The Natural History of Preclinical Diastolic Dysfunction
A Population-Based Study

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Background—Preclinical diastolic dysfunction (PDD) has been broadly defined as subjects with left ventricular diastolic dysfunction, without the diagnosis of congestive heart failure (HF) and with normal systolic function. Our objective was to determine the risk factors associated with the progression from PDD (stage B) HF to symptomatic (stage C) HF.

Methods and Results—Using the resources of the Rochester Epidemiology Project, all residents of Olmsted County, MN, who underwent echocardiography between January 1, 2004, and December 31, 2005, and had grade 2–4 diastolic dysfunction and ejection fraction ≥50% were identified. Patients with a diagnosis of HF before or within 30 days of the echocardiogram were excluded. Patients were also excluded if they had a diagnosis of atrial fibrillation or severe mitral or aortic valve regurgitation at the time of the echocardiogram. A total of 388 patients met the inclusion criteria. The mean age of the cohort was 67±12 years, with a female (57%) predominance. Prevalence of renal insufficiency (estimated glomerular filtration rate <60 mL/min per 1.73 m^2) was 34%. The 3-year cumulative probabilities of development of (stage C) HF, development of atrial fibrillation, cardiac hospitalization, and mortality were 11.6%, 14.5%, 17.7%, and 10.1% respectively. In multivariable Cox proportional hazard regression analysis, we determined that age, renal dysfunction, and right ventricular systolic pressure were independently associated with the development of HF.

Conclusions—This population-based study demonstrated that in PDD (stage B) HF, there was a moderate degree of progression to symptomatic (stage C) HF over 3 years, and renal dysfunction was associated with this progression independent of age, sex, hypertension, coronary disease, and ejection fraction. **(*Circ Heart Fail*. 2012;5:144-151.)**

Key Words: diastolic dysfunction ■ heart failure ■ preserved ejection fraction

Heart failure (HF) is an epidemic with a prevalence of 5.3 million in Americans ages 20 years and older in 2005.[1] It is being increasingly recognized that 30–50% of HF patients have normal or near-normal ejection fraction (EF), and multiple studies have shown that HF with preserved EF (HFpEF) carries a similar prognosis to HF with decreased systolic function.[2–9]

Clinical Perspective on p 151

In the American Heart Association/American College of Cardiology Foundation classification of HF, stage B is defined as structural heart disease without signs/symptoms of HF.[10] Preclinical diastolic dysfunction (PDD), which is part of stage B HF, has therefore been defined as patients with diastolic dysfunction (DD), normal EF, and without HF symptoms/diagnosis. The importance of PDD is that these patients may progress to symptomatic HF and they are at increased risk for adverse cardiac events including atrial fibrillation (AF).[11,12] Despite this importance, there are few studies that have focused on the natural history of PDD.

In a population-based study from Olmsted County, MN, the prevalence of mild PDD was 20.6%, and moderate to severe PDD was 6.8% among subjects ages 45 years and older. In addition, it was shown that PDD patients had higher mortality than subjects with normal diastolic function.[5] These findings were similar to another population-based study from Canberra, Australia, which found a prevalence of 23.5% for mild DD with normal EF and 5.6% for moderate or severe DD with normal EF.[13]

Beyond these prevalence data, we have recently reported that among a small cohort of PDD subjects the 2-year cumulative probability of development of any HF symptoms was 31.1%. Furthermore, hypertension, hyperlipidemia, coronary artery disease, and renal dysfunction were prevalent in PDD.[14] However, our previous study was limited to only 82 patients and a short mean follow-up of 721 days.

It is notable that for symptomatic HF patients, it has been previously shown that renal dysfunction is an independent predictor of all-cause mortality. However, to this point, it has remained unclear whether or not renal dysfunction holds prognostic value for PDD patients.[15]

Our objectives were to confirm and extend our previous preliminary findings, to determine the clinical phenotype and

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natural history of PDD, and to identify clinical characteristics that could predict the progression to symptomatic HF. To the best of our knowledge, our study is the largest to date focused broadly on PDD patients.

Methods

Study Setting

This study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards. Population-based epidemiological research is feasible in Olmsted County, MN, because all care is provided by either Mayo Clinic or Olmsted Medical Center, which together maintain a unified medical record which is sustained by the Rochester Epidemiology Project.[16] This record includes an indexed diagnosis for every medical encounter including outpatient, inpatient, emergency department, and death certification.[16,17]

We used the resources of the Rochester Epidemiology Project and the Mayo Clinic echocardiography database to identify all patients in Olmsted County, MN, who underwent echocardiography between January 1, 2004, and December 31, 2005. For included patients, the first echocardiogram during this period is subsequently referred to as the inclusion echocardiogram. Inclusion criteria were echocardiographic evidence of grade 2–4 diastolic dysfunction and EF ≥50%. Exclusion criteria were HF diagnosis before or within 30 days of the inclusion echocardiogram or AF at the time of the inclusion echocardiogram or severe mitral valve or aortic valve regurgitation. Data collection was obtained through complete review of the medical records both at Mayo Clinic and Olmsted Medical Center.

