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Left Ventricular Diastolic Function and Long-Term Outcomes in Patients with a Normal Exercise Echocardiogram

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Abstract

The objective of this study was to determine whether diastolic dysfunction (DD) is associated with outcomes in the absence of myocardial ischemia. We studied 2,835 patients undergoing exercise echocardiography (ExEcho) from January 2006 through December 2006 who had normal systolic function (ejection fraction ≥ 50%) and absence of exercise-induced wall motion abnormalities. Diastolic function was graded as normal, mild DD, or moderate/severe DD. Medical record review and patient contact was undertaken to determine mortality, cardiovascular events (i.e., death, myocardial infarction (MI), or stroke), incident heart failure (HF) and hospitalization. Mean (SD) age was 58.9 (12.8) years; 54.0% were female. DD was present in 40.0% of participants; 28.2% had mild DD and 11.8% had moderate/severe DD. Over a median follow-up of 4.4 years there were 81 deaths and 114 cardiovascular events, and DD was associated with higher rates of mortality, cardiovascular events, and HF events or hospitalizations (all $p < 0.001$). In multivariate analysis, mild or moderate/severe DD (referent; normal) was associated with HF or hospitalization (HR 1.45 (95% CI 1.18–1.78; $p < 0.001$ for mild DD; HR 1.75 (95% CI 1.37–2.24; $p < 0.001$ for moderate/severe DD) but was not independently associated with death or cardiovascular events. The diastolic index of filling pressure (E/e') was independently associated with mortality, cardiovascular events, and HF or hospitalizations. In conclusion, among patients without demonstrable myocardial ischemia, left ventricular DD was associated with higher event rates over long-term follow up but did not independently predict hard endpoints other than HF or hospitalization. E/e' was independently associated with clinical outcomes and may be an important echo-derived parameter to identify in patients undergoing ExEcho.

Keywords

diastolic function; outcomes; exercise echocardiogram

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Introduction

Guidelines recommend diastolic assessment during a comprehensive echocardiographic examination, including estimation of left ventricular (LV) filling pressure and grading diastolic dysfunction (DD)¹. DD parameters, whether assessed as individual indices^{2–5} or algorithmically graded^{6–8}, have been associated with outcomes^{2–8}. It is noteworthy that the observed relationship between DD and outcome has been particularly strong in those with coronary artery disease (CAD)^{9, 10}. For instance, in patients with ischemic cardiomyopathy, DD has been associated with reduced cardiac survival and incident heart failure (HF)^{11,12}. Therefore, it has been difficult to elucidate whether it is primarily CAD or DD that contributes to worse outcome, as ischemia may confound the association of DD with events. Recent studies have identified the prognostic implication of DD, as assessed on resting echocardiograms, on long-term survival or HF^{7,8,13}; however, whether similar findings exist in patients without clinically important ischemia has not been well studied. We assessed the relationship between DD and clinical events in patients referred for an exercise echocardiogram (ExEcho) in 2006, a 12-month time period in which we performed diastolic function assessment in our stress echocardiography laboratory. Our primary research hypothesis was to test whether DD was associated with mortality and major cardiovascular events in patients who had normal resting LV systolic function (ejection fraction (EF) 50%) and no evidence of myocardial ischemia (i.e., negative ExEcho).

Methods

From January 2006 – December 2006, patients who underwent a clinically indicated ExEcho at Mayo Clinic, Rochester, MN and were without evidence of exercise-induced wall motion abnormalities were studied. All study patients performed symptom-limited treadmill exercise utilizing the Bruce protocol and had been referred for testing based on the following reasons: 1424 (50.2%) for chest pain/dyspnea, 558 (19.7%) with multiple cardiovascular risk factors and suspected CAD, 286 (10.1%) for an abnormal electrocardiogram, 259 (9.1%) for further evaluation of known CAD, 243 (8.6%) for pre-operative risk stratification, and 65 (2.3%) for abnormal coronary calcium study on computed tomography. Patients with non-sinus rhythm (n = 120), valvular heart disease (n = 76), poor image quality (n = 7), resting ejection fraction <50% (n = 88), echocardiographic evidence of stress-induced myocardial ischemia (n = 790), and those not consenting to research participation (n = 143) were excluded. From the 3,105 patients that met eligibility criteria for the study, 169 patients outside of the US were excluded due to difficulty verifying mailing addresses. There were 101 patients excluded due to inability to accurately assess diastolic function grade, leaving a final study population of 2,835 patients.

