Cardiac Dysfunction Assessed by Echocardiographic Tissue Doppler Imaging Is an Independent Predictor of Mortality in the General Population

Rasmus Mogelvang, MD, PhD; Peter Sogaard, MD, DMSc; Sune A. Pedersen, MD; Niels T. Olsen, MD; Jacob L. Marott, MSc; Peter Schnohr, MD, DMSc; Jens P. Goetze, MD, DMSc; Jan S. Jensen, MD, PhD, DMSc

Background—Tissue Doppler imaging (TDI) detects left ventricular dysfunction in patients with heart failure and normal ejection fraction, but the prognostic significance of left ventricular dysfunction by TDI in the general population is unknown.

Methods and Results—Within the Copenhagen City Heart Study, a large community-based population study, cardiac function was evaluated in 1036 participants by both conventional echocardiography and TDI. Averages of peak systolic (s’), early diastolic (e’), and late diastolic (a’) velocities from 6 mitral annular sites were used. TDI was furthermore quantified by a combined index (eas index) of diastolic and systolic performance: e’/(a’×s’). During follow-up (median, 5.3 years), 90 participants died. Left ventricular dysfunction by TDI, in terms of low s’ (hazard ratio, 1.23 per 1-cm/s decrease; \( P < 0.05 \)) and a’ (hazard ratio, 1.20 per 1-cm/s decrease; \( P = 0.001 \)), were significant predictors of death in Cox proportional-hazards models adjusted for clinical variables (age, sex, body mass index, heart rate, hypertension, diabetes mellitus, and ischemic heart disease) and conventional echocardiography. The adjusted hazard ratio for death in the third tertile compared with the first tertile of the combined index of systolic and diastolic performance by TDI was 2.5 (\( P < 0.005 \)).

Conclusions—In the general population, in which most are free of left ventricular systolic dysfunction and restrictive diastolic filling using conventional echocardiographic parameters, left ventricular dysfunction by TDI is a powerful and independent predictor of death, especially when systolic performance and diastolic performance are considered together, recognizing their interdependency and their complex relation to deteriorating cardiac function. (Circulation. 2009;119:2679-2685.)

Key Words: echocardiography | echocardiography, Doppler | heart failure | population | survival

Heart failure is a condition of high morbidity and mortality, and its incidence is increasing.1,2 In the era of constantly advancing medical therapies and devices, early identification of high-risk subjects with left ventricular dysfunction remains mandatory to prevent heart failure and to improve prognosis. In addition to history and physical examination, echocardiography is essential in the evaluation of patients with suspected left ventricular dysfunction.3 An abnormal conventional echocardiogram yields valuable diagnostic and prognostic information; however, only about half of the subjects with congestive heart failure (according to the Framingham criteria) in the general population have definitive evidence of systolic or diastolic dysfunction as measured by the conventional echocardiographic parameters.4

Clinical Perspective on p 2685

Tissue Doppler imaging (TDI) is a new echocardiographic technique well suited for the evaluation of longitudinal myocardial function, which is suspected to be initially affected in various cardiac diseases.5 Clinical studies have shown that TDI provides diagnostic and prognostic information incremental to conventional echocardiography in some cardiac diseases,6–13 although the primary TDI measure remains to be established. Conventional echocardiography is a strong predictor of death even in the general population,14,15 but whether preclinical left ventricular dysfunction by TDI has prognostic significance is unknown.

The aim of the present study was to evaluate the prognostic value of TDI compared with conventional echocardiographic...
measures in a large population-based study. Because considerable interdependence of systolic and diastolic parameters by TDI has been reported, the prognostic value of a combined TDI measure of systolic and diastolic myocardial performance also was evaluated.

**Methods**

**Study Population**

This study was performed as a substudy of the Fourth Copenhagen City Heart Study, a longitudinal cohort study of cardiovascular disease and risk factors. The present study includes 1100 randomly selected men and women (age, 20 to 93 years) who underwent an echocardiographic examination that included color TDI. Whether a participant underwent echocardiography was completely independent of his or her health status and other risk factors. All subjects gave written informed consent to participate, and the study was performed in accordance with the second Helsinki Declaration and approved by the regional ethics committee.