Echocardiographic Data

Echocardiography was performed according to the guidelines of the American Society of Echocardiography and diastolic function was classified integrating pulsed-wave Doppler examination of mitral inflow before and during Valsalva maneuver and pulmonary venous inflow and Doppler tissue imaging of the mitral annulus.[5,18]

Diastolic dysfunction was classified as grade 1, impaired relaxation (E/A ≤0.75, E/e′ <10); grade 1a, impaired relaxation (E/A ≤0.75, E/e′ >10); grade 2, "pseudonormal" pattern (0.75<E/A <1.5, DT >140 and PV S/D ≥1 or E/e′ ≥10); and grade 3/4, restrictive (E/A >1.5, and/or DT <140 ms and/or PV S/D <1 ≥ and/or E/e′ ≥10).[5] We also collected data on left atrial volume (LAV) index and right ventricular systolic pressure (RVSP): E is the early component of mitral filling; A, atrial component of mitral filling; E/A, ratio of the mitral early (E) and atrial (A) components of the mitral inflow velocity profile; e′, velocity of mitral annulus early diastolic motion; E/e′, ratio of early diastolic mitral inflow velocity and early diastolic mitral annular velocity; DT, deceleration time; PV, pulmonary vein; S, systolic forward flow; and D, diastolic forward flow.

Additional Data

For all included patients, the following data were collected from the medical record: inclusion echocardiogram information; comorbidities; date of birth; sex; body mass index (BMI); laboratory values (electrolytes, creatinine, lipid panel) closest in time to the inclusion echocardiogram; and, if applicable, date of death. Glomerular filtration rate (GFR) was calculated by means of the Modification of Diet in Renal Disease (MDRD) equation.[19]

International Classification of Disease (ICD) and Diagnosis Related Group (DRG) codes were used to identify heart failure, AF, and all comorbidities. Specifically, heart failure patients were identified by searching the electronic medical record for a diagnosis of heart failure as denoted by International Classification of Disease (ICD9) code 428 and Diagnosis-Related Group (DRG) codes 127, 291, 292, and 293. AF patients were identified by searching the electronic medical record for a diagnosis of AF as denoted by International Classification of Disease (ICD9) code 427.

Mortality data were obtained through review of the medical records and confirmed through an automated check of registration data.

For those patients who had HF, AF, or cardiac hospitalization, the medical record was reviewed in detail to gather the laboratory values listed above and also the complete blood counts were recorded that were closest in time to the date of the diagnosis and closest to the end of the follow-up period. Also, for these patients, cardiac medications were recorded closest in time after the inclusion echocardiogram, after the diagnosis of AF or HF, and closest to the end of the follow-up period.

Additionally, for patients who had HF, the echocardiogram data closest to the date of diagnosis was recorded. Finally, hospitalization

Table 1. Baseline Clinical and Echocardiography Data for Total Cohort

Variable	No.	%
Age, y	388 (mean age, 67.1; SD, 12.4)	
Female sex	223	57
BMI	388 (mean BMI, 29.2; SD, 6.9)	
CV comorbidities		
Hypertension	338	87
Coronary artery disease	200	52
History of myocardial infarction	94	24
Peripheral vascular disease	42	11
CV risk factors		
Hyperlipidemia	293	76
GFR <60 mL/min per 1.73 m^2	133	34
Diabetes mellitus	116	30
Laboratories	**Mean**	**SD**
Total cholesterol	170.5	39.9
Triglycerides	134.1	75.1
HDL	53.0	16.6
LDL	90.4	32.8
BUN	22.9	13.1
Creatinine	1.2	1.0
Hemoglobin	13.1	1.7
Hematocrit	38.3	4.9
Sodium	139.5	4.0
Potassium	4.3	0.5
GFR	72.0	33.2
Echocardiography Data	**No.**	**%**
DD degree		
2	368	95%
3	18	5%
4	2	1%
	Mean	**SD**
Ejection fraction	63.6	6.1
E/e′	15.5	5.4
E/A baseline	1.3	0.7
DT baseline	200.6	38.6
LAV index	41.5	12.1
RVSP	37.5	11.9

BMI indicates body mass index; CV, cardiovascular; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BUN, blood urea nitrogen; DD, diastolic dysfunction, E, early component of mitral filling; A, atrial component of mitral filling; E/A, ratio of the mitral early (E) and atrial (A) components of the mitral inflow velocity profile; e′, velocity of mitral annulus early diastolic motion; E/e′, ratio of early diastolic mitral inflow velocity and early diastolic mitral annular velocity; DT, deceleration time; LAV, left atrial volume; RVSP, right ventricular systolic pressure.