Echocardiographic assessment of diastolic function included pulsed-wave Doppler of early (E) and late (A) transmitral velocities, deceleration time (DT), early velocity of the medial (septal) mitral annulus (e') using tissue Doppler, non-invasive assessment of LV filling pressures (E/e'), and left atrial (LA) volume. E/e' was measured at rest and post-exercise, within 4 minutes of regional wall motion assessment. Elevated LV filling pressures were defined as an $E/e' \geq 15$ ^{14,15}. LA volume was measured in biplane views and indexed to body surface area. Resting diastolic function was graded as normal, mild DD or moderate/severe DD and classified as such based on previously published definitions^{15,16}. Normal diastolic function was defined as an E/A between 0.75 and 1.5, normal LA volume index (<28ml/m²), and normal LV filling pressure ($E/e' < 10$). Mild DD included patients with an E/A of less than 0.75 and $E/e' < 10$. Moderate/severe DD included patients with an E/A >1.5, LA volume index ≥ 28 ml/m², and $E/e' \geq 10$.

Outcomes were assessed through medical records review and by contact of study participants using a standardized mailed survey packet. Prospective contact of study participants was included to reduce the likelihood of missing events that may have occurred within the patient's community health system. An initial survey packet was sent to all participants, followed by a second mailing and/or telephone contact to non-responders 60 to 90 days after the initial mailing. Excluding 76 patients identified as deceased during medical records abstraction, surveys were sent to 2,759 patients, but 108 surveys were returned non-deliverable. Of the remaining 2,651 surveys, 1,172 were returned over the time period of the study (response rate; 44.2%). All patients, regardless of response status, had their records reviewed for clinical events that had occurred since their index ExEcho in 2006.

Study end-points included all-cause mortality, cardiovascular events (i.e., death, MI, or stroke), and heart failure or time to first hospitalization for any cause. An *a priori* event definitions form was used to determine clinical endpoints. MI had occurred if 2 out of 3 of the following were observed: symptoms of myocardial ischemia and biomarker evidence of myocardial injury (elevated cardiac biomarkers) or new Q waves present in at least two leads. Stroke had occurred if there was a neurological deficit of acute onset and neuroimaging confirmation of stroke or, in patients without neuroimaging data, suspected stroke based on evaluation by a neurologist. An HF event was defined as clinical symptoms with supporting signs based on modified Framingham criteria¹⁷, and including treatment with an intravenous diuretic or vasodilator that required hospitalization of the patient for 24 hours. Hospitalization for any cause (except HF) was defined as inpatient admission for acute medical care. The institutional review board approved this study and participants provided written informed consent for participation.

