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Hospitalizations Due to Unstable Angina Pectoris in Diastolic and Systolic Heart Failure

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Abstract

Patients with diastolic heart failure (HF) i.e. clinical HF with normal or near normal left ventricular ejection fraction (LVEF) may experience unstable angina pectoris (UAP) due to epicardial atherosclerotic coronary artery disease (CAD) and/or to subendocardial ischemia, even in the absence of CAD. However, the risk of UAP among ambulatory diastolic HF patients has not been well studied. We examined incident hospitalizations due to UAP among 916 diastolic HF (LVEF >45%) patients without significant valvular heart disease and 6800 systolic HF (LVEF ≤45%) patients in the Digitalis Investigation Group trial. During a 38-month median follow-up, 12% (797/6,800) of systolic HF patients (incidence rate, 435/10,000 person-years) and 15% (138/916) of diastolic HF patients (incidence rate, 536/10,000 person-years) were hospitalized for UAP (adjusted hazard ratio for diastolic HF, 1.22; 95% confidence interval, 1.02–1.47; p=0.032). There was a graded increase in incident hospital admissions for UAP with increasing LVEF. Hospitalizations for UAP occurred in 11% (520/4,808; incidence rate, 407/10,000 person-years), 14% (355/2556; incidence rate, 496/10,000 person-years) and 17% (60/352; incidence rate, 613/10,000 person-years) of HF patients, respectively, with LVEF <35%, 35–55%, and >55%. Compared with HF patients with LVEF <35%, the adjusted hazard ratios (95% confidence intervals) for UAP hospitalization in those with LVEF 35–55% and >55% were respectively 1.17 (1.02–1.34; p=0.028) and 1.57 (1.20–2.07; p=0.026). In conclusion, in ambulatory chronic HF patients, higher LVEF was associated with increased risk of

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hospitalizations due to UAP. As in patients with systolic HF, those with diastolic HF should be routinely evaluated for myocardial ischemia and managed accordingly.

Keywords

heart failure; diastolic; systolic; UAP; hospitalization

Diastolic heart failure (HF) is common and often associated with hypertensive heart disease and left ventricular (LV) hypertrophy, which may lead to subendocardial ischemia and unstable angina pectoris (UAP), even in the absence of atherosclerotic coronary artery disease (CAD).[1–7] In addition, among diastolic HF patients with CAD, myocardium is likely to be viable rather than infarcted. Systolic HF patients, on the other hand, may be likely to have less viable myocardium due to prior myocardial infarction and may therefore be at lower risk for UAP.[5,8,9] These observations suggest that the incidence of UAP may be increased in diastolic HF. However, the risk of hospitalizations due to UAP in ambulatory patients with chronic diastolic HF is unknown. The objective of this study, therefore, was to determine the incidence of hospitalization due to UAP in patients with diastolic HF compared to those with systolic HF.

Methods

Study design and patients

This is a post-hoc retrospective analysis of the Digitalis Investigation Group (DIG) trial.[10,11] Of 7788 participants in the DIG trial, 6800 had systolic HF (LVEF ≤45%) and 988 had diastolic HF (LVEF >45%). Of the 988 diastolic HF patients, 72 had valvular heart disease as the primary etiology of their HF and were excluded from this analysis. Most patients were receiving angiotensin-converting enzyme inhibitors and diuretics. Data on beta-blocker use were not collected. However, many patients had prior myocardial infarction[11] and may have been receiving beta blockers for this indication.[12,13]

Assessment of left ventricular ejection fraction

LV ejection fraction (LVEF) was measured upon enrollment into the DIG trial. An LVEF obtained during the 6 months prior to randomization was accepted if the patient remained stable during that period.[14] LVEF was assessed using two-dimensional echocardiography, radionuclide ventriculography or contrast left ventriculography, without core laboratory adjudication. When more than one technique was used to measure LVEF, results of angiographic or radionuclide measurements were given priority over those from echocardiography.

Outcomes

Hospitalization due to UAP was a pre-specified secondary outcome in the DIG trial and was the primary outcome for this analysis. The diagnoses leading to hospitalizations were classified by DIG investigators but were not centrally adjudicated. Vital status was collected up to December 31, 1995 and was ascertained for 99% of the patients.