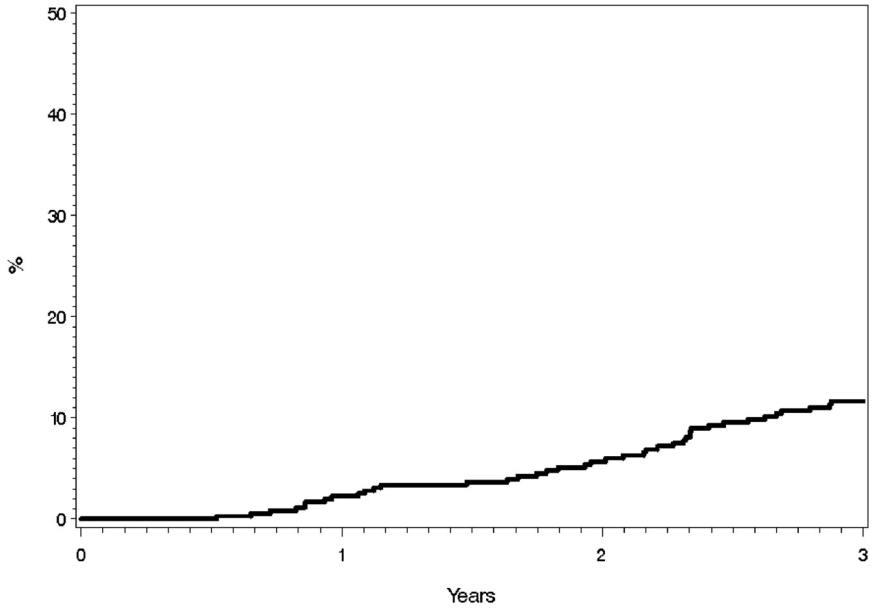

Figure 1. Cumulative probability of development of heart failure by Kaplan-Meier.

data were recorded for all cardiac hospitalizations during the follow-up period. A cardiac hospitalization was defined as a hospitalization during which any of the following were primary discharge diagnoses: heart failure, arrhythmias, valvular pathologies, coronary artery disease, and acute coronary syndromes. A manual review of the medical record was carried out to confirm the primary discharge diagnosis.

The beginning and end of follow-up were the inclusion echocardiogram and June 30, 2009, respectively. The primary end point was development of HF. The secondary end points were development of AF, cardiac hospitalization, and all-cause mortality. In addition, an analysis was completed for the composite end point of heart failure or death due to any cause.

Study Design

The study was retrospective in design since all events (exposures and outcomes) occurred before the start of the study period. The end of follow-up was June 30, 2009.

Statistical Analysis

Overall summaries are presented as means and standard deviations for continuous variables. Categorical variables are summarized as percentages. The cumulative probability of HF, AF, cardiac hospitalization, and death outcomes were estimated using the Kaplan-Meier method. Potential risk factors for these end points were evaluated using Cox proportional hazards models. The multivariable models were selected using a stepwise selection method. Only variables in the model that had a probability value of <0.10 were included in the final model. In addition, for those patients who had HF, we used a paired *t* test to compare laboratory and echocardiographic parameters at the time of inclusion to those closest in time to HF diagnosis.

Results

Baseline Characteristics

Three hundred eighty-eight patients were eligible and included. Mean follow-up was 3.9 years. Baseline clinical characteristics, cardiovascular comorbidities and risk factors, laboratories, and inclusion echocardiogram information are reported in Table 1. Mean age was 67.1 years (SD, 12.4) and there was a female preponderance (57%). Cardiovascular diseases were prevalent: hypertension, 87%; coronary artery disease, 52%; history of myocardial infarction, 24%; and peripheral vascular disease, 11%. Cardiovascular disease risk factors were also prevalent: hyperlipidemia, 76%; estimated GFR <60 mL/min per 1.73 m^2, 34%; and diabetes mellitus, 30%. On the inclusion echocardiogram, the mean EF was 63.6% (SD 6.1); 368 patients (94.8%) had grade 2 DD, 18 (4.64%) had grade 3 DD, and 2 (0.52%) had grade 4 DD. RVSP was elevated at a mean of 37.5 mm Hg (SD 11.9), and the mean LAV index was 41.5 (SD 12.1).