Summary data for continuous variables were expressed as mean $\pm$ SD or median (25th–75th interquartile range) if distributions were not normally distributed and counts/percentages for categorical variables. Patients were categorized into 3 groups: normal diastolic function, mild DD (impaired relaxation), moderate/severe DD (pseudonormal or restrictive filling). Univariate analysis across groups was performed using ANOVA and Pearson χ^2 . Time to event analyses for mortality, cardiovascular events (i.e., composite of mortality, stroke, or MI), and HF or hospitalization for any cause were computed according to the Kaplan-Meier method, and compared using the log-rank test. Patients without events were censored at last follow up using our institution's administrative records or the date from a completed survey. Cox proportional hazards regression was used to assess the association of variables of interest with outcomes. The first set of variables examined were clinical variables, which included hypertension, history of CAD, smoking status, body mass index, diabetes, history of MI, history of percutaneous coronary intervention or coronary artery bypass grafting, and systolic and diastolic blood pressures on the day of the ExEcho. These variables were considered for the multivariate model if age and sex adjusted $p < 0.2$. The second set of variables evaluated were echocardiographic variables, which included LV EF, wall motion score index, LV end diastolic dimension, LA volume index, E/A, E/e', and e'. Again, variables with age and gender adjusted $p < 0.2$ were assessed for association with outcome after adjusting for previously included clinical variables. Finally, diastolic grade was forced into the Cox proportional hazard regression model. Individual diastolic indices used to grade diastolic function were not fitted in the same models as diastolic grade in order to avoid potential problems with collinearity. SAS version 9.2 (Cary, NC) was used for all analyses and tests performed were two-sided with p significant at < 0.05 .

Results

Mean age (SD) of participants was 58.9 ± 12.8 ; 1,304 (46.0%) were men, 875 (31.0%) had body mass index $> 30 \text{ kg/m}^2$. The prevalence of comorbidities included 1,409 (49.7%) with

hypertension, 407 (14.4%) with CAD, 289 (10.2%) with diabetes, 193 (6.8%) with prior MI, and 1,247 (44.0%) with history of smoking. Overall, 60.0% of participants had normal diastolic function, 28.2% had mild DD, and 11.8% had moderate/severe DD. Table 1 lists demographic and clinical characteristics of the study participants by diastolic function group. Table 2 lists echocardiographically determined characteristics of participants by diastolic function group at rest and after exercise.

Clinical events are summarized in Table 3. Five-year mortality rate was 2.9% in patients with normal diastolic function as compared to 5.6% and 8.0% in patients with mild DD and moderate/severe DD, respectively. Figure 1A shows the cumulative mortality rate in patients by diastolic function grade over the study period ($p < 0.001$ by log-rank). Figure 1B illustrates cumulative rates of the composite outcome of death, MI, or stroke. Patients with DD were more likely to experience the composite of HF or hospitalization as compared to those with normal diastolic function (Figure 1C). When patients were categorized by the single diastolic index of E/e' , cumulative event rates for death and the composite of death, MI, or stroke were higher in those with $E/e' \geq 15$ as compared to those with $E/e' < 15$ (Figures 2A and 2B).

There were 1,424 patients (50.2%) that were referred for testing based on symptoms of chest pain/dyspnea. Survival estimates for mortality in this subgroup demonstrated that DD was associated with higher mortality over long-term follow up (Figure 3). In age and sex adjusted models, moderate/severe DD, but not mild DD, was associated with mortality (HR 2.48; 95% CI 1.05–5.88, $p = 0.04$); however, this association was attenuated after adjustment for prior CABG (HR 2.20; 95% CI 0.90–2.60, $p = 0.08$).

Age and sex adjusted associations with outcome are shown in Table 4. Smoking status was the only baseline covariate significantly associated with mortality (hazard ratio (HR) 1.65; 95% CI 1.05–2.61). Echocardiographic variables associated with mortality included LV EF, higher E/e' , and higher E/A ratios, although the magnitude of these estimates were modest. Greater exercise capacity was associated with reduced risk for all endpoints.

Multivariate analysis was performed to identify factors independently associated with outcome using clinical and echocardiographic variables (Table 5). DD was not found to be independently associated with mortality or the composite outcome of death, MI, or stroke, though it was independently associated with HF or hospitalization for any cause (Table 5). Of the individual diastolic indices assessed in the multivariable models, only E/e' was significantly associated with clinical outcome. Each 1 unit increase in E/e' was associated with increased mortality risk (HR 1.06; 95% CI 1.01–1.10, $p = 0.01$), cardiovascular events (HR 1.05; 95% CI 1.02–1.09, $p = 0.005$), and HF or hospitalizations (HR 1.04; 95% CI 1.02–1.06, $p < 0.001$).