Statistical analysis

We calculated incidence rates for UAP hospitalization for patients with systolic and diastolic HF, and used Kaplan-Meier and bivariate and multivariable Cox regression analyses to estimate the association of diastolic HF with hospitalization due to UAP. To test if there was a graded relationship between LVEF and UAP hospitalization, we categorized patients into three LVEF groups: <35%, 35–55% and >55% and repeated the above analyses. We also repeated our analysis using LVEF as a continuous variable. To assess for heterogeneity in the

association between LVEF and UAP hospitalization, we conducted subgroup analyses using multivariable Cox regression and tested for first-order interactions. All statistical tests were evaluated using a two-tailed 95% confidence level, and a p value <0.05 was required to reject the null hypothesis. All data analyses were performed using SPSS version 14.[15]

Results

Baseline patient characteristics are displayed in Table 1. Patients with diastolic HF were older, more likely to be women, and to have hypertensive heart disease. Kaplan-Meier plots for time to first UAP hospitalization are shown in Figure 1. During a median follow-up of 38 months, UAP hospitalizations occurred in 12% (797/6,800) of systolic HF patients (incidence rate, 435/10,000 person-years) and 15% (138/916) of diastolic HF patients (incidence rate, 536/10,000 person-years). Adjusted hazard ratio for UAP hospitalization for diastolic HF, when compared with systolic HF was 1.22 (95% confidence interval, 1.02–1.47; p=0.032; Table 2).

There was a graded increase in hospital admissions due to UAP with increasing LVEF. UAP hospitalizations occurred in 11% (520/4,808), 14% (355/2556) and 17% (60/352) of patients respectively with LVEF <35%, 35–55%, and >55% (Table 2). Incidence rates per 10,000 person-years of follow up were 407, 496, and 613 hospital admissions due to UAP, respectively, in HF patients with LVEF <35%, 35–55%, and >55% (Table 2). Compared to patients with LVEF <35%, the adjusted hazard ratios (95% confidence intervals) for UAP hospitalization for those with LVEF 35–55% and >55% were respectively 1.17 (1.02–1.34; p=0.028) and 1.57 (1.20–2.07; p=0.026). Each percent increase in LVEF was associated with a significant 0.8% increase in the risk of hospitalization for UAP (Table 2).

Associations between other baseline patient characteristics and hospitalization due to UAP are displayed in Table 3. The associations of diastolic HF and hospitalization due to UAP in various subgroups of patients are displayed in Figure 2. There were no significant interactions between LVEF and any of these subgroups.

Discussion

Our data indicate that over half of ambulatory patients with chronic mild to moderate diastolic HF enrolled in the DIG trial had CAD, and that compared with systolic HF patients, those with diastolic HF were at increased risk for hospitalization due to UAP. In addition, female sex, CAD, prior myocardial infarction, current angina, and diabetes were associated with increased UAP hospitalizations. These findings are important because diastolic HF patients may not be routinely evaluated and treated for myocardial ischemia. Furthermore, the prevalence of diastolic HF is expected to increase over the next several decades. Our data suggest that this trend could also lead to an increase in hospitalizations for UAP.

A possible explanation for the increased risk of UAP in diastolic HF patients is that these patients may be more susceptible to myocardial ischemia, in particular subendocardial ischemia.[16–19] Diastolic HF is often associated with concentric LV hypertrophy, which may in turn be associated with relatively inadequate growth of the coronary arteries, reduction in coronary flow reserve, and increases in coronary medial thickness and perivascular fibrosis.[20] The ensuing decreased capillary density and increased capillary to myocyte oxygen diffusion distance make hypertrophied myocardium more susceptible to ischemia, even in the absence of epicardial coronary atherosclerosis or stenosis.[3]

CAD, prior myocardial infarction and baseline angina were significantly associated with increased risk of incident UAP (Table 3). Diastolic HF patients with myocardial ischemia, with or without CAD, may have more viable myocardium than those with systolic HF, thus

predisposing them to an increased risk for ischemia and UAP. A recent report by Nijland et al supports this possibility.[21] In that study, HF patients with prior myocardial infarction who had viable myocardium in the infarct zone experienced more subsequent hospitalizations for UAP than those without viable myocardium (20% vs. 5%, p=0.006). Moreover, myocardial viability was the only predictor of UAP.

