Am J Cardiovasc Dis 2011;1(2):167-175
www.AJCD.us /ISSN: 2160-200X/AJCD1106006

Original Article

Influence of myocardial ischemia on outcomes in patients with systolic versus non-systolic heart failure

Thomas E. Vanhecke[1], Barry A. Franklin[2], Prem Soman[3], Avijit Lahiri[4], Jennifer H. Mieres[5], Tina Sias[6] Dennis A. Calnon[7], David Wolinsky[8], James E. Udelson[9], Peter A. McCullough[10]

[1]Genesys Regional Medical Center/Ascension Health System, Grand Blanc, MI, [2]William Beaumont Hospital, Royal Oak, MI, [3]The University of Pittsburgh Medical Center, Pittsburgh, PA, [4]The Wellington Hospital, London, UK, [5]New York University School of Medicine, New York, NY, [6]Marshall University School of Medicine, Huntington, WV, [7]Mid-West Cardiology Research Foundation, Columbus, OH, [8]Albany Associates in Cardiology, Albany, NY,[9]Tufts Medical Center, Boston MA, [10]St. John Providence Health System/Ascension Health System, Providence Park Heart Institute, Novi, MI, USA.

Received June 30, 2011; accepted July 20, 2011; Epub July 27, 2011; published August 15, 2011

Abstract: Background: Heart failure (HF) is a leading cause of adult hospitalization, morbidity, and mortality. We evaluated the influence of myocardial ischemia and left ventricular ejection fraction (LVEF) on outcomes in patients who were hospitalized with new onset HF. Methods: We prospectively recruited 201 consecutive patients hospitalized for a first episode of HF from 17 medical centers across Europe and North America. All patients received gated single-photon emission computed tomographic testing with standardized study interpretations by trained core laboratory investigators. Predefined data from routine care were collected and aggregated. Computerized scoring was performed at the core laboratory and participants with a summed difference score ≥4 were defined as having myocardial ischemia. Participants were categorized as having systolic heart failure (SHF) (LVEF<40%) or nonsystolic heart failure (NS-HF) (LVEF≥40%). A proportional hazards model was used to assess the impact of clinical predictors on the outcomes of mortality, cardiac rehospitalization and a combined outcome within 2 years of study enrollment. Results: 180 patients (mean age was 65.5 ± 14.6 years and 57.2% male) fulfilled study criteria and were included. Myocardial ischemia was present in 45 (41.2%) patients with SHF and 19 (27.5%) patients with NS-HF (p <0.01). During the follow-up period, 11.1% (n=20) died and 42.2% (n=76) experienced a recurrent hospitalization. Patients with NS-HF and ischemia had the highest (73.7%) event rate compared with the other cohorts (multivariate OR=3.29, 95% CI 1.69-6.42, p=0.001). Conclusions: In new-onset HF, those with NS-HF and myocardial ischemia are at the highest risk for poor outcomes.

Keywords: Heart failure, new onset heart failure, myocardial ischemia, recurrent hospitalizations, outcomes

Introduction

We are in the midst of a chronic heart failure (HF) epidemic with its attendant healthcare expenditures, morbidity, and mortality [1, 2]. An individual born today has a 1 in 5 chance of developing HF within their lifetime.

The clinical and pathophysiological heterogeneity of patients with HF and its effect on patient outcome has limited our progress to understand and treat this common medical condition [3, 4]. For example, the diagnostic evaluation and treatment differs according to the presence or absence of systolic dysfunction [1]. Approximately two thirds of patients with systolic heart failure (SHF) have cardiac ischemia as an etiologic factor; however, the relative determinants of non-systolic heart failure (NS-HF) are less clear [3, 5].

The present study evaluated the influence of myocardial ischemia on outcomes in patients with new-onset HF according to the classification of systolic and non-systolic HF.

Methods

Study population

The IMAGING in HF study was a multinational trial designed to explore the role of single-