Development of HF

Fifty-one patients developed HF. The 1-, 2-, and 3-year cumulative probabilities for development of HF were 2.2%, 5.7%, and 11.6%, respectively (Figure 1). Univariable analysis (Table 2) showed that age, E/e′ ratio, E/A ratio, RVSP, and GFR <60 mL/min/1.73m^2 were significantly associated with the development of HF. Multivariable analysis (Table 3) showed that age, RVSP, and GFR <60 mL/min per 1.73 m^2 were independently associated with the development of HF. Furthermore, for every 1-U increase in the plasma creatinine, the hazard of developing HF increased by 26% (hazard ratio [HR]$=1.26$, 95% confidence interval [CI]$=1.08–1.47$; $P=0.0039$).

We also wished to address whether the risk factors for the development of HF were equally predictive in the absence of diastolic abnormalities. Therefore, we included the Doppler E/e′ ratio, E/A ratio, LA volume index, and deceleration time in our multivariable analysis. Even after adjusting for E/e′ ratio, E/A ratio, LA volume index, and deceleration time, we found that age, RSVP, and GFR <60 mL/min per 1.73 m^2 remained independently associated with the development of HF in the multivariable analysis.

Of the 51 patients who had HF, 33 (65%) had a subsequent echocardiogram after the inclusion echocardiogram. In this repeat echocardiogram there were no significant changes in EF, DD grade, E/e′, E/A, DT, or RVSP.

Development of AF

Fifty-two patients developed AF. The 1-, 2-, and 3-year cumulative probabilities for development of AF were 8.0%,

Table 2. Univariable Analysis

Outcome	HR	95% CI	*P* Value
Development of heart failure			
Age	1.067	1.035–1.100	<0.001
E/e′ ratio	1.063	1.021–1.106	0.003
E/A ratio	1.327	1.049–1.680	0.019
RVSP	1.037	1.025–1.050	<0.001
GFR<60 mL/min per 1.73 m^2	2.779	1.597–4.838	<0.001
Development of atrial fibrillation			
Age	1.065	1.033–1.097	<0.001
Ejection fraction	1.052	1.003–1.102	0.036
DD grade	2.213	1.148–4.264	0.018
E/A ratio	1.413	1.133–1.762	0.002
RVSP	1.020	1.003–1.038	0.022
GFR <60 mL/min per 1.73 m^2	1.805	1.048–3.110	0.033
Cardiac hospitalization			
Age	1.021	1.001–1.042	0.039
LAV index	1.018	1.000–1.036	0.047
CAD	3.401	2.010–5.754	<0.001
COPD	1.952	1.165–3.271	0.011
HTN	2.840	1.039–7.763	0.042
MI	3.373	2.168–5.249	<0.001
PVD	2.663	1.574–4.505	<0.001
Hyperlipidemia	2.079	1.099–3.931	0.024
Mortality			
Age	1.069	1.036–1.104	<0.001
BMI	0.927	0.880–0.977	0.005
LAV index	1.020	1.002–1.038	0.029
COPD	1.883	1.003–3.535	0.049
CVA	2.243	1.241–4.053	0.007
Hemoglobin	0.692	0.527–0.909	0.008
Hematocrit	0.883	0.803–0.970	0.009
Composite end point of heart failure or death			
Age	1.066	1.042–1.089	<0.001
Female sex	1.564	1.026–2.384	0.038
E/e′ ratio	1.034	1.001–1.069	0.043
RVSP	1.027	1.015–1.039	<0.001
CVA	2.033	1.312–3.150	0.001
GFR <60 mL/min per 1.73 m^2	2.219	1.496–3.292	<0.001
BUN	1.013	1.002–1.025	0.027

HR indicates hazard ratio; CI, confidence interval; E, early component of mitral filling; A, atrial component of mitral filling; E/A, ratio of the mitral early (E) and atrial (A) components of the mitral inflow velocity profile; e′, velocity of mitral annulus early diastolic motion; E/e′, ratio of early diastolic mitral inflow velocity and early diastolic mitral annular velocity; RVSP, right ventricular systolic pressure; GFR, glomerular filtration rate; DD, diastolic dysfunction; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; HTN, hypertension; MI, myocardial infarction; PVD, peripheral vascular disease; BMI, body mass index; LAV, left atrial volume; CVA, history of cerebrovascular accident.

14.2%, and 14.5% respectively (Figure 2). Univariable analysis (Table 2) showed that age, EF, DD grade, E/A ratio, RVSP, and GFR <60 mL/min per 1.73 m^2 were significantly associated with the development of AF. Multivariable analysis (Table 3) showed that age, EF, and E/A ratio were independently associated with the development of AF.