**Health Examination**

Hypertension was defined as systolic blood pressure $\geq 140$ mm Hg, diastolic blood pressure $\geq 90$ mm Hg, or use of antihypertensive medication. Diabetes mellitus was defined as plasma glucose concentration $\geq 11.1$ mmol/L, use of insulin or other antidiabetic medicine, self-reported disease, or hemoglobin A$_1C$ level $>7.0\%$. Ischemic heart disease (IHD) was defined as a history of hospital admission for acute coronary artery occlusion, percutaneous coronary intervention or coronary artery bypass grafting, or major ischemic alterations on the ECG as defined by Minnesota codes 1.1 to 3. The plasma pro-brain natriuretic peptide (proBNP) concentration was quantified with a processing-independent assay as previously described.

**Echocardiography**

Three experienced echocardiographic technicians using GE Vivid ultrasound’s Vivid Five with a 2.5-MHz probe (Horton, Norway) performed all echocardiograms. All subjects were examined with color TDI and 2-dimensional and M-mode echocardiography in the left lateral decubitus position. All images were recorded with second-harmonic imaging at the time of end expiration. The collected data were stored on magneto-optical disks and an external FireWire hard drive (LaCie, France) and analyzed offline with commercially available software (EchoPac, GE Medical, Horton, Norway) by an investigator blinded to other information.

**Conventional Echocardiography**

The 16 standard segments model, as suggested by the American Society of Echocardiography, was used to evaluate regional function. Evaluation of left ventricular ejection fraction was made by 1 observer on the basis of the wall motion index score. Left ventricular systolic dysfunction was defined as left ventricular ejection fraction $<50\%$. An M-mode still frame between the tips of the mitral leaflets and the tips of the papillary muscles was recorded in the parasternal long-axis view. If the correct 90° angle to the long axis of the ventricle could not be obtained, 2-dimensional images were used instead to quantify the myocardial thickness and the dimensions of the left ventricle. Left ventricular mass index was calculated as the anatomic mass divided by body surface area. Left ventricular hypertrophy was defined as left ventricular mass index $\geq 104$ g/m$^2$ for women and $\geq 116$ g/m$^2$ for men. Left ventricular dilatation was considered present if the ratio of diameter of the left ventricle at end diastole to height was $\geq 3.3$ cm/m$^2$.

Pulsed-wave Doppler at the apical position was used to record mitral inflow between the tips of the mitral leaflets. Peak velocities of early (E) and atrial (A) diastolic filling and deceleration time of the E wave were measured, and the E/A ratio was calculated. Severe diastolic dysfunction was defined as deceleration time $<140$ ms and E/A $<0.8$, E/A 0.8 to 2, or E/A $>2$. A normal conventional echocardiographic examination identified subjects without left ventricular hypertrophy, dilation, ejection fraction $<50\%$, or severe diastolic dysfunction.

**Color TDI**

Color TDI loops were obtained in the apical 4-chamber, 2-chamber, and long-axis views at the highest possible frame rate. Peak systolic (s'), early diastolic (e'), and late diastolic (a') velocities were measured within a 6-mm circular sample volume. Smoothing of the curves by averaging velocities over 30 ms was done by the software. Left ventricular longitudinal function was assessed by averaging myocardial velocities and displacement in the septal, lateral, inferior, anterior, posterior, and anteroseptal mitral annular positions. Ratios of E/e', e'/a', and e'(a'×s') (eas index) were calculated as measures of left ventricular filling pressure, diastolic performance, and combined systolic and diastolic performance, respectively. Previous studies have reported significant interdependencies between the myocardial velocities. This implies that whether a given e' should be considered high or low depends on the level of the preceding s'. Standardizing e' to the preceding s' avoids this problem, which led us to our hypothesis that the standardized e'/a' ratio, e'(a'×s'), is a better estimator of cardiac function than the established e'/a' ratio.

**Outcome**

Participants were followed up from the examination in 2002 through 2003 until August 2007 or time of death; each participant had a unique personal identification number in the Central Office of Civil Registration. Follow-up was 100% complete.