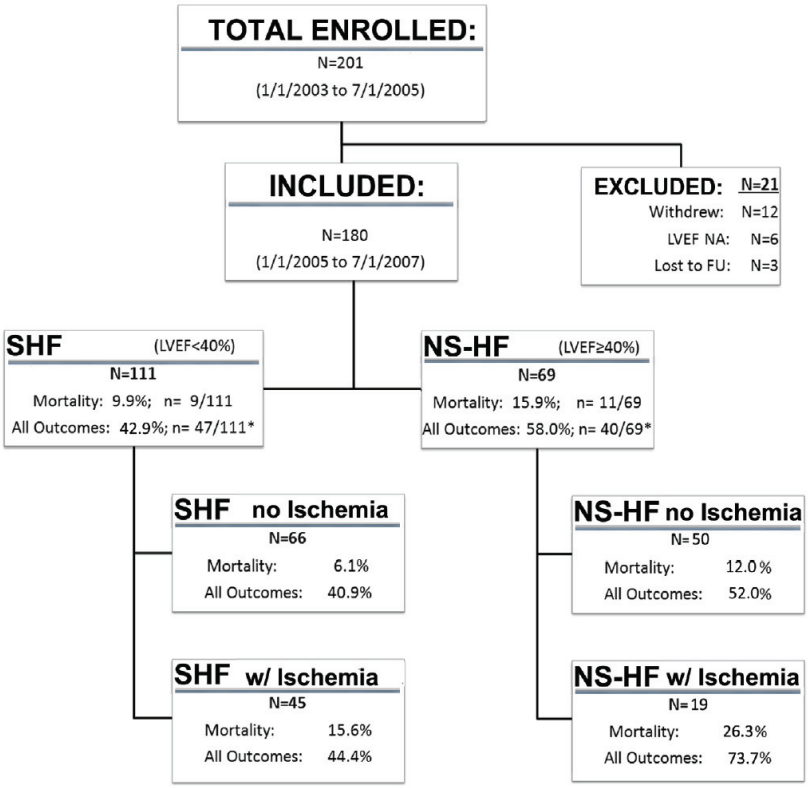

Figure 1. Flow chart of participant inclusion and outcomes stratified by HF cohort and presence/absence of myocardial ischemia. *All outcomes include death, myocardial infarction, or recurrent cardiovascular rehospitalization **left ventricular ejection fraction (LVEF), not available (NA), follow-up (FU), systolic heart failure (SHF), non-systolic heart failure (NS-HF),

photon emission computed tomography (SPECT) myocardial perfusion imaging as an initial diagnostic strategy in patients hospitalized with new -onset HF, as previously described [6]. Consecutive adult patients who presented to the emergency department and admitted as an inpatient with first onset of HF symptoms were prospectively recruited. In brief, a total of 201 patients from 17 sites were enrolled between January 1st 2003 through July 1st 2005. Of these, 180 patients completed the two-year study follow-up and were included in this analysis (**Figure 1**).

Study procedure

Participants were eligible for participation if they were older than 18 years, able to provide informed consent, and hospitalized with their first presentation of HF at participating trial sites. Patients were ineligible if HF was secondary to acute myocardial infarction, or if they had prior hospitalization or treatment for HF, based on their history, medication profile, or medical record. Similarly, patients were excluded if they developed HF due to non-cardiac reasons or if they had any co-morbid condition (advanced cancer) that is associated with a reduced life expectancy.

Participating research site coordinators approached eligible patients and provided relevant information explaining the purposes of the trial and obtained written informed consent. Comprehensive patient demographics, medical history, and cardiac signs and symptoms were documented. Baseline evaluations were performed by study investigators and included physical examination, clinical laboratory tests (serum creatinine, potassium, hemoglobin and blood-urea values) and standard 12-lead electrocardiograms.

Following clinical stabilization, all patients underwent stress/rest Tc99m sestamibi gated SPECT imaging using either 1 or 2-day protocols according to the practice of the respective nuclear laboratory. Data from the initial hospitalization course, including cardiac catheterization, coronary angiography, and echocardiography were recorded in each patient. Upon discharge, patients were contacted at 6-month intervals by study coordinators to determine vital status, rehospitalization and clinical events.

The study was approved by the Institutional Review Boards of all participating IMAGING in HF trial centers. Informed consent was obtained from all patients, followed by a detailed assessment of demographic characteristics, medical history, and physical examination performed by the physician investigator at each respective study location. The clinical diagnosis of HF was established by the presence of 2 major or 1

major and 2 minor Framingham criteria [7]. Chest radiographic imaging was performed on each patient as part of routine clinical care during the initial hospitalization. Radiographic interpretations at each respective institution were used to define the presence or absence of radiographic cardiomegaly, vascular congestion and pulmonary edema.

Measurement of LV function

Although HF has been traditionally classified as 'diastolic' or 'systolic'; this nomenclature has become controversial [7]. In the present study, we used 'nonsystolic HF' (NS-HF) rather than 'diastolic HF' because this terminology has been adopted by the American College of Cardiology/ American Heart Association [7] and European Society of Cardiology [8].

Of the total population, LVEF measurement data were available in most participants from both gated single-photon emission computed tomography myocardial perfusion imaging (SPECT-MPI) and transthoracic echocardiography during the index hospitalization.