Table 3. Multivariable Analysis

Outcome	HR	95% CI	*P* Value
Development of heart failure			
Age	1.075	1.039–1.113	<0.001
RVSP	1.053	1.036–1.071	<0.001
GFR <60 mL/min per 1.73 m^2	2.003	1.122–3.577	0.019
Development of atrial fibrillation			
Age	1.063	1.031–1.096	<0.001
Ejection fraction	1.048	1.000–1.099	0.050
E/A ratio	1.301	1.065–1.588	0.010
Cardiac hospitalization			
CAD	2.066	1.127–3.788	0.019
MI	2.275	1.378–3.758	0.001
PVD	2.033	1.189–3.475	0.010
Mortality			
Age	1.060	1.027–1.094	<0.001
BMI	0.942	0.892–0.995	0.031
LAV index	1.018	0.998–1.037	0.076
Composite end point of heart failure or death			
Age	1.058	1.033–1.083	<0.001
RVSP	1.034	1.019–1.049	<0.001
CVA	1.660	1.048–2.630	0.031
GFR <60 mL/min per 1.73 m^2	1.711	1.135–2.579	0.010

HR indicates hazard ratio; CI, confidence interval; RVSP, right ventricular systolic pressure; GFR, glomerular filtration rate; E, early component of mitral filling; A, atrial component of mitral filling; E/A, ratio of the mitral early (E) and atrial (A) components of the mitral inflow velocity profile; CAD, coronary artery disease; MI, myocardial infarction; PVD, peripheral vascular disease; BMI, body mass index; LAV, left atrial volume; CVA, history of cerebrovascular accident.

Cardiac Hospitalization

Seventy-nine patients had cardiac hospitalizations during the follow-up period. The 1-, 2-, and 3-year cumulative probabilities for cardiac hospitalization were 9.0%, 13.0%, and 17.7%, respectively (Figure 3). Univariable Analysis (Table 2) showed that age, LAV index, coronary artery disease, chronic obstructive pulmonary disease, hypertension, myocardial infarction, PVD (peripheral vascular disease), and hyperlipidemia were significantly associated with the development of a cardiac hospitalization. Multivariable analysis (Table 3) showed that coronary artery disease, myocardial infarction, and PVD were independently associated with the development of a cardiac hospitalization. The most common discharge diagnoses were coronary artery disease (n=26, 33%) and atrial rhythm disorders (n=11, 14%).

Mortality

Fifty-one patients died during the follow-up period. The 1-, 2-, and 3-year cumulative probabilities for all-cause mortality were 5.0%, 8.2%, and 10.1%, respectively (Figure 4). Univariable analysis (Table 2) showed that age, BMI, LAV index, chronic obstructive pulmonary disease, cerebrovascu-

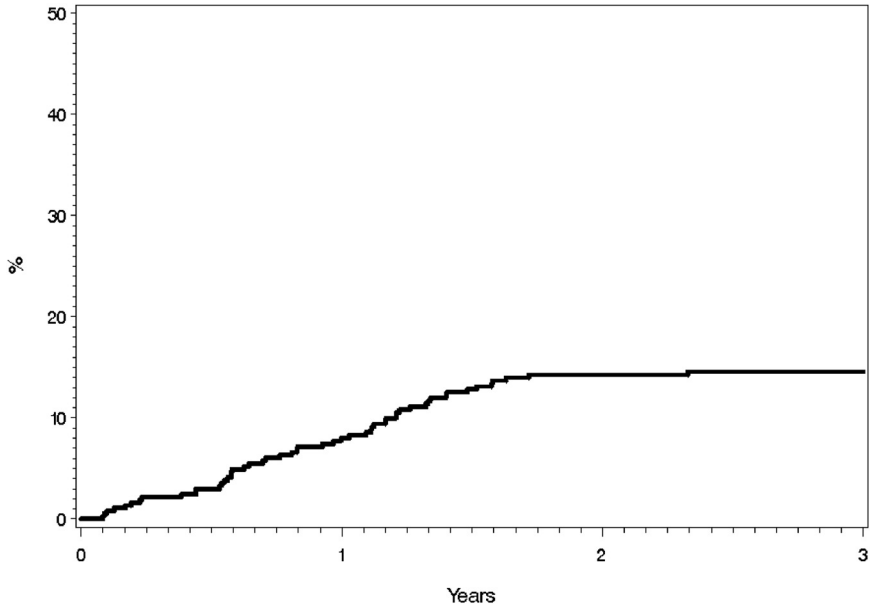

Figure 2. Cumulative probability of development of atrial fibrillation by Kaplan-Meier.

lar accident (CVA), hemoglobin, and hematocrit were significantly associated with mortality. Multivariable analysis (Table 3) showed that age and BMI were independently associated with mortality, and LAV index approached but did not meet significance (probability value, 0.076).