Discussion

We observed that diastolic function grade in a large cohort of patients with normal LV systolic function and absence of ischemia was associated with higher rates of death and cardiovascular events. However, after adjustment, diastolic function grade was not incrementally predictive of hard outcomes over long-term follow up. Superior to this was the single diastolic index, E/e' ; each 1 point increase in E/e' was associated with an average 5% increase in the risk of death, cardiovascular events, or HF or hospitalization.

The prognostic value of diastolic indices, including E/A, DT, and E/e' , for mortality risk has previously been recognized in patients with cardiomyopathies^{10,18–20}. Our observation that E/e' , but not diastolic function grade, was independently associated with outcomes raises considerations regarding the echocardiographic assessment of diastolic function. Although

tissue Doppler imaging to assess myocardial relaxation is less load dependant than other diastolic parameters^{21,22}, estimates obtained may not accurately reflect invasively measured pressures²³. Unzek et al reported the variability in diastolic grading among readers, with high concordance (92%) for grading mild DD but low concordance (<65%) for moderate/severe DD as compared to a reference standard²⁴. Importantly, there were high concordance rates (71%–95%) among readers for E/e', suggesting that this index, though having its own set of limitations²³, may be more reproducible. The observed variation among expert readers suggests that grading of DD is challenging, and that the complex mechanistic properties of LV relaxation, suction, and filling are not described in their entirety by commonly used diastolic indices.

Our findings have similarities to other studies that have not found independent associations between diastolic function and outcomes or had conflicting observations^{25,26}. Leibowitz et al noted that diastolic indices were not independent predictors of 5-year mortality in older adults, with only reduced LV systolic function predictive of long-term survival²⁵. Our study assessed diastolic properties on relevant outcomes other than mortality, and used the novel approach of studying patients with a normal ExEcho to reduce confounding from clinically important ischemia. Outcomes data were collected using both medical records review and prospective patient contact, the latter being necessary in single center studies where the institution is often a large referral center and its record system may not capture events that occur in the patient's community setting. Finally, we used diastolic function grade in addition to individual diastolic indices to study its association with outcomes.

Although diastolic indices have been associated with outcome in prior studies^{2,3,6}, few investigations have studied the association of diastolic function grade with outcome in patients with preserved LV systolic function. Redfield et al studied patients, only half of whom had LV ejection fraction >50%, and observed that DD was independently predictive of all-cause mortality, albeit with wide confidence limits⁶. However, only age, sex, and ejection fraction were controlled for in multivariable analysis. In addition, the burden of clinically important ischemia in the cohort was unknown, despite nearly 60% of patients with known CAD by history having resting DD⁶. Halley et al evaluated the association of diastolic function grade with mortality using propensity matching and observed that moderate and severe DD, but not mild DD, was independently predictive of mortality⁷; however, nearly 40% of patients were excluded because of inability to grade DD and tissue Doppler imaging was not implemented in all patients. Differences in our study's findings as compared to these prior works may be related to differences in study population, as our participants were included based on a negative ExEcho. However, such a strategy is critical to reduce confounding from ischemia when making inferences regarding the association of DD as an independent predictor of outcome. Because only resting echocardiograms were used in prior epidemiological studies^{2,6,7}, information on ischemia or exercise capacity, both being important predictors of outcome, were lacking.

We identified DD as independently associated with HF or hospitalization, with events being driven primarily by the latter. DD in its preclinical form^{27,28} has been previously shown to be associated with hospitalizations²⁹. In our cohort, we showed an incremental and graded association between worsening diastolic function and risk of hospitalization. We also observed that even mild DD was associated with a 50% increase risk of hospitalization. Therefore, identification of DD, specifically in the absence of myocardial ischemia, may provide important information as it identifies a population at increased risk for hospitalizations. The mechanism by which DD, particularly in the absence of diastolic HF, leads to future hospitalizations may be driven by unaccounted comorbid health conditions, and this requires further study.