SPECT– myocardial perfusion imaging

Stress and rest SPECT- myocardial perfusion imaging with technetium-99m sestamibi was performed using either a 1-day rest –stress or 2 -day protocol according to the methodology used by the participating laboratory. Exercise or pharmacological stress testing was based on standard clinical indications at the discretion of the treating physician. Gating was performed on the high dose, post-stress acquisition, and the imaging results were made available to the attending physicians.

Myocardial perfusion data were analyzed in a core laboratory by blinded investigators as previously described [6]. Summed stress scores, summed rest scores and summed difference scores (SDS) were calculated on each patient. Left ventricular volumes and ejection fraction were analyzed using standard automated software (Cedars-Sinai QGS). Based on previously validated criteria, a SDS ≥ 4 signified the presence of myocardial ischemia [9].

Primary outcomes

The primary composite outcome included the occurrence of death, myocardial infarction, or subsequent cardiovascular rehospitalization as preformulated by the prospective study design. Events were recorded by research clinicians and analyzed with data from the core laboratory in relation to presence/absence of myocardial ischemia and presence/absence of impaired systolic performance at baseline.

Statistical analysis

For the total population and each HF cohort, clinical, physical exam, laboratory and imaging variables were collected and expressed as mean $\pm$ standard deviation (SD) or counts with proportions as appropriate. Univariate comparisons were made with Student's t-test, Fishers Exact test, Chi-square, and Chi-square for trend as appropriate. A p-value < 0.05 was considered statistically significant. Cox proportional hazard model was applied for the composite outcome and the individual events of all-cause mortality, rehospitalization, and/or rehospitalization and mortality within the 2-years of study follow-up. Variables in the multivariate model included the primary analytic groups or baseline variables with $p < 0.05$ from the univariate analysis. Using data derived from the univariate/multivariate analysis, a second multivariate analysis was performed. In this analysis, the cohort with the least likelihood of future events was assigned as the reference category and multinominal regression analysis was performed with forced entry of presence/absence of ischemia and presence/absence of SHF. Goodness of fit chi-square statistics with Hosmer-Lemeshow testing were used to evaluate the performance of each multivariate model. Kaplan-Meier survival curves were generated and stratified by patient cohorts, based on the presence of myocardial ischemia and LVEF. Statistical analysis was performed with SPSS software, version 16.0, Chicago, IL, USA.

Results

Patient distribution and follow-up

The study population included 201 patients who fulfilled initial presentation criteria and were consented to participate. Twelve patients voluntarily withdrew from the study and three patients were lost to follow-up. Six patients did not have assessment of LVEF upon initial hospitalization and were excluded from analysis. The remaining 180 patients met the study requirements and had complete 2-year study follow-up

Table 1. Baseline characteristics, left ventricular ejection fraction, presence of myocardial ischemia and outcomes of participants by cohort.

N=180	TOTAL (180)	SHF, no ischemia (66)	SHF, ischemia (45)	NS-HF, no ischemia (50)	NS-HF, ischemia (19)	P-Value
Patient factors (% [N])						
Male Gender	57.2% (103)	72.7% (48)	64.4% (29)	40.0% (20)	31.6% (6)	<0.01
Age (years) ±SD	65.5 (14.6)	63.1 (13.7)	64.2 (15.4)	67.4 (15.5)	69.6 (14.7)	0.23
Age ≥ 65 years	54.4% (98)	47.0% (31)	51.1% (23)	62.0% (31)	68.4% (13)	0.23
Body Mass Index (kg/m^2) ±SD	28.2 (6.4)	27.6 (5.4)	28.3 (6.7)	28.0 (6.4)	30.9 (7.5)	0.15
Medical History (% [N])						
Previous MI	26.7% (48)	30.3% (20)	28.9% (13)	22.0% (11)	21.1% (4)	0.71
Previous stroke	8.9% (16)	9.1% (6)	11.1% (5)	2.0% (1)	21.1% (4)	0.08
Hypertension	57.2% (103)	60.6% (40)	44.4% (20)	62.0% (31)	63.2% (12)	0.26
Diabetes	32.8% (59)	30.3% (20)	35.6% (16)	30.0% (15)	42.1% (8)	0.74
Current smoker	22.2% (40)	28.8% (19)	22.2% (10)	18.0% (9)	10.5% (2)	0.30
Hyperlipidemia	27.8% (50)	19.7% (13)	31.1% (14)	28.0% (14)	47.4% (9)	0.11
Family History of CAD	36.1% (65)	34.8% (23)	35.6% (16)	28.0% (14)	63.2% (12)	0.06
Chronic angina	11.7% (21)	12.1% (8)	15.6% (7)	10.0% (5)	5.6% (1)	0.70
Arrhythmias	16.1% (29)	16.7% (11)	8.9% (4)	24.0% (12)	10.5% (2)	0.22
Prior PCI	12.8% (23)	10.6% (7)	17.8% (8)	10.0% (5)	15.8% (3)	0.62
Prior CABG	12.8% (23)	16.7% (11)	13.3% (6)	10.0% (5)	5.3% (1)	0.53
Prior PVD	8.3% (15)	10.6% (7)	6.7% (3)	6.0% (3)	10.5% (2)	0.79
Prior CAD	33.0% (66)	37.9% (25)	33.3% (15)	28.0% \(14)	31.6% (6)	0.74
LVEF and Ischemia (% [N])						
Mean LVEF % (±SD)	35.2 (16.3)	24.3 (7.9)	24.5 (8.2)	52.6 (9.7)	52.7 (10.2)	<0.01
SDS Score	2.89 (±4.92)	0.15 (±0.61)	8.33 (±5.42)	-0.06 (±1.2)	7.32 (±4.16)	<0.01