Composite End Point for HF or Death From Any Cause

Ninety-nine patients had the composite end point of HF or death from any cause. The 1-, 2-, and 3-year cumulative probabilities for this composite end point were 7.1%, 12.7%, and 20.0%, respectively (Figure 5). Univariable analysis (Table 2) showed that age, female sex, E/e′ ratio, RVSP, CVA, GFR <60 mL/min per 1.73 m^2, and BUN were significantly associated with the composite end point. Multivariable analysis (Table 3) showed that age, RVSP, CVA, and GFR <60 were independently associated with the composite end point.

Other Composite End Points

Eighty-seven patients had the composite end point of HF or AF, and 113 patients had the composite end point of HF or cardiac hospitalization.

Discussion

The current study confirmed the findings of previous studies that showed that PDD (stage B HF) patients are commonly female, elderly, and have a high prevalence of cardiovascular comorbidities and risk factors. Our study also extended previous PDD studies by demonstrating that the 3-year cumulative probabilities of development of (stage C) HF, cardiac hospitalization, development of AF, and mortality were 11.6%, 17.7%, 14.5%, and 10.1%, respectively. Most importantly, we report for the first time that renal insufficiency, defined as estimated GFR <60 mL/min per 1.73 m^2, was independently associated with the progression of PDD to overt HF (stage C) after adjustment for

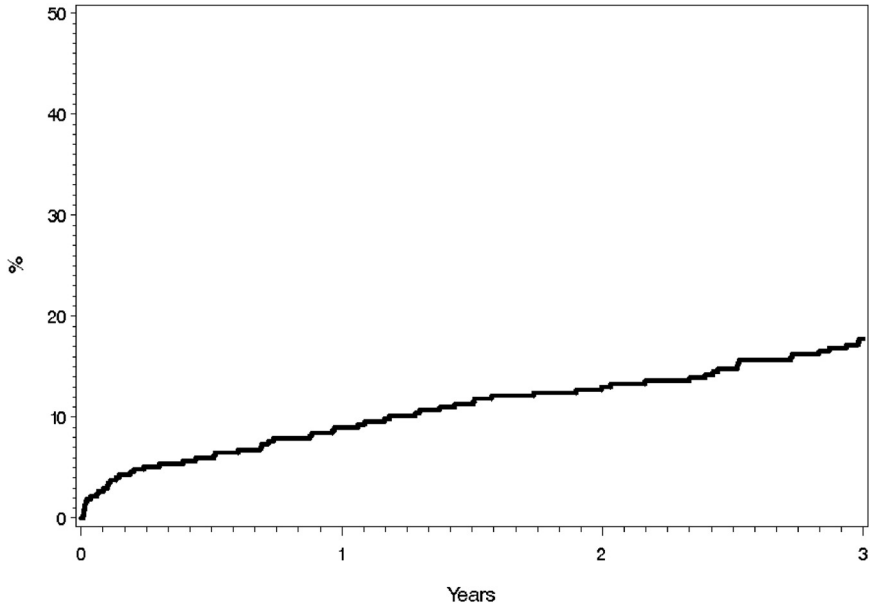

Figure 3. Cumulative probability of cardiac hospitalization by Kaplan-Meier.

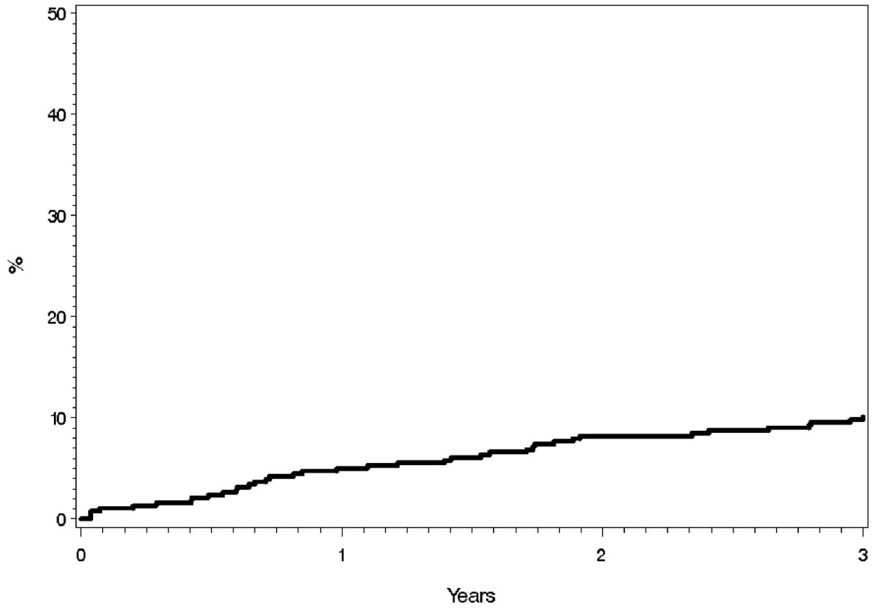

Figure 4. Cumulative probability of all-cause mortality by Kaplan-Meier.

age, sex, BMI, hypertension, coronary disease, EF, left atrial volume, and deceleration time. Furthermore, we found that age, RVSP, CVA, and GFR <60 mL/min per 1.73 m^2 were independently associated with the composite end point of HF or death from any cause.