Our findings should be interpreted within the context of several potential limitations. Although the medical records of all participants were reviewed for the endpoints of interest, only 44% of participants responded to our mailed survey, despite a study protocol involving a second survey and/or telephone contact to initial non-responders. However, characteristics of responders vs non-responders with regard to age, sex, and comorbidities in our study were similar, likely reducing the impact of a non-response bias. There were higher estimates of pulmonary pressures in patients with diastolic dysfunction at baseline and post-exercise; however, because information on comorbid conditions associated with pulmonary hypertension was not available, and since increases in pulmonary pressures may be observed in healthy individuals with exercise, we could not attribute higher pulmonary pressures as being directly related to diastolic dysfunction. Since E/e' after exercise was obtained after assessment for wall motion abnormalities, underestimation of LV filling pressures may have occurred, though unlike heart rate recovery, diastolic function recovery tends to be more gradual. Potential misclassification of diastolic function grade could introduce biased estimates, and even among expert echocardiographers, concordance for grading DD has a kappa of 0.7²⁴. Depending on specific cutoffs used for defining abnormal diastolic function with single indices, the potential for inconsistent or indeterminate grading exists.

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Mild DD	99.7 (686)	99.0 (654)	97.6 (621)	96.6 (540)	94.4 (144)
Mod/Severe DD	97.6 (260)	96.2 (264)	94.7 (250)	93.5 (228)	92.0 (44)
Normal	99.6 (1284)	99.2 (1205)	98.6 (1127)	97.8 (989)	97.1 (294)

Mild DD	98.7 (677)	97.5 (643)	95.7 (607)	94.4 (524)	92.3 (142)
Mod/Severe DD	96.9 (278)	95.5 (262)	94.4 (249)	93.2 (227)	89.6 (44)
Normal	99.3 (1279)	98.8 (1200)	98.0 (1120)	96.8 (979)	95.7 (289)

Figure 1.

Figure 1A. Survival of patient cohort after negative exercise echocardiogram by diastolic function grade.

Figure 1B. Cumulative incidence of the composite outcome of death, myocardial infarction, or stroke by diastolic function grade.

Figure 1C. Cumulative incidence of heart failure or hospitalization for any cause by diastolic function grade.

Mild DD	99.7 (339)	98.8 (325)	97.6 (310)	96.9 (274)	93.9 (67)
Mod/Severe DD	97.3 (140)	95.1 (132)	93.6 (125)	91.3 (113)	90.4 (22)
Normal	99.7 (649)	99.5 (611)	99.4 (577)	98.5 (509)	97.6 (167)

$E/e' < 15$	99.8 (2048)	99.1 (1931)	98.3 (1824)	97.5 (1601)	96.4 (445)
$E/e' \geq 15$	95.2 (176)	95.2 (169)	92.9 (156)	91.7 (142)	89.2 (30)

Figure 2.

Figure 2A. Survival of patient cohort after negative exercise echocardiogram by Doppler derived E/e' .

Figure 2B. Cumulative incidence of the composite outcome of death, myocardial infarction, or stroke by Doppler derived E/e' .

Figure 3.
Survival in the cohort of patients with chest pain/dyspnea as indication for exercise echocardiography by diastolic function grade.