**Statistical Analyses**

Absolute values of diastolic tissue velocities were used in the statistical analyses and are described as such in the text. E/e', e'/a', the eas index, and plasma proBNP concentrations were positively skewed and therefore logarithmically transformed (using the binary logarithm) before further statistical analyses; the mean values presented in the text refer to geometric mean values. Values in parentheses are 95% confidence intervals (CIs) unless otherwise stated. Linear associations were examined by scatterplots and reported as the Pearson product-moment correlation coefficient, r. Univariable and multivariable Cox proportional-hazards regression models were used to examine the associations of TDI parameters and baseline variables, including conventional echocardiographic variables (both as dichotomous and continuous variables), with the risk of death. Misspecification of the functional form of the covariates and the assumption of proportional hazards were evaluated by plots of the cumulative martingale residuals. E/e', e'/a', and the eas index had to be transformed (logarithmically) to avoid functional form misspecification. To establish the most significant TDI predictor of death, multivariable analysis with forward selection of e', a', s', e'/a', E/e', eas index, age, sex, body mass index, and heart rate was performed. Forward selection was preferred in view of the multicollinearity among the TDI parameters, but backward elimination yielded the same result.

Age- and sex-adjusted tertiles of the eas index were constructed from residuals of a fitted linear model. Linearity, variance homogeneity, and the assumption of normality were tested with plots of residuals. Cumulative survival curves were established by the Kaplan–Meier method, and the curves were compared by use of the log-rank test. To explore the incremental value in predicting mortality of conventional echocardiography and TDI to other risk markers, a model was fitted for clinical and echocardiographic variables. This model was then tested using log likelihoods against the 2 smaller nested models with clinical and conventional echocardiographic variables and clinical variables only. Values of P $<0.05$ in 2-sided tests were considered significant. All analyses were performed with SAS software (SAS System for Windows, release 9.1.3, SAS Institute Inc, Cary, NC).
Table 1. Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Study Sample (n=1036)</th>
<th>Age, y</th>
<th>59.8 (± 15.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, %</td>
<td>41.7</td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.6 (± 4.0)</td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>69.1 (± 10.9)</td>
<td></td>
</tr>
<tr>
<td>Plasma proBNP, pmol/L</td>
<td>12.2 (± 4.6)</td>
<td></td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>44.9</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>7.6</td>
<td></td>
</tr>
<tr>
<td>IHD, %</td>
<td>9.0</td>
<td></td>
</tr>
<tr>
<td>Severe diastolic dysfunction, %</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>LVEF &lt;50%, %</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>LV dilatation, %</td>
<td>5.9</td>
<td></td>
</tr>
<tr>
<td>LV hypertrophy, %</td>
<td>16.7</td>
<td></td>
</tr>
<tr>
<td>Peak systolic velocity (s’), cm/s</td>
<td>6.0 (± 1.3)</td>
<td></td>
</tr>
<tr>
<td>Peak early diastolic velocity (e’), cm/s</td>
<td>7.1 (± 2.6)</td>
<td></td>
</tr>
<tr>
<td>Peak late diastolic velocity (a’), cm/s</td>
<td>6.6 (± 2.0)</td>
<td></td>
</tr>
<tr>
<td>E/e’</td>
<td>10.5 (± 1.4)</td>
<td></td>
</tr>
<tr>
<td>e’/a’</td>
<td>1.10 (± 1.9)</td>
<td></td>
</tr>
<tr>
<td>Eas index</td>
<td>0.18 (± 1.8)</td>
<td></td>
</tr>
</tbody>
</table>

LV indicates left ventricular; EF, ejection fraction. Eas index = e’(a’ ×s’). SDs are given in parentheses. The values for plasma proBNP, E/e’, e’/a’, and the eas index represent geometric means, so they have to be multiplied/divided by the SD.