At present, there are currently no specific therapeutic approaches which have been proven to decrease mortality in patients with HFpEF. Both this and the knowledge that DD is thought to be the major cause of HFpEF (or diastolic heart failure, DHF) highlight the need for a better understanding of DD.[20,21]

One area in which we are starting to have a more clear understanding of DD is its association with renal insufficiency. Previously, it has been shown that renal insufficiency is associated with adverse events in HF patients and in patients with left ventricular systolic dysfunction.[22–24] It has also been specifically reported that there is a high prevalence of renal insufficiency in DD and DHF patients.[4,14,25] However, with the finding of renal insufficiency being independently associated with the progression of PDD to overt HF, our study is, to the best of our knowledge, the first to show a prognostic significance for renal dysfunction in PDD patients. Indeed, we found that for every 1-U increase in the plasma creatinine, the hazard of developing HF increased by 26% (HR=1.26, 95% CI=1.08–1.47; P=0.0039).

In addition to age and renal insufficiency, RVSP was also independently associated with the progression of PDD to (stage C) HF. This complements the work by Lam et al,[26] who found that pulmonary arterial hypertension was present in 83% of HFpEF patients. In addition, it was found that pulmonary artery systolic pressure strongly predicted mortality in HFpEF patients. In combination with the findings from the present study, these data suggest that in addition to optimizing renal function, monitoring for and treating pulmo-

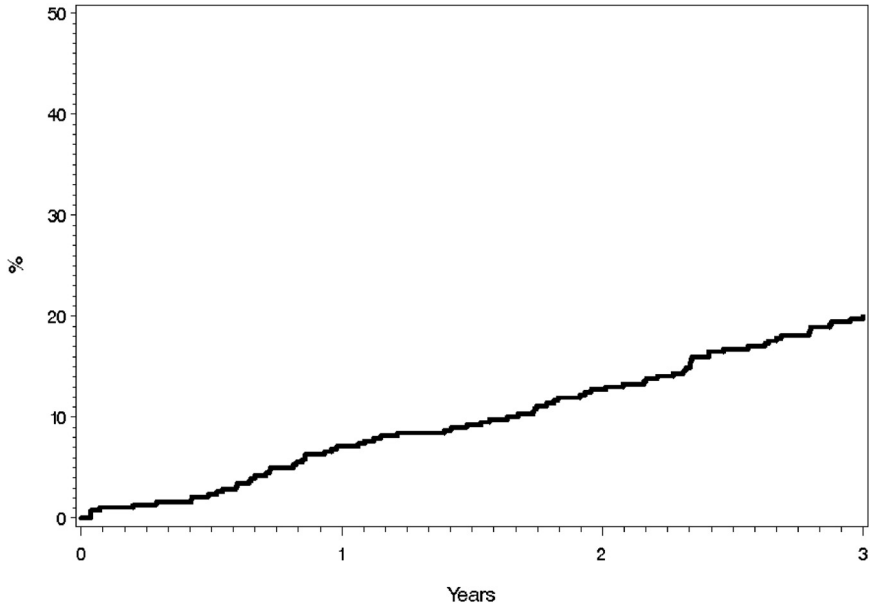

Figure 5. Cumulative probability of heart failure or death by Kaplan-Meier.

nary arterial hypertension may be of particular significance in the management of DD and HFpEF.

In our study, we found a moderate degree of progression from PDD (stage B HF) to symptomatic HF (stage C) with 1-, 2-, and 3-year cumulative probabilities of 2.2%, 5.7%, and 11.6%, respectively. Of the 51 patients who had (stage C) HF in our study, 33 (64.7%) had a subsequent echocardiogram after the inclusion echocardiogram. It is notable that among these 33 patients, there were no significant changes in EF or DD grade indicating that the progression to HF was not simply due to a decline in systolic function or a progression of DD. This observation provides support for the discussion by Achong et al,[27] who have suggested that the division of DD into stages or classes may erroneously imply that progression naturally occurs from one stage to the next. However, our study shows that there is a modest progression from PDD to HF, and further work is needed to delineate the factors that influence this progression.