Table 1

Baseline demographic and clinical characteristics by diastolic function

Characteristics	Left Ventricular Diastolic Dysfunction			p value
	None (N=1703)	Mild (N=801)	Moderate/Severe (N=331)	
Age (SD) (years)	53.5 (11.6)	67.5 (9.1)	65.7 (11.4)	<0.001
Male	797 (46.8%)	353 (44.1%)	154 (46.5%)	0.43
Body mass index (kg/m ²)	27.6 (4.8)	28.4 (4.5)	29.5 (5.8)	<0.001
Body mass index >30 (kg/m ²)	485 (28.6%)	258 (32.3%)	132 (39.9%)	<0.001
Hypertension	668 (39.2%)	508 (63.4%)	233 (70.4%)	<0.001
History of coronary artery disease *	168 (9.9%)	155 (19.4%)	84 (25.4%)	<0.001
Previous/current smoker	708 (41.6%)	378 (47.3%)	161 (48.6%)	0.006
Diabetes mellitus	105 (6.2%)	126 (15.7%)	58 (17.5%)	<0.001
Prior coronary artery bypass grafting	48 (2.8%)	49 (6.1%)	42 (12.7%)	<0.001
Prior myocardial infarction	88 (5.2%)	68 (8.5%)	37 (11.2%)	<0.001
Prior percutaneous coronary intervention	106 (6.2%)	93 (11.6%)	37 (11.2%)	<0.001
Baseline diastolic blood pressure, mean (SD) (mmHg)	75.6 (10.7)	75.3 (10.3)	75.4 (10.5)	0.81
Baseline systolic blood pressure, mean (SD) (mmHg)	123.4 (18.2)	129.9 (19.4)	132.3 (10.3)	<0.001
Baseline heart rate, mean (SD) (beats per minute)	74.5 (12.9)	75.6 (14.0)	68.2 (13.0)	<0.001
Cardiac-related medications				
Beta blockers	363 (21.3%)	276 (34.5%)	190 (57.4%)	<0.001
Calcium blockers	98 (5.8%)	105 (13.1%)	52 (15.7%)	<0.001
Angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers	294 (17.3%)	267 (33.3%)	130 (39.3%)	<0.001
Statins	527 (31.0%)	361 (45.1%)	149 (45.0%)	<0.001

* as defined by presence of coronary atherosclerosis by invasive coronary angiography

Table 2

Echocardiographic variables at rest and exercise by diastolic function

Variable	Left Ventricular Diastolic Dysfunction			p value
	None (N=1703)	Mild (N=801)	Moderate/Severe (N=331)	
Left ventricular hypertrophy	66 (3.9%)	63 (7.9%)	32 (9.7%)	<0.001
Wall motion score index at rest	1.02 (0.10)	1.08 (0.24)	1.11 (0.28)	<0.001
Left ventricular ejection fraction at rest (%)	61.2 (4.4)	60.4 (6.6)	59.7 (8.5)	<0.001
Left ventricular end diastolic dimension, mean (SD) (mm)	47.3 (4.5)	47.2 (5.5)	49.0 (5.8)	<0.001
Baseline left atrial volume index	25.2 (7.0)	28.6 (9.0)	37.0 (9.7)	<0.001
E/e' at rest	8.1 (2.3)	9.7 (3.6)	13.9 (5.1)	<0.001
Medial e' at rest (cm/s)	9.5 (2.4)	6.4 (1.8)	6.5 (1.8)	<0.001
Deceleration time at rest, mean (SD) (ms)	198.5 (34.2)	239.1 (51.1)	200.8 (37.9)	<0.001
E/A ratio	1.25 (0.36)	0.72 (0.14)	1.22 (0.40)	<0.001
Tricuspid regurgitation velocity at rest (m/s)	2.37 (0.29)	2.43 (0.27)	2.57 (0.32)	<0.001
Tricuspid regurgitation velocity post exercise (m/s)	2.78 (0.40)	2.90 (0.46)	3.08 (0.48)	<0.001
Medial e' post exercise (cm/s)	11.2 (2.9)	8.8 (2.4)	8.4 (2.4)	<0.001
E/e' post exercise	8.5 (2.9)	10.1 (4.4)	13.8 (8.0)	<0.001
Peak heart rate, mean (SD) (beats per minute)	155.0 (20.9)	139.3 (20.8)	132.3 (21.6)	<0.001
Peak systolic blood pressure, mean (SD) (mmHg)	165.6 (23.1)	166.4 (24.4)	165.6 (25.0)	0.69
Peak diastolic blood pressure, mean (SD) (mmHg)	79.1 (12.5)	80.6 (42.3)	78.1 (13.4)	0.20
Exercise capacity, mean (SD) (METs)	10.7 (2.6)	8.5 (2.3)	8.0 (2.2)	<0.001