Results

Population Characteristics

A total of 1100 persons were examined with TDI in the Copenhagen City Heart Study. Of these, 19 were excluded because atrial fibrillation or significant valvulopathy, and 45 were excluded because of inadequate quality of the echocardiographic examination. Characteristics of the remaining persons constituting the study population (n=1036) are displayed in Table 1. The mean age at the time of enrollment was 60 years, and the median follow-up was 5.3 years. During follow-up, 90 (8.7%) persons died. Compared with the survivors, the persons who died were older at enrollment and had a higher proportion of IHD (and risk factors for IHD) and a higher proportion of structural heart disease and impaired cardiac function assessed by conventional echocardiography.

Tissue Doppler Imaging

Correlation analyses showed a marked relationship between myocardial velocities and age; s’ (r = −0.41, P < 0.001) and e’ (r = −0.77, P < 0.001) decreased whereas a’ (r = 0.31, P < 0.001) increased with age. These parameters also correlated mutually, ie, e’ and s’ (r = 0.52, P < 0.001) and e’ and a’ (r = −0.33, P < 0.001), even after adjustment for age, sex, body mass index, and heart rate. The eas index correlated negatively with age (r = −0.49).

TDI and Overall Mortality

Systolic dysfunction and diastolic dysfunction as assessed by TDI were associated with overall mortality (Table 2), even after multivariable adjustment for age, sex, body mass index, heart rate, hypertension, diabetes, IHD, and conventional echocardiography (model 1, Table 2). Decreasing peak systolic (s’) and late diastolic (a’) velocity and increasing ratio between early and late diastolic velocities (e’/a’) were all significantly associated with increased risk of mortality. Interestingly, besides these established parameters, increasing eas index also was significantly associated with a higher risk of death. Conversely, e’ and E/e’ were not associated with overall mortality in this community sample.

Among all the TDI parameters, the eas index was the best predictor of death; in forward selection, only the eas index (together with age, sex, and heart rate) was selected (P < 0.001). Figure 1 shows the Kaplan–Meier curves depicting the cumulative probability of survival for persons stratified into age- and sex-adjusted eas tertiles (Table 3). The relative mortality risk increased with increasing eas tertiles (P < 0.001); thus, persons with an eas index in the third tertile had a risk of death nearly 3 times as high as persons with an eas index in the first tertile (hazard ratio [HR], 2.8; 95% CI, 1.6 to 4.9; P < 0.001). Multivariable adjustment (age, sex, body mass index, and heart rate) yielded similar results (HR, 2.7; 95% CI, 1.5 to 4.9; P < 0.001), and additional adjustment for hypertension, diabetes mellitus, IHD, and plasma proBNP resulted in an HR of 2.5 (95% CI, 1.4 to 4.7; P < 0.005).

TDI and Conventional Echocardiography

To further evaluate the effect of conventional echocardiographic parameters and the eas index on mortality, left ventricular ejection fraction, mass index, and ratio of end-diastolic diameter to height. In model 3, only persons with a normal conventional echocardiography are included.

Table 2. TDI Predictors of Mortality by Cox Proportional-Hazards Regression Models

<table>
<thead>
<tr>
<th></th>
<th>Adjusted for Age and Sex</th>
<th>Model 1, Multivariable Adjustment</th>
<th>Model 2, Multivariable Adjustment</th>
<th>Model 3, Multivariable Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>s’ per 1-cm/s decrease</td>
<td>1.25 (1.04–1.52)</td>
<td>&lt;0.02</td>
<td>1.23 (1.01–1.50)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>e’ per 1-cm/s decrease</td>
<td>0.97 (0.85–1.10)</td>
<td>0.59</td>
<td>0.98 (0.86–1.11)</td>
<td>0.77</td>
</tr>
<tr>
<td>a’ per 1-cm/s decrease</td>
<td>1.18 (1.07–1.30)</td>
<td>&lt;0.001</td>
<td>1.20 (1.08–1.34)</td>
<td>0.001</td>
</tr>
<tr>
<td>e’/a’ per doubling</td>
<td>1.42 (1.14–1.77)</td>
<td>&lt;0.002</td>
<td>1.41 (1.12–1.78)</td>
<td>&lt;0.004</td>
</tr>
<tr>
<td>E/e’ per doubling</td>
<td>1.13 (0.70–1.81)</td>
<td>0.62</td>
<td>0.90 (0.56–1.45)</td>
<td>0.68</td>
</tr>
<tr>
<td>Eas index per doubling</td>
<td>1.46 (1.19–1.78)</td>
<td>&lt;0.001</td>
<td>1.48 (1.19–1.83)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Multivariable adjustment includes adjustment for age, sex, body mass index, heart rate, hypertension, diabetes mellitus, and IHD. Model 1 is also adjusted for conventional echocardiography. Models 2 and 3 are adjusted for left ventricular ejection fraction, mass index, and ratio of end-diastolic diameter to height. In model 3, only persons with a normal conventional echocardiography are included.
diastolic diameter to height were included as continuous variables in the multivariable models (models 2 and 3, Table 2). Even in the subgroup of persons with a normal conventional echocardiography, systolic and diastolic performance as assessed by TDI continued to be of significant predictive value. Inclusion of systolic blood pressure in the models did not change this pattern significantly.