Our study has several potential limitations. UAP hospitalizations were not centrally adjudicated. Because beta-blocker use in HF patients has evolved considerably since the DIG trial was completed, the results of our analysis may not be generalizable to contemporary HF patients. However, the likely lower use of beta-blockers by DIG participants, in retrospect, has allowed us to study the association of LVEF with incident UAP in the natural history of HF. Greater use of beta-blockers in today's systolic HF patients might further reduce UAP hospitalizations in this group, resulting in an even wider gap in UAP admissions between systolic and diastolic HF patients. Since CAD was more prevalent in systolic HF patients in the DIG trial, it is possible that more systolic HF patients were receiving beta-blockers, thus accounting for their lower incidence of UAP. However, at the time of the DIG trial, use of beta-blockers in systolic HF patients was low.[22–25] Therefore, our results are unlikely to be explained entirely by a differential use of beta-blockers in systolic and diastolic HF patients. Finally, HF patients in this study were relatively young, predominantly men, and had normal sinus rhythm. The applicability of these findings to elderly HF patients, particularly older women and patients with atrial fibrillation is uncertain.

Over half of all community-dwelling HF patients have normal or near normal LVEF.[4,7,26] Although these patients are often considered less likely to have CAD than those with systolic HF, the true burden of CAD in this population may be underestimated. The findings of the current analysis indicate that diastolic HF patients are at greater risk for hospitalization for UAP than those with systolic HF, and suggest that treatment of CAD in diastolic HF patients could result in fewer hospitalizations for UAP. Prospective studies are needed to test this hypothesis.

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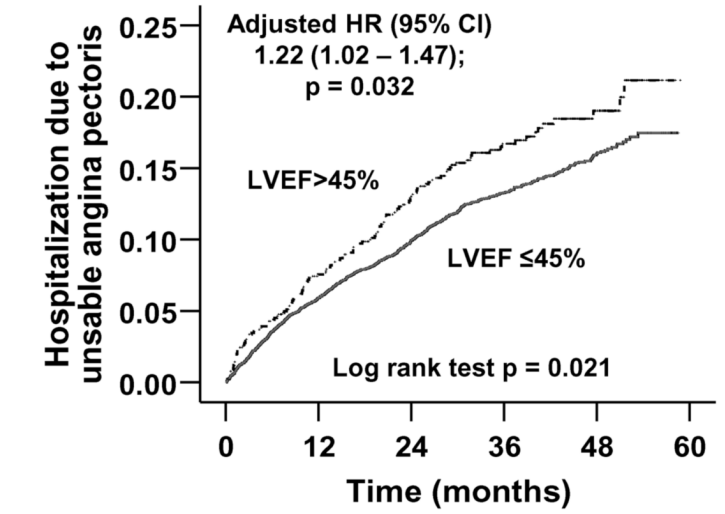
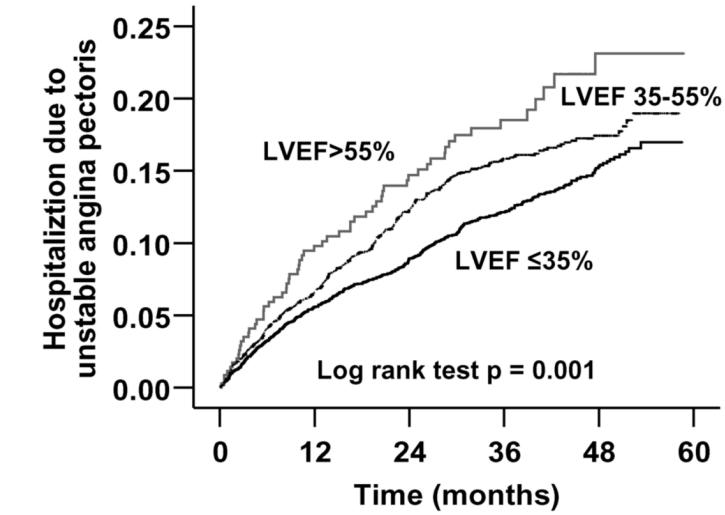


Number at risk					
LVEF ≤45%	6800	5673	4820	3272	1275
LVEF >45%	916	799	702	453	171



Number at risk					
LVEF <35%	4808	3959	3331	2253	886
LVEF 35-55%	2556	2211	1925	1302	495
LVEF >55%	352	302	268	168	66

Figure 1.
Kaplan-Meier plots demonstrating cumulative risk of hospitalizations due to unstable angina pectoris LVEF = left ventricular ejection fraction