Table 3

Clinical events observed over study period by diastolic function

Clinical Events	Left Ventricular Diastolic Dysfunction			p value
	None (N=1703)	Mild (N=801)	Moderate/Severe (N=331)	
Death (5 year rate %)	31 (2.9%)	30 (5.6%)	20 (8.0%)	<0.001
Myocardial infarction (5 year rate %)	16 (1.6%)	7 (1.1%)	2 (0.9%)	0.72
Heart failure (5 year rate %)	4 (0.4%)	6 (1.0%)	3 (1.2%)	0.16
Stroke (5 year rate %)	0 (0%)	7 (1.1%)	1 (1.7%)	0.001
Hospitalizations (5 year rate %)	276 (24.3%)	223 (39.2%)	103 (47.8%)	<0.001
Heart failure or hospitalizations (5 year rate %)	279 (26.9%)	228 (39.9%)	106 (48.3%)	<0.001
Death, myocardial infarction, or stroke (5 year rate %)	47 (4.3%)	44 (7.7%)	23 (10.4%)	0.001

Table 4

Univariate clinical and echocardiographic associations with clinical events

	Death		Death, myocardial infarction, or stroke		Heart failure or hospitalization	
	HR (95% CI)	p value*	HR (95% CI)	p value*	HR (95% CI)	p value*
Body mass index (kg/m ²)	0.98 (0.93–1.03)	0.49	1.00 (0.96–1.04)	0.98	1.03 (1.02–1.05)	<0.001
Hypertension	1.26 (0.78–2.04)	0.35	1.28 (0.86–1.92)	0.23	1.30 (1.09–1.54)	0.003
Left ventricular hypertrophy	0.89 (0.36–2.21)	0.80	0.91 (0.42–1.96)	0.81	1.11 (0.79–1.55)	0.55
History of coronary artery disease	1.21 (0.73–2.02)	0.46	1.84 (1.22–2.77)	0.004	1.55 (1.26–1.89)	<0.001
Previous/current smoker	1.65 (1.05–2.61)	0.03	1.78 (1.21–2.61)	0.004	1.29 (1.10–1.51)	0.002
Diabetes mellitus	0.89 (0.45–1.78)	0.74	0.85 (0.47–1.55)	0.59	1.51 (1.21–1.88)	<0.001
Prior coronary artery bypass grafting	1.54 (0.80–2.96)	0.19	1.46 (0.82–2.59)	0.20	1.28 (0.94–1.76)	0.12
Prior myocardial infarction	0.78 (0.36–1.70)	0.53	1.02 (0.56–1.87)	0.94	1.67 (1.30–2.14)	<0.001
Prior percutaneous coronary intervention	1.03 (0.53–2.02)	0.92	1.91 (1.19–3.06)	0.007	1.50 (1.18–1.91)	<0.001
Wall motion score index at rest	2.04 (0.99–4.21)	0.05	1.97 (1.05–3.71)	0.03	1.36 (0.93–1.98)	0.12
Left ventricular ejection fraction at rest (per 5%)	0.97 (0.94–1.00)	0.02	0.98 (0.95–1.00)	0.04	0.98 (0.97–1.00)	0.01
Baseline systolic blood pressure, mean (SD) (per 10 mmHg)	1.00 (0.99–1.01)	0.62	1.00 (0.99–1.01)	0.47	1.00 (1.00–1.01)	0.35
Baseline diastolic blood pressure, mean (SD) (per 10 mmHg)	0.99 (0.97–1.01)	0.25	1.00 (0.98–1.02)	0.97	1.00 (1.00–1.01)	0.44
Left ventricular end diastolic dimension, mean (SD) (per 1 mm)	1.01 (0.96–1.06)	0.79	1.02 (0.98–1.07)	0.36	1.02 (1.00–1.04)	0.04
Left atrial volume index (per 1 mL/m ²)	1.01 (0.98–1.03)	0.57	1.01 (0.99–1.03)	0.40	1.01 (1.00–1.02)	0.004
E/e' at rest	1.06 (1.02–1.11)	0.008	1.06 (1.03–1.10)	<0.001	1.05 (1.03–1.07)	<0.001
Mitral septal (medial) e'	1.01 (0.91–1.13)	0.80	0.96 (0.88–1.05)	0.39	0.91 (0.88–0.95)	<0.001
Deceleration time at rest (per 10 ms)	1.00 (1.00–1.01)	0.88	1.00 (0.99–1.00)	0.91	1.00 (0.99–1.00)	0.19
E/A ratio	2.08 (1.05–4.10)	0.04	1.43 (0.79–2.58)	0.24	0.71 (0.55–0.92)	0.01
Exercise capacity (per 1 metabolic equivalent)	0.76 (0.68–0.86)	<0.001	0.78 (0.71–0.86)	<0.001	0.85 (0.82–0.89)	<0.001
Normal diastolic function	1.0 (ref)		1.0 (ref)		1.0 (ref)	
Mild diastolic dysfunction	0.74 (0.42, 1.29)	0.29	0.88 (0.56–1.39)	0.59	1.59 (1.30–1.94)	<0.001
Moderate/severe diastolic dysfunction	1.30 (0.70, 2.39)	0.40	1.19 (0.70–2.04)	0.52	2.00 (1.57–2.54)	<0.001
Normal diastolic function	1.0 (ref)		1.0 (ref)		1.0 (ref)	
Mild/Mod/Severe diastolic dysfunction	0.89 (0.54, 1.48)	0.66	0.97 (0.63–1.48)	0.88	1.71 (1.42–2.06)	<0.001

