

EDITORIAL COMMENT

Asymptomatic Left Ventricular Dysfunction

To Screen or Not to Screen?*

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Heart failure (HF) is a syndrome, the progressive nature of which is well recognized. The guidelines emphasize the importance of its early, preclinical stages and divide the disorder into 4 stages (1). Two stages (A and B) are asymptomatic. Stage A denotes a “high risk for heart failure but without structural heart disease” and includes individuals with known risk factors for HF, such as hypertension, diabetes, or atherosclerotic disease. Individuals with asymptomatic left ventricular dysfunction (ALVD) are an important component of stage B: “structural heart disease but without symptoms of HF.” Stages C and D, respectively, include patients with symptomatic and refractory HF. Transitions across stages of HF are poorly understood, which hinders prevention.

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The dearth of data on the subject, the magnitude of the public health burden of HF, and the unfavorable outcomes of HF, once clinically manifest, all constitute a robust rationale to focus on ALVD. In this issue of the *JACC: Heart Failure*, Echouffo-Tcheugui et al. (2) report a systematic overview and meta-analysis on the important and challenging topic of progression from ALVD to overt HF (2). Using MEDLINE and EMBASE, the authors analyzed 13 reports based on 11 studies on the progression from asymptomatic left ventricular systolic (ALVSD) or diastolic dysfunction (ALVDD) to overt HF. The combined data pertain to a

total of 25,369 participants followed for approximately 8 years. The absolute risks of progression to HF were substantially greater for those with ALVSD than for those with ALVDD (8.4 per 100 person-years, 95% confidence interval [CI]: 4.0 to 12.8 vs. 2.8 per 100 person-years, 95% CI: 1.9 to 3.7). Similarly, the adjusted relative risk of HF for ALVSD was 4.6 (95% CI: 2.2 to 9.8) for ALVSD and 1.7 (95% CI: 1.3 to 2.2) for ALVDD. Predictors of progression include age, sex, blood pressure, diabetes, and body mass index. The authors conclude that ALVSD chiefly but also ALVDD are associated with a risk of progression toward incident HF. Quantifying the risk of progression, as in this meta-analysis, brings further support to developing interventions and considering screening. These important results prompt the following reflections.

TAXONOMY AND VARIABILITY

ALVD consists of LV dysfunction without symptoms or signs of HF. In most investigations of ALVSD, more than 50% of individuals were free of HF (3), but criteria for defining HF have varied. More stringent criteria that require physical examination findings or established cardiac disease in addition to symptoms resulted in a larger proportion of individuals classified as having ALVD. Furthermore, some individuals with ALVD in published reports have shortness of breath or pedal edema but do not meet criteria for clinical HF (3). The definitions of “asymptomatic” LV systolic dysfunction in clinical trials, on which most practice guidelines are based, were even less stringent. Thirty-three percent of participants in the SOLVD (Studies of Left Ventricular Dysfunction) Prevention trial were in New York Heart Association functional class II, and 41% of patients in the placebo group of the SAVE (Survival and Ventricular Enlargement) trial were categorized as Killip class II or greater (4), although all participants were described as “asymptomatic.”

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Hence, many patients categorized as ALVD may have symptoms and functional limitations, either unrecognized because of a sedentary lifestyle or attributed to other factors. This is particularly consequential in the context of the obesity epidemic.

Ascertaining the presence and type of ventricular dysfunction is another key step. LVSD is typically defined as reduction in cardiac pump function, as surrogate for myocardial contractile dysfunction. LV systolic function is most commonly assessed by echocardiography using the LV ejection fraction (LVEF). Cutpoints have been recently recommended (5). Generally, LVEF <0.40 indicates moderate or greater degree of LVSD, and LVEF between 0.40 and 0.50 indicates mild LVSD (3).

LVDD is in turn defined as impairment of cardiac filling, using the latter as a surrogate for diastolic dysfunction. Diastolic function is most often assessed with Doppler echocardiography by evaluation of transmitral flow patterns along with 1 or more of the following: pulmonary venous flow profile, Doppler tissue imaging of mitral annular descent in diastole, or velocity of flow propagation of transmitral flow (6). Patterns of diastolic filling indicate increasing degrees of dysfunction: normal, delayed relaxation, pseudo-normal pattern, or restrictive pattern (7). Distinguishing the Doppler patterns indicative of physiological from those suggesting pathological aging is challenging, and there is lack of consensus on whether ALVDD is the main precursor of HF with a normal LVEF.

These considerations underscore the variability of the appraisal of asymptomatic status and of the classification into ALVSD or ALVDD. These factors of variability in turn influence the estimates reported in the Echouffo-Tcheugui review.

AVAILABILITY OF AN INTERVENTION

The predictors of progression identified in the present meta-analysis include age, sex, blood pressure, diabetes, and body mass index. Three of these key risk factors are modifiable through well-established clinical and population strategies to optimize blood pressure, weight, and effectively manage diabetes. We clearly need to do more to improve the cardiovascular health of all Americans (8). Doing so will reduce the risk of cardiovascular disease in general and particularly HF (9). Early studies documented that angiotensin-converting enzyme inhibitors could reduce progression to overt HF and of complications as shown in clinical trials including SAVE (4) and SOLVD Prevention (10). More recently, the STOP-HF (Screening to Prevent Heart Failure) trial reported on an intervention relying on B-type natriuretic

peptide and imaging tested rigorously through a randomized design to prevent the progression of HF. The intervention, which included multistep screening and risk factor modification, reduced the occurrence of asymptomatic LV dysfunction and HF (11).

RATIONALE FOR SCREENING

For a screening test to be useful, the target condition should cause substantial morbidity, mortality, and health care costs, and the screening test must have satisfactory intrinsic performance (sensitivity, specificity, reproducibility). To yield the optimal positive predictive value, which is the measure that matters clinically, the disease should be prevalent enough in the population screened. The prevalence of asymptomatic LVSD ranges from 2% to 8% of adults depending on the cutoff and with the aforementioned measurement caveats (12). These numbers will adversely impact the performance of any screening test in the general population. Hence, to be scientifically and economically viable, a screening strategy in this setting must be customized. For example, if a patient at risk for ALVSD is already on an angiotensin-converting enzyme inhibitor or an angiotensin-receptor blocker for hypertension, screening for ALVD would not change management. Clearly, the emergence of a new drug, efficacious at preventing HF, would change this approach and broaden the indications for screening. Moreover, many patients at risk for ALVSD have a clinical indication for echocardiography (e.g., after myocardial infarction, and if a heart murmur is present). In these situations, screening would not be needed either. Screening can thus be justified among patients with an expected high prevalence of moderate-to-severe systolic ALVD and at risk for progression as characterized in the review (e.g., older individuals with hypertension, diabetes, and larger body mass index). In this setting, screening is appropriate if patients do not otherwise have an indication for clinically indicated imaging or for treatment with angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker. In such populations, a targeted stepwise approach following that of the STOP-HF trial would be compelling (11). The Echouffo-Tcheugui paper is quite useful in supporting this strategy by documenting both the rate of progression of ALVD and by upholding the approach to identify patients at higher risk for progression.

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