**Incremental Value of TDI to Other Risk Markers**

To examine the incremental value of conventional echocardiography and TDI to other risk markers on the risk of mortality, we fitted a model combining all the clinical information (age, sex, heart rate, body mass index, hypertension, diabetes mellitus, IHD, and plasma proBNP). We then added the information from the conventional echocardiographic examination, which improved the model but not significantly (Figure 2). However, further addition of the information from TDI (eas index) to the model significantly improved risk prediction (Figure 2).

In the multivariable model (model 2, Table 2) assessing all parameters, the eas index (HR, 1.66; \( P<0.001 \)), left ventricular ejection fraction (HR, 0.92; \( P<0.01 \)), age (HR, 1.10; \( P<0.001 \)), and male sex (HR, 2.00; \( P<0.01 \)) remained significant independent predictors of mortality. Adding plasma proBNP and systolic blood pressure to a model containing the independent significant predictors revealed similar results (eas index: HR, 1.49; \( P<0.001 \); left ventricular ejection fraction: HR, 0.93; \( P<0.001 \); age: HR, 1.10; \( P<0.001 \); and male sex: HR, 1.74; \( P<0.02 \)).

**Discussion**

In the present large prospective study, we demonstrated that left ventricular systolic and/or diastolic dysfunction assessed by TDI is an independent predictor of death in the general population (Table 2), even in the subgroup with normal conventional echocardiography. Furthermore, we observed that the predictive information of TDI was incremental to clinical information: age, sex, body mass index, heart rate, hypertension, diabetes mellitus, IHD, plasma proBNP, and conventional echocardiography.

**TDI in a Population at Low Risk**

TDI has been reported to have independent prognostic value in the hospital setting in some cardiac diseases,\(^6\)–\(^{13}\) although no consensus has been reached on the main prognostic parameter. Population-based studies, however, are essential in investigations of initial cardiac dysfunction; this information cannot be extrapolated from studies in patient populations. To the best of our knowledge, our study is the first to evaluate the isolated prognostic impact of TDI in the general population, which is why our findings on s’ and a’, but not e’ and E/e’ (Table 2), as significant independent predictors of mortality is difficult to compare. In a population-based study, Redfield et al\(^4\) used E/e’ as 1 of 4 measures to discriminate between mild and moderate to severe diastolic dysfunction.

### Table 3. Tertiles of the Eas Index According to Age and Sex

<table>
<thead>
<tr>
<th>Eas Index</th>
<th>First–Third Tertile, (cm/s) (^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age &lt;40 y</td>
</tr>
<tr>
<td>Women</td>
<td>0.336–0.541</td>
</tr>
<tr>
<td>Men</td>
<td>0.254–0.392</td>
</tr>
</tbody>
</table>
dysfunction; however, the isolated prognostic effect of E/e’ (or e’) was not reported.

The prognostic significance of TDI has been evaluated in various patient populations, and in general, similar to our findings, s’ and a’ also seem to provide prognostic information in clinical populations. In contrast, some of the clinical studies also found E/e’ to be a significant prognosticator. E/e’ has been shown to correlate reasonably well with left ventricular filling pressures in patients referred for cardiac catheterization but not in patients with preserved ejection fraction or in healthy subjects. Our results that E/e’ provides no prognostic information in the community might reflect that E/e’ is not a robust measure of left ventricular filling pressures in such populations.