* Left ventricular ejection fraction (LVEF), kilograms (kg), systolic heart failure (SHF), non-systolic heart failure (NS-HF), standard deviation (SD), percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG), peripheral vascular disease (PVD), coronary artery disease (CAD), summed difference score (SDS)
** Myocardial ischemia is defined as having a summed difference score on SPECT perfusion imaging as ≥4.
***Chi-square for trend or ANOVA

data (**Figure 1**). The baseline characteristics for the overall study group (n=180) (and subgroups as discussed below) are shown in **Table 1**. The mean age was 65.5 ± 14.6 years, 57.2% (n = 103) were male. The mean body-mass index was 28.2 ± 6.4 kg/m^2.

In the study population, the prevalence of malignant arrhythmias was 16.1% (n = 29), diabetes 32.8% (n = 59), chronic angina 11.7% (n = 21),

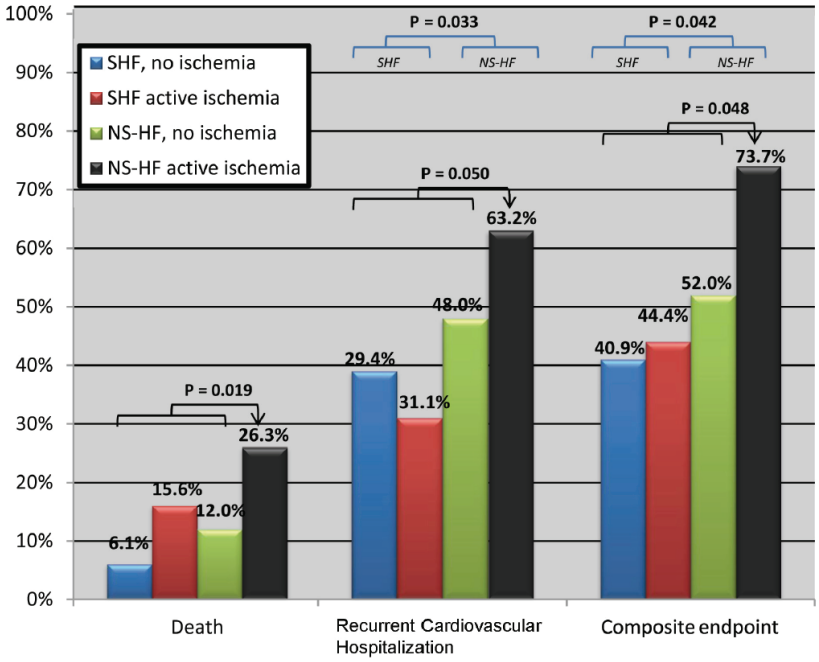

Figure 2. Differences in study endpoints between cohorts with and without myocardial ischemia and presence of SHF or NS-HF. *Systolic heart failure (SHF), nonsystolic heart failure (NS-HF), left ventricular ejection fraction (LVEF) **No statistical difference (P>0.05) for all other comparisons between individual cohorts with univariate analysis.

current smokers 22.2% (n = 40), and family history of coronary artery disease (CAD) 33.0% (n = 60), history of hypertension 57.2% (n = 103) or hyperlipidemia 27.8% (n = 50). Prior myocardial infarction and prior stroke were present in 26.7% (n =48) and 8.9% (n =16), respectively, of the total study population.