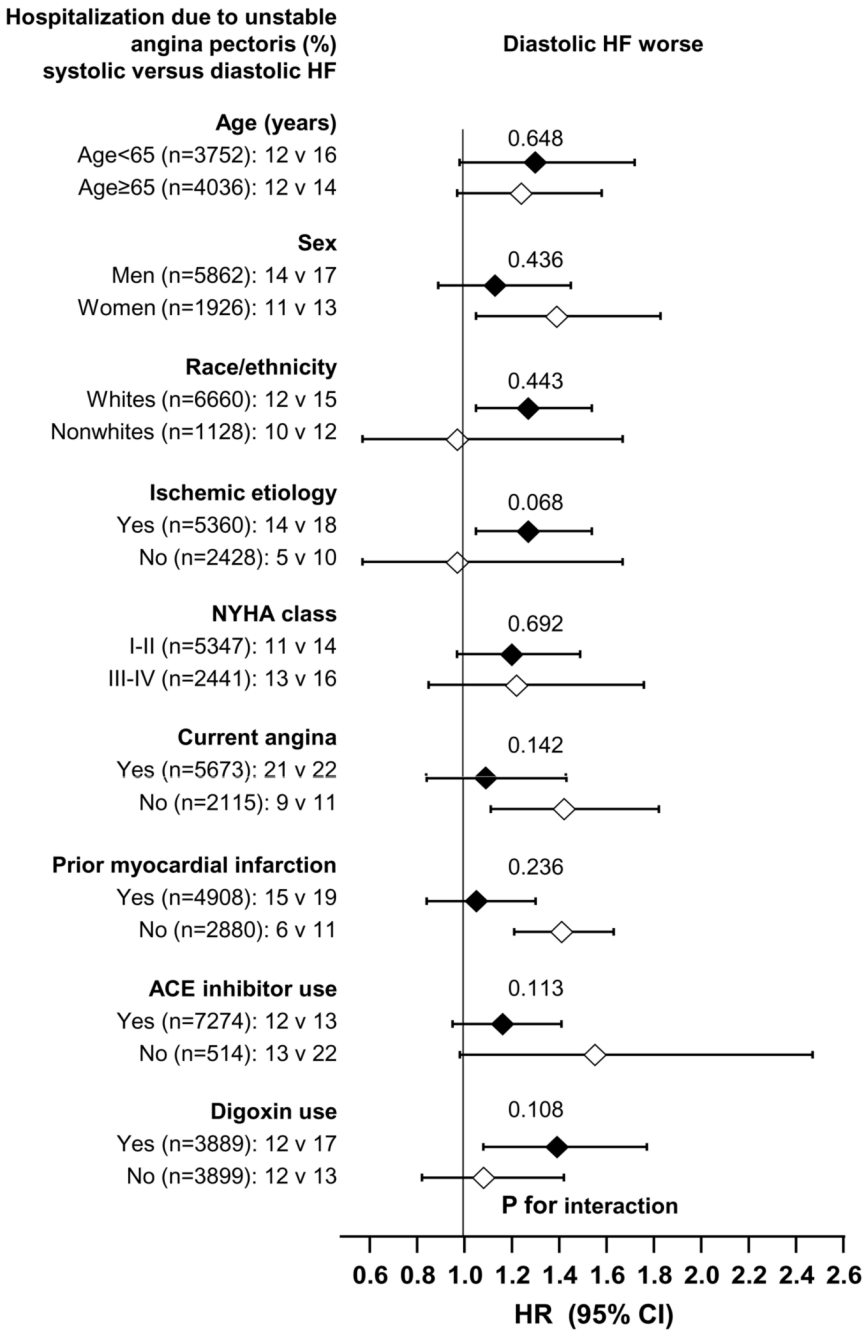


Figure 2.

Hazard ratios (HR) and 95% confidence intervals (CI) for subgroups of patients with diastolic versus systolic heart failure (HF) ACE=angiotensin-converting enzyme; NYHA=New York Heart Association