Like others, we found that mitral annular velocities are highly associated with age (especially e’), emphasizing the necessity of age adjustment when evaluating the isolated prognostic effect of TDI. The fact that e’ and E/e’ are highly correlated to age might impair their predictive abilities in low-risk populations like ours in which age has a huge impact on the risk of death. In high-risk populations, the effect of chronological age is less powerful, and it is possible in such populations that e’ and E/e’ are more tightly associated with biological than chronological age.

However, our results emphasize that the independent predictive power of systolic and diastolic measures such as s’ and a’ is not limited to clinical populations only. The fact that cardiac dysfunction as assessed by TDI identifies subjects at high risk in a population in which <25% have significant systolic or diastolic dysfunction using conventional measures motivates the introduction of TDI as an integral part of the standard echocardiographic examination.

**Myocardial Velocities and Combined Measures**

In concordance with other studies, we observed a positive correlation between s’ and e’ and a negative correlation between e’ and a’. The internal dependency between these parameters supports our hypothesis that systolic and diastolic mitral annular velocities should be evaluated together, not individually.

Early diastolic motion is dependent on the highly energy-consuming ventricular relaxation, and e’ has been found to be a sensitive parameter of myocardial dysfunction. Because impaired relaxation is a normal part of aging and the initial component of diastolic dysfunction, e’ may not provide much independent prognostic information in the general population. To discriminate between low-risk and high-risk subjects in the general population, we need ways to separate mild from more severe cardiac dysfunction.

Late diastolic motion adds significant information when it is also taken into consideration. With normal aging, e’ decreases and a’ increases accordingly. In late diastole, a’ reflects passive ventricular motion and is dependent on left atrial contractility and the viscoelastic properties of the left ventricle. With myocardial deterioration, in contrast to simply impaired relaxation, left ventricular stiffness is increased (and atrial contractility itself may also be reduced) and the left atrium will struggle to stretch the stiff left ventricle. Further deterioration therefore results in reduced a’. Because the effect of increased left ventricular stiffness is most pronounced in late diastole, when the myocardium is already stretched, e’ is affected less, and e’/a’ increases with further myocardial deterioration, as opposed to the decrease related to aging. In accordance with this, we find increased e’/a’ to be independently associated with increased mortality.

Systolic motion is important for both its information about the contractile strength of the left ventricle and its impact on diastole. In healthy persons with preserved systolic function, e’ has been shown to change with preload altering maneuvers. In a study by Naghieh et al., e’ was shown to be independent of pulmonary capillary wedge pressure in patients with impaired relaxation or pseudonormal left ventricular filling (diastolic dysfunction grades 1 and 2). Peak systolic velocity, s’, on the other hand, was significantly lower in the pseudonormal group. It appears that the preload dependence of e’ is lost in the presence of more severe myocardial dysfunction, possibly because of the counteracting influence of decreasing systolic function of the heart. During systole, the ventricle contracts below its equilibrium volume, which stores potential energy in elastic myocardial components. This contributes to the relengthening during early diastole. The elastic restoring forces during early diastole are therefore related to the amount of systolic deformation, as seen in the relationship between e’ and the preceding s’. Because early diastolic performance is determined partly by systolic performance, low s’ in itself should lead to low e’, but this effect seems to be balanced by the higher preload of individuals with more marked myocardial dysfunction. Standardizing e’ to s’ would solve this problem; if e’/s’ is increased, we would expect it to be due to increased preload, reduced systolic performance, or both.

Because e’/s’ provides information on systolic dysfunction and increased preload and e’/a’ on increased left ventricular stiffness, combining these indexes seems logical to embrace all of these important manifestations of cardiac dysfunction in 1 measure. Substituting e’ with e’/s’ in the e’/a’ ratio would theoretically provide a more accurate single-parameter measure of significantly impaired cardiac function. A high eas index would indicate increased preload with systolic dysfunction, diastolic dysfunction, or both. This is supported by our findings that the eas index is significantly associated with mortality and is superior to e’/a’ and other echocardiographic parameters. In this community sample, the eas index stratified the population into tertiles of low, medium, and high risk. Furthermore, although the tertiles were adjusted for age and sex, subjects in the highest tertile had a risk of death that was nearly 3 times higher than subjects in the lowest tertile.