Heart failure symptoms and physical exam findings

Mean resting systolic blood pressure of study participants was 136.9 mmHg (SD ± 23.9; range = 88 to 215 mmHg), mean diastolic blood pressure was 80.6 mmHg (SD ± 15.4; range = 49 to 165 mmHg), and mean heart rate was 83.5 bpm (SD ± 18.1; range = 49 to 170 bpm). Diabetes, dyslipidemia, and a family history of CAD were all more common in those with ischemic NS-HF. Prior coronary revascularization was similar across the groups. All patients fulfilled Framingham diagnostic criteria for HF and the distribution of various criteria are shown in **Table 1**.

Prevalence of myocardial ischemia, LVEF and assignment to HF cohort

Left ventricular ejection fraction was measured by both SPECT and transthoracic echocardiography in 86.0% (N=155) of the total population. Twelve participants (6.5%) had LVEF determined by gated SPECT alone, and 10.2% (N=19) had transthoracic echocardiography alone. Mean LVEF from gated SPECT-MPI was 35.3% (SD ±16.3). Mean LVEF from those with transthoracic echocardiography was 37.2% (SD ±16.8). The composite LVEF of the 180 patients was 35.2% (SD ±16.3). Therefore, 61.6% (N=111) of the participants had LVEF < 40% and were assigned to the SHF cohort and 38.3% (N=69) had LVEF ≥ 40% and were classified as the NS-HF cohort.

Myocardial ischemia (SDS score ≥4) was present in 45 (40.5%) patients with SHF and 19 (27.5%) patients with NS-HF (p <0.01). Based on LVEF and the presence of myocardial ischemia, patients were divided into 4 cohorts: SHF without ischemia, (N=66; 36.6% of total) SHF with ischemia (N=45; 25.0% of total), NS-HF without ischemia (N=50; 27.7% of total) and NS-HF with ischemia (N=19; 10.5% of total).

Death, myocardial infarction, cardiovascular rehospitalization and composite endpoint

During the 2-year follow-up period, there were 20 (11.1%) fatalities, 6 participants (3.3%) experienced a myocardial infarction, 76 participants (42.2%) underwent recurrent cardiovascular hospitalization and 87 participants (48.3%) experienced a combined outcome (**Figure 1**, **Table 1**) Participants in the NS-HF cohort were more likely to experience a recurrent cardiovascular hospitalization or composite endpoint compared to those with SHF (**Figure 2**).

