderly: the Cardiovascular Health Study. J Am Coll Cardiol 2001;37:1042–8.

9. Pandhi J, Gottdiener JS, Bartz TM, Kop WJ, Mehra MR. Comparison of characteristics and outcomes of asymptomatic versus symptomatic left ventricular dysfunction in subjects 65 years old or older (from the Cardiovascular Health Study). Am J Cardiol 2011;107:1667–74.

10. Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med 2001;3 Suppl 20:21–35.

11. Yeboah J, Rodriguez CJ, Stacey B, et al. Prognosis of individuals with asymptomatic left ventricular systolic dysfunction in the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation 2012;126:2713–9.

12. The Cochrane Collaboration. Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. Available from www.cochrane-handbook.org. Accessed November 23, 2015.

13. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1992;327:685–91.

14. Correa de Sa DD, Hodge DO, Slusser JP, et al. Progression of preclinical diastolic dysfunction to the development of symptoms. Heart 2010;96:528–32.

15. From AM, Scott CG, Chen HH. The development of heart failure in patients with diabetes mellitus and pre-clinical diastolic dysfunction: a population-based study. J Am Coll Cardiol 2010;55:300–5.

16. Verdecchia P, Angeli F, Gattobigio R, Sardone M, Porcellati C. Asymptomatic left ventricular systolic dysfunction in essential hypertension: prevalence, determinants, and prognostic value. Hypertension 2005;45:412–8.

17. Bibbins-Domingo K, Pletcher MJ, Lin F, et al. Racial differences in incident heart failure among young adults. N Engl J Med 2009;360:1179–90.

18. Ren X, Ristow B, Na B, Ali S, Schiller NB, Whooley MA. Prevalence and prognosis of asymptomatic left ventricular diastolic dysfunction in ambulatory patients with coronary heart disease. Am J Cardiol 2007;99:1643–7.

19. Vogel MW, Slusser JP, Hodge DO, Chen HH. The natural history of preclinical diastolic dysfunction: a population-based study. Circ Heart Fail 2012:5144–51.

20. Kane GC, Karon BL, Mahoney DW, et al. Progression of left ventricular diastolic dysfunction and risk of heart failure. JAMA 2011;306:856–63.

21. Heart Failure Society of America. Section 7: heart failure in patients with left ventricular systolic dysfunction. J Card Fail 2006;12:e38–57.

22. Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction. Experimental observations and clinical implications. Circulation 1990;81:1161–72.

23. Mann DL. Mechanisms and models in heart failure: a combinatorial approach. Circulation 1999;100:999–1008.

24. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling—concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. J Am Coll Cardiol 2000;35:569–82.

25. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877–83.

26. Kuznetsova T, Thijs L, Knez J, et al. Longitudinal changes in left ventricular diastolic function in a general population. Circ Cardiovasc Imaging 2015;8:e002882.

27. Wan S-H, Vogel MW, Chen HH. Pre-clinical diastolic dysfunction. J Am Coll Cardiol 2014;63:407–16.

28. Zile MR, Baicu CF, Ikonomidis J, et al. Myocardial stiffness in patients with heart failure and a preserved ejection fraction: contributions of collagen and titin. Circulation 2015;131:1247–59.

29. Exner DV, Dries DL, Waclawiw MA, Shelton B, Domanski MJ. Beta-adrenergic blocking agent use and mortality in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a post hoc analysis of the Studies of Left Ventricular Dysfunction. J Am Coll Cardiol 1999;33:916–23.

30. Colucci WS, Kolias TJ, Adams KF, et al. Metoprolol reverses left ventricular remodeling in patients with asymptomatic systolic dysfunction: the REversal of VEntricular Remodeling with Toprol-XL (REVERT) trial. Circulation 2007;116:49–56.

31. Ledwidge M, Gallagher J, Conlon C, et al. Natriuretic peptide-based screening and collaborative care for heart failure: the STOP-HF randomized trial. JAMA 2013;310:66–74.

32. Bursi F, Weston SA, Redfield MM, et al. Systolic and diastolic heart failure in the community. JAMA 2006;296:2209–16.

33. Redfield MM, Jacobsen SJ, Burnett JC, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA 2003;289:194–202.

34. Coglianese EE, Wang TJ. Clinical monitoring of stage B heart failure: echocardiography. Heart Fail Clin 2012;8:169–78.

35. Kalogeropoulos AP, Georgiopoulou VV, Defilippi CR, Gottdiener JS, Butler J. Echocardiography, natriuretic peptides, and risk for incident heart failure in older adults: the Cardiovascular Health Study. J Am Coll Cardiol Img 2012;5:131–40.

36. Gupta DK, Solomon SD. Imaging in heart failure with preserved ejection fraction. Heart Fail Clin 2014;10:419–34.

37. Partington SL, Cheng S, Lima JAC. Cardiac magnetic resonance imaging for stage B heart failure. Heart Fail Clin 2012;8:179–90.

KEY WORDS asymptomatic, diastolic dysfunction, heart failure, systolic dysfunction, ventricular dysfunction

APPENDIX For supplemental tables and figures, please see the online version of this article.