Our results show that the mitral annular velocities provide valuable prognostic information in the general population, especially when they are considered together, recognizing their interdependency and their complex relation to deteriorating cardiac function. The fact that e’/a’ and s’ are independent predictors underscores the validity of the eas index. However, our finding that the eas index is superior to e’/a’ and s’ emphasizes the significance of the eas index.

**Future Implications**

Current guidelines for the diagnosis and management of heart failure emphasize the need for early identification of...
and intervention in subjects at high risk of developing heart failure. These guidelines differentiate between high-risk subjects with (stage B) or without (stage A) structural heart disease. Our findings that persons with normal conventional echocardiography but left ventricular dysfunction by TDI are at increased risk of dying prompt future studies to explore the benefit of applying therapeutic interventions for stage B heart failure (including treatment with β-blockers and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers) to persons with preclinical left ventricular dysfunction by TDI. Furthermore, examination of the cost-effectiveness of screening high-risk subjects (eg, persons with hypertension, diabetes mellitus, or stable angina pectoris) with TDI would be very interesting. Although our findings indicate that TDI might be a potential screening tool, we have to await the results of studies evaluating the cost-effectiveness before echocardiography can be introduced as a screening test in the community. However, the fact that impaired cardiac function as assessed by TDI is associated with a higher risk of mortality in a community sample independently of plasma proBNP (as a marker of global cardiac dysfunction) underscores the importance of impaired longitudinal cardiac function in itself.

Study Limitations
We recognize the limitations of the present study. We did not measure pulmonary venous flow or mitral inflow at peak Valsalva maneuver and were therefore unable to differentiate between grade 2 (pseudonormal) and normal diastolic function by conventional echocardiography. However, it is unlikely that many of our participants were pseudonormalized without concomitant left ventricular hypertrophy, dilatation, or ejection fraction <50%. Left atrial size has lately been shown to be an interesting variable that can help identify patients with moderate to severe diastolic function. Because we did not measure left atrial size, we cannot compare the prognostic significance of this diastolic variable with systolic and diastolic cardiac function as assessed by TDI in the community. Although color TDI yields the same mechanical information as pulsed TDI, comparison of myocardial velocities obtained by the 2 methods is complicated by the velocities being 20% to 30% higher when measured by pulsed TDI. In addition, the fact that our study sample was predominantly white limits the generalizability of our findings. Unfortunately, we do not know the causes of death. However, we assume that persons with cardiac dysfunction by TDI are more likely to die as a result of cardiovascular causes and that, if we were able to limit our analysis to cardiovascular deaths, the prognostic impact of TDI would be even higher.

Conclusions
Left ventricular dysfunction measured by TDI is a powerful and independent predictor of death in the general population. When the information on systolic and diastolic performance provided by TDI is combined, the prognostic value of TDI is further strengthened.

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Disclosures
Dr Sogaard has received honoraria from GE Healthcare. The other authors report no conflicts.

References
Tissue Doppler imaging (TDI) is a relatively recent echocardiographic technique well suited for evaluation of longitudinal myocardial function, which is suspected to be initially affected in various cardiac diseases. Most modern echocardiographic equipment has the ability to perform TDI and its use only prolongs the examination by a couple of minutes. The present study shows that in the general population where the majority is free of significant systolic and diastolic dysfunction using conventional echocardiography, TDI is able to identify systolic and diastolic cardiac dysfunction associated with an increased risk of mortality. The prognostic value of TDI was found to be incremental to age, sex, heart rate, body mass index, hypertension, diabetes, ischemic heart disease, plasma proBNP, and conventional echocardiography. These findings introduce TDI as an integral part of the standard echocardiographic examination of low-risk subjects and suggest that TDI may have a possible role as a screening tool of the general population.
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