The prevalence of myocardial ischemia in each

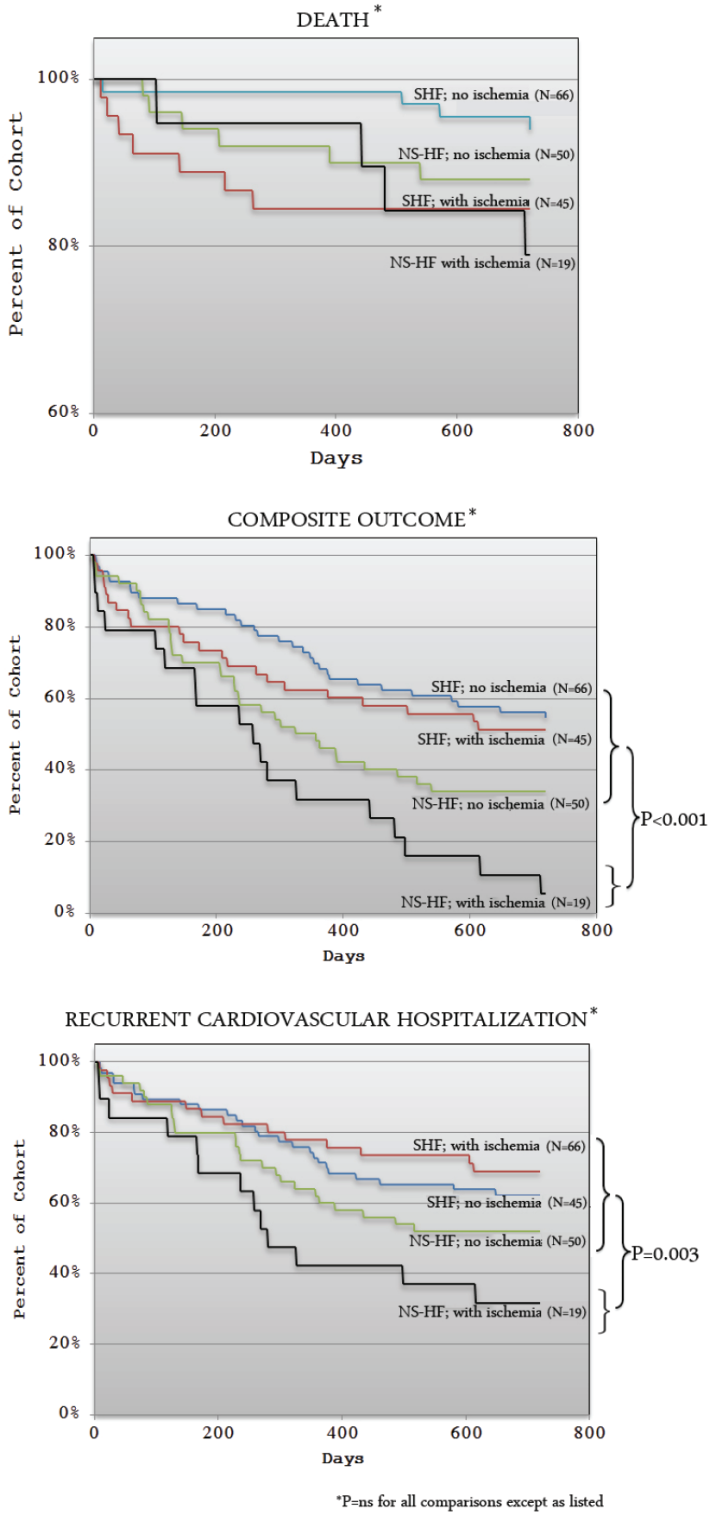

Figure 3. Survival analysis of study population by HF cohort and presence of myocardial ischemia. ** P-value represents significant increased independent risk of study endpoint occurrence by presence of NS-HF and myocardial ischemia with Cox survival regression multivariate analysis.

category of HF is described in **Figure 1**. The mortality rate in the SHF without ischemia cohort was not significantly different than those with SHF and myocardial ischemia (6.1% vs. 15.6%, p= 0.10). Similarly, for the participants with NS-HF, there was no difference in those with versus those without myocardial ischemia (26.3% vs. 12.0%; p=0.15) (**Figure 1**). However, when compared to the SHF cohorts, with and without myocardial ischemia, patients with NS-HF demonstrated a higher mortality rate, recurrent cardiovascular hospitalizations and adverse composite outcomes (**Figure 3**).

Multivariate Predictors of Outcomes

Stepwise multivariate analysis was performed on factors associated with outcomes upon univariate analysis. The presence of NS-HF with ischemia was strongly predictive of death (O.R. 3.26 [95% C.I. 1.03-10; p=0.044], recurrent cardiovascular hospitalization (O.R. 2.62 [95% C.I. 1.38-4.97; p=0.003] and the composite endpoint of death and recurrent cardiovascular hospitalization (O.R. 3.29 [95% C.I. 1.69-6.42; p=0.001]. For comparative purposes, the cohort with the least likelihood of adverse outcomes (SHF without ischemia cohort) was used as the referent group. A second multivariate analysis was performed and the remaining likelihood for each outcome in the other 3 cohorts is shown in **Table 2.**

Discussion

We found in patients with first hospitalizations for HF, that myocardial ischemia was more common in systolic compared to non-systolic HF. However, the cohort with NS-HF and myocardial ischemia experienced significantly higher event rates and worse outcomes over the two-year follow-up period when compared to the other cohorts. Over the past 2 decades CAD has emerged as the predominant cause of HF in Western

Table 2. Multinominal regression analysis of factors predictive of death, recurrent cardiovascular hospitalization and composite outcome based on presence/absence of ischemia and HF cohort LVEF category (N=180).

	NS-HF	SHF
Ischemia	Composite: OR=4.04; (95% CI 1.03-12.56), p=0.016 Rehospitalization: OR=2.64; (95% CI 0.92-7.57), p=0.072 Death: OR=5.54; (95% CI 1.32-23.30), p=0.020	Composite: OR=1.16; (95% CI 0.54-2.49), p=0.711 Rehospitalization: OR=0.70; (95% CI 0.31-1.55), p=0.373 Death: OR=2.85; (95% CI 0.78-10.41), p=0.112
No Ischemia	Composite: OR=1.57; (95% CI 0.75-3.28) p=0.236 Rehospitalization: OR=1.42; (95% CI 0.68-2.99), p=0.355 Death: OR=2.11; (95% CI 0.56-7.94), p=0.27	Composite: OR=1.0* Rehospitalization: OR=1.0* Death: OR=1.0*

*Reference category is set to O.R. of 1.0; **Odd Ratio (O.R.), confidence interval (C.I.), Systolic heart failure (SHF), non-systolic heart failure (NS-HF)

society [1,10,11]. It appears that CAD and myocardial ischemia are prime causes of NS-HF as well as SHF. Moreover improved investigative tools have now shown that ischemia and CAD are directly attributable to upwards of 60% of cases of new-onset HF [10]. In the present study, we extend these results by confirming that the presence of myocardial ischemia raises the risk of future events (death and rehospitalization) in patients with new onset NS-HF.