It has previously been shown by Redfield et al[5] that in the general population, even mild DD conferred an increased risk of mortality compared with subjects with normal diastolic function. Our study further shows that in PDD patients, there is also a moderate risk of death over 3 years with the 1-, 2-, and 3-year cumulative probabilities for all-cause mortality being 5.0%, 8.2%, and 10.1%, respectively. Diastolic dysfunction is also known to be associated with LA enlargement and thereby it increases the risk of AF. In addition, AF is likely to be poorly tolerated in subjects with PDD as the decrease in diastolic filling time and the loss of atrial contraction will result in increased LV end-diastolic-pressure. In our study, a diagnosis of AF was particularly common, being present in 80 patients by the end of follow-up.

Although our work was focused on PDD and did not address the natural history of preclinical systolic dysfunction (PSD) or asymptomatic left ventricular systolic dysfunction (ALVD) or the risk factors associated with progression of PSD or ALVD to symptomatic HF, we note that this has been well characterized previously in 2 key reports.

In a study focused on the natural history of ALVD (or PSD), Wang et al,[28] from the Framingham group, have shown that individuals with ALVD in the community are at high risk of HF and death even when only mild impairment of EF is present. In addition, Dries et al[29] published an elegant retrospective analysis of the Studies of Left Ventricular Dysfunction (SOLVD) Prevention Trial. In multivariate analyses it was shown that moderate renal insufficiency was associated with an increased risk for all-cause mortality in ALVD or PSD patients (relative risk [RR], 1.41; $P<0.001$) which was largely explained by an increased risk for pump-failure death (RR, 1.68; $P<0.007$). In addition, moderate renal insufficiency was also associated with the combined end-point of death or hospitalization for HF (RR, 1.33; $P<0.001$). In summary, it was concluded that moderate renal insufficiency was independently associated with an increased risk for all-cause mortality and HF progression in patients with ALVD or PSD.[29]

Additionally, although our study did not assess risk factors for the development of HF in the general population; this information is nicely summarized by the work of Listerman et al.[30] The authors noted that, among other variables, renal insufficiency has been linked to increased risk for development of heart failure. Additionally, they noted that this risk persisted even after between-group differences in other risk factors such as coronary artery disease were taken into account.

Furthermore, Dhingra et al[31] recently studied the relationship between chronic kidney disease and nonfatal HF and cardiovascular death. They found that chronic kidney disease, even in absence of diabetes and hypertension at baseline, is associated with a higher risk of development of HF and the combined end point of cardiovascular death/HF in men.

By reflecting on these previous findings together with the findings of our own study, we see that in PDD, PSD (or ALVD), and, in the general population, renal function, is an important prognostic indicator.

Limitations

The study was retrospective, and our data relied heavily on the International Classification of Disease-9th revision coding variables to define HF. Although these codes have been validated as a diagnostic and research tool in Olmsted County, MN, they do allow for potential bias. Also, because the majority of our patients had grade 2 DD, this could certainly have impaired the analysis of echocardiography data as predictors of outcomes. In addition, the patients were not recruited from the community but were clinically referred for echocardiography by their primary physicians, which may decrease the generalizability of the results. Also, although the diversity in Olmsted County is increasing, per the 2000 census, the characteristics of the Olmsted County population are similar to those of US whites, and these findings should, therefore, be examined in other racial and ethnic groups.[16,32] Additionally, we do not know if the risk factors for HF that we identified in PDD patients are also risk factors for the future progression of patients without PDD.

Conclusions

In this population-based study, our findings are consistent with previous studies that show that PDD (stage B HF) patients are commonly female, elderly, and have a high prevalence of cardiovascular comorbidities and risk factors. Our study also showed a modest degree of progression from PDD to symptomatic HF (stage C) over 3 years. In addition, by showing that renal insufficiency is independently associated with the progression of PDD to overt HF, our study is, to the best of our knowledge, the first to show a prognostic significance for renal dysfunction in PDD patients.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Preclinical diastolic dysfunction (PDD) (stage B heart failure [HF]) is an entity that remains poorly understood yet has clear clinical significance. It has been shown that PDD is prevalent even among patients with normal systolic function and there is a clear progression from PDD to symptoms including dyspnea, edema, and fatigue. In addition, it has been previously shown that in the general population even mild diastolic dysfunction confers an increased risk of mortality compared with subjects with normal diastolic function. The objectives of our study were to determine the clinical phenotype and natural history of PDD and to identify clinical characteristics that could predict the progression to symptomatic HF. This population-based study demonstrated that in PDD, there was a moderate degree of progression to symptomatic (stage C) HF over 3 years, and renal dysfunction was associated with this progression independent of age, sex, hypertension, coronary disease, and ejection fraction.