* age and sex adjusted

CI = confidence interval; HR = hazard ratio.

Table 5

Multivariate analysis of variables associated with clinical events

	Death		Death, myocardial infarction, or stroke		Heart failure or hospitalization	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Age	1.09 (1.06–1.11)	<0.001	1.06 (1.04–1.08)	<0.001	1.01 (0.99–1.02)	0.11
Male sex	0.84 (0.52–1.37)	0.49	0.79 (0.52–1.20)	0.27	1.08 (0.91–1.28)	0.38
History of coronary artery disease	--	--	1.78 (1.18–2.69)	0.006	1.42 (1.15–1.77)	0.001
Body mass index (kg/m ²)	--	--	--	--	1.02 (1.00–1.04)	0.04
Previous/current smoker	1.58 (1.00–2.51)	0.05	1.74 (1.18–2.57)	0.005	1.22 (1.03–1.43)	0.02
Diabetes mellitus	--	--	--	--	1.33 (1.06–1.67)	0.01
Left ventricular ejection fraction at rest (%)	0.97 (0.95–1.00)	0.03	--	--	0.98 (0.96–1.00)	0.03
E/e' *	1.06 (1.01–1.10)	0.01	1.05 (1.02–1.09)	0.005	1.04 (1.02–1.06)	<0.001
Normal diastolic function †	1.0 (ref)		1.0 (ref)		1.0 (ref)	
Mild diastolic dysfunction	0.67 (0.38–1.18)	0.17	0.84 (0.53–1.33)	0.46	1.45 (1.18–1.78)	<0.001
Moderate/severe diastolic dysfunction	1.17 (0.64–2.17)	0.61	1.07 (0.63–1.84)	0.80	1.75 (1.36–2.24)	<0.001

* Model does not include diastolic dysfunction.

† Model does not include E/e'

CI = confidence interval; HR = hazard ratio.