To date, our study is the first to provide data on patients with new-onset HF with protocol-driven myocardial perfusion screening using modern stress-gated SPECT. Most large scale registry databases such as the European Heart Failure Survey, Acute Decompensated Heart Failure National Registry (ADHERE), and Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF) do not systematically evaluate HF cases via coronary angiography and/or nuclear imaging studies to accurately assign etiology of HF [12-15]. In addition, most registry reports are comprised of patients with recurrent HF and do not represent patients with a first episode of HF [15].

Our data extend earlier reports that describe first or refractory HF in patients with recent acute coronary syndromes by extent of prior myocardial ischemia [3,16]. Nakata et al. used perfusion parameters by stress-gated perfusion SPECT to identify patients at increased risk of future refractory HF [16]. Stratification of patients based on stress-induced perfusion abnormalities and other clinical features showed that high-risk patients had upt to 17.3 times greater risk compared to patients without ischemia and lower-risk clinical profiles. Although this study included only patients with CAD, our results reflect increased risk in all patients with new-onset HF by severity of stress-induced perfusion defects. Data from the OPTIMIZE registry demonstrated that patients with "ischemia/acute coronary syndromes" as a precipitant of HF had increased 60-90 day post discharge mortality (O.R. 1.52; 1.2-1.93) independent of other risk factors [17].

Our study has major implications for patients with HF and preserved LV function. Almost 1 in 4 patients with NS-HF and myocardial ischemia died and >70% experienced a rehospitalization for HF within the 2-year follow-up. These data suggest that not only should an evaluation for ischemia be undertaken in these patients, but consideration should be given for revascularization and/or and anti-ischemic therapies. In a small trial comprising only 137 patients with LVEF >50%, therapy with hydroxymethylglutaryl-coenzyme A reductase inhibitors significantly reduced long-term mortality (unadjusted hazard ratio (HR) =0.22, 95% CI 0.07-0.64) [18]. Another study of 146 patients with symptomatic HF and preserved LVEF showed that hydroxymethylglutaryl-coenzyme A reductase inhibitors were independently associated with a reduction of all-cause mortality that was apparent within 90 days and persisted beyond the one-year follow-up period [19]. Thus, it is possible that lipid lowering with statins influence the natural his-

tory of NS-HF patients with ischemia. With respect to revascularization, a Canadian registry of patients with a history of HF and with documented CAD suggested improved survival in those with revascularization [20]. D'Egidio et al. [21] examined myocardial hibernation in SHF patients using F-18-fluorodeoxyglucose positron emission tomography imaging. In post hoc analysis, patients with ischemic cardiomyopathy with larger amounts of mismatch were found to have improved outcomes with revascularization [21]. To date, there are no published comparative outcomes data outcome of studies examining the impact of patients with NS-HF and significant myocardial ischemia.

Limitations

Our study has all the limitations of small observational datasets. Approximately 80% of patients hospitalized with HF have a prior diagnosis of HF [12,14]. We enrolled patients with new -onset HF; therefore, our results may not be applicable to patients with recurrent HF. We did not examine diastolic function by transthoracic Doppler echocardiography or gated SPECT imaging methods because reporting of these variables was not standardized across study centers. Although most patients with NS-HF have diastolic HF, not all do, and many patients with SHF also have concomitant diastolic dysfunction [1,13]. We did not measure plasma BNP or NT-proBNP levels. Most importantly, we did not record the approaches for revascularization or ischemic therapy management during the follow -up period, which undoubtedly influenced event rates.

Conclusions

Myocardial ischemia is more common in the initial presentation of systolic compared to NS-HF. Patients with new-onset NS-HF have worse 2-year prognosis than patients with reduced EF (LVEF <40%). Furthermore, the presence of myocardial ischemia in conventionally managed patients with NS-HF is a robust predictor of combined recurrent events and poor survival compared to NS-HF patients without myocardial ischemia.

Disclosures

No authors have relationships with industry or financial conflicts of interest

Acknowledgements

We recognize the participation provided by Drs. George A. Beller, Kenneth Burnham, Laurence Conway, Joseph Wight, Mary N. Walsh, Edouard Daher, and Gary V. Heller.

This study was funded by an unrestricted educational grant from BMS-Medical Imaging, Billerica, MA.