Table 1

Baseline patient characteristics

Variables	Left ventricular ejection fraction		P
	≤45% (n=6800)	>45% (n=916)	
Age (years)	63.4 (±10.9)	66.6 (±10.2)	<0.0001
Female	1519 (22.3%)	367 (40.1%)	<0.0001
Non-white	991 (14.6%)	130 (14.2%)	0.803
Duration of heart failure (months)	30.2 (±36.8)	26.1 (±33.2)	0.005
Etiology of heart failure			
Coronary ischemic	4803 (70.6%)	557 (60.8%)	
Hypertensive	583 (8.6%)	222 (24.2%)	<0.0001
Others	1414 (20.8%)	137 (15.0%)	
Prior myocardial infarction	4419 (65.0%)	480 (52.4%)	<0.0001
Current angina pectoris	1821 (26.8%)	280 (13.3%)	0.049
Hypertension	3084 (45.4%)	561 (61.2%)	<0.0001
Diabetes mellitus	1933 (28.4%)	281 (30.7%)	0.161
Chronic kidney disease*	3042 (44.7%)	441 (48.1%)	0.052
New York Heart Association functional class			
I	907 (13.3%)	176 (19.5%)	
II	3670 (54.0%)	532 (58.1%)	<0.0001
III–IV	2223 (32.7%)	205 (22.4%)	
Laboratory findings at randomization			
Serum creatinine (mg/dL)	1.28 (±0.37)	1.26 (±0.39)	0.002
Pulmonary congestion (current)	1008 (14.8%)	95 (10.4%)	<0.0001
Cardiothoracic ratio >0.5	4194 (61.7%)	450 (49.1%)	<0.0001
Ejection fraction (%)	28.5 (±8.8)	55.1 (±7.9)	<0.0001
Medications at randomization			
Pre-trial digoxin use	3017 (44.4%)	312 (34.1%)	<0.0001
Digoxin by randomization	3397 (50.0%)	461 (50.3%)	0.833
Angiotensin-converting enzyme inhibitors	6422 (94.4%)	795 (86.8%)	<0.0001
Non-potassium sparing diuretics	5325 (78.3%)	691 (75.4%)	0.051
Nitrates	2898 (42.6%)	374 (40.8%)	0.319

*Chronic kidney disease was defined as glomerular filtration rate <60 ml/1.73 m^2 body surface area

Table 2

Hospitalization due to unstable angina pectoris (UAP) by left ventricular ejection fraction (LVEF)

	Number of events	Total follow up in years	Rate	Rate difference	Hazard ratio (95% confidence interval)	
			Per 10000 person-year of follow up		Unadjusted	Adjusted*
LVEF ≤45% (N=6800)	797	18331	435	Reference	Reference	Reference
LVEF >45% (N=916)	138	2573	536	+101	1.24 (1.03 – 1.48); p=0.022	1.22 (1.02 – 1.47); p=0.032
LVEF <35% (N=4808)	520	12766	407	Reference	Reference	Reference
LVEF 35–55% N=(2556	355	7159	496	+89	(1.07 – 1.40); p=0.003	(1.02 – 1.34); p=0.028
LVEF >55% (N=352)	60	979	613	+206	1.51 (1.16 – 1.97); p=0.003	1.57 (1.20 – 2.07); p=0.026
LVEF as a continuous variable (N=7788)	---	---	---	---	1.009 (1.004 – 1.014); p<0.0001	1.008 (1.002 – 1.013); p=0.005

*Adjusted for age, female sex, non-white race, body mass index, duration and etiology of heart failure, past myocardial infarction, current angina, hypertension, diabetes, pre-trial use of digoxin, digoxin use during trial, use of angiotensin-converting enzyme inhibitors, combined use of hydralazine and nitrates, use of non-potassium sparing diuretics, potassium-sparing diuretics, dyspnea at rest, dyspnea on exertion, activity limitation, New York Heart Association class, elevated jugular venous pressure, third heart sound, pulmonary râles, lower extremity edema, presence of 6 or more symptoms or signs, heart rate, blood pressure (systolic and diastolic), serum creatinine and potassium levels, pulmonary congestion and cardiothoracic ratio >0.5 by chest x-ray.

Table 3

Other predictors of hospitalization due to unstable angina pectoris

Variables	Hazard ratio (95% confidence interval)	
	Unadjusted	Adjusted*
Women	1.34 (1.17 – 1.54); p<0.0001	1.40 (1.22 – 1.62); p<0.0001
Coronary ischemic etiology	2.57 (2.15– 3.07); p<0.0001	1.71 (1.35 – 2.16); p<0.0001
Prior myocardial infarction	2.23 (1.90 – 2.61); p<0.0001	1.49 (1.21 – 1.83); p<0.0001
Current angina	2.60 (2.29 – 2.96); p<0.0001	2.08 (1.82 – 2.37); p<0.0001
Diabetes	1.46 (1.28 – 1.67); p<0.0001	1.32 (1.15 – 1.51); p<0.0001
Prior digoxin use	0.77 (0.68 – 0.88); p<0.0001	0.79 (0.69 – 0.91); p=0.001
Current dyspnea at rest	1.39 (1.20 – 1.61); p<0.0001	1.26 (1.09 – 1.47); p=0.002

* Adjusted for the same covariates as in Table 2