Abbreviations: Heart Failure (HF), Non-Systolic Heart Failure (NS-HF), Systolic Heart Failure (SHF), Left Ventricular Ejection Fraction (LVEF), Single-Photon Emission Computed Tomography (SPECT), Summed Difference Score (SDS)

Address correspondence to: Dr. Thomas E. Vanhecke, Department of Cardiovascular Medicine Genesys Regional Medical Center/Ascension Health System, 1 Genesys Parkway, Grand Blanc, MI 48439 Tel: 248-259-6025 Fax: 248-551-8880 E-mail: tvanhecke@gmail.com

References

[1] Gheorghiade M, Pang PS. Acute heart failure syndromes. J Am Coll Cardiol 2009; 53(7): 557-573.

[2] McCullough PA, Philbin EF, Spertus JA, Kaatz S, Sandberg KR, Weaver WD. Confirmation of a heart failure epidemic: findings from the Resource Utilization Among Congestive Heart Failure (REACH) study. J Am Coll Cardiol 2002; 39(1): 60-69.

[3] Flaherty JD, Bax JJ, De Luca L, Rossi JS, et al. Acute heart failure syndromes in patients with coronary artery disease early assessment and treatment. J Am Coll Cardiol 2009; 53(3): 254-263.

[4] Chinnaiyan KM, Alexander D, McCullough PA. Role of angiotensin II in the evolution of diastolic heart failure. J Clin Hypertens (Greenwich) 2005; 7(12): 740-747.

[5] Chinnaiyan KM, Alexander D, Maddens M, McCullough PA. Curriculum in cardiology: integrated diagnosis and management of diastolic heart failure. Am Heart J 2007; 153(2): 189-200.

[6] Soman P, Lahiri A, Mieres JH, et al. Etiology and pathophysiology of new-onset heart failure: evaluation by myocardial perfusion imaging. J Nucl Cardiol 2009; 16(1): 82-91.

[7] Hunt SA, Abraham WT, Chin MH, et al. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in

Collaboration With the International Society for Heart and Lung Transplantation. J Am Coll Cardiol 2009; 53(15): e1-e90.
[8] Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J 2008; 29(19): 2388-2442.
[9] Bounous EP, Mark DB, Pollock BG, et al. Surgical survival benefits for coronary disease patients with left ventricular dysfunction. Circulation 1988; 78(3 Pt 2): I151-157.
[10] Fox KF, Cowie MR, Wood DA, et al. Coronary artery disease as the cause of incident heart failure in the population. Eur Heart J 2001; 22 (3): 228-236.
[11] Fox KF, Cowie MR, Wood DA, Coats AJ, Poole-Wilson PA, Sutton GC. New perspectives on heart failure due to myocardial ischaemia. Eur Heart J 1999; 20(4): 256-262.
[12] Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. J Am Coll Cardiol 2006; 47(1): 76-84.
[13] Fonarow GC, Stough WG, Abraham WT, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol 2007; 50(8): 768-777.
[14] Cleland JG, Swedberg K, Cohen-Solal A, et al. The Euro Heart Failure Survey of the EURO-HEART survey programme. A survey on the quality of care among patients with heart failure in Europe. The Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The Medicines Evaluation Group Centre for Health Economics University of York. Eur J Heart Fail 2000; 2(2): 123-132.
[15] McMurray JJ, Carson PE, Komajda M, et al. Heart failure with preserved ejection fraction: clinical characteristics of 4133 patients enrolled in the I-PRESERVE trial. Eur J Heart Fail 2008; 10(2): 149-156.
[16] Nakata T, Hashimoto A, Wakabayashi T, Kusuoka H, Nishimura T. Prediction of new-onset refractory congestive heart failure using gated myocardial perfusion SPECT imaging in patients with known or suspected coronary artery disease subanalysis of the J-ACCESS database. JACC Cardiovasc Imaging 2009; 2(12): 1393-1400.
[17] Fonarow GC, Abraham WT, Albert NM, et al. Association between performance measures and clinical outcomes for patients hospitalized with heart failure. JAMA 2007; 297(1): 61-70.
[18] Fukuta H, Sane DC, Brucks S, Little WC. Statin therapy may be associated with lower mortality in patients with diastolic heart failure: a preliminary report. Circulation 2005; 112(3): 357-363.
[19] Roik M, Starczewska MH, Huczek Z, Kochanowski J, Opolski G. Statin therapy and mortality among patients hospitalized with heart failure and preserved left ventricular function--a preliminary report. Acta Cardiol 2008; 63(6): 683-692.
[20] Tsuyuki RT, Shrive FM, Galbraith PD, Knudtson ML, Graham MM. Revascularization in patients with heart failure. CMAJ 2006; 175 (4): 361-365.
[21] D'Egidio G, Nichol G, Williams KA, et al. Increasing benefit from revascularization is associated with increasing amounts of myocardial hibernation: a substudy of the PARR-2 trial. JACC Cardiovasc Imaging 2009; 2(9): 1060-1068.