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Heart failure hospitalization in women with signs and symptoms of ischemia: A report from the women's ischemia syndrome evaluation study

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ABSTRACT

Background: Women with signs and symptoms of ischemia, no obstructive coronary artery disease, and preserved left ventricular ejection fraction enrolled in the National Heart Lung and Blood Institute (NHLBI) sponsored Women's Ischemia Syndrome Evaluation (WISE) study have an unexpectedly high rate of subsequent heart failure (HF) hospitalization. We sought to verify and characterize the HF hospitalizations.
Methods: A retrospective chart review was performed on 223 women with signs and symptoms of ischemia, undergoing coronary angiography for suspected coronary artery disease followed for 6 ± 2.6 years. Data were collected from a single site in the WISE study.
Results: At the time of study enrollment, the women were 57 ± 11 years of age, all had preserved left ventricular ejection fraction, and 81 (36%) had obstructive CAD (defined as >50% stenosis in at least one epicardial artery). Among the 223 patients, 25 (11%) reported HF hospitalizations, of which 14/25 (56%) had recurrent HF hospitalizations (>2 hospitalizations). Medical records were available in 13/25 (52%) women. Left ventricular ejection fraction was measured in all verified cases and was found to be preserved in 12/13 (92%). HF hospitalization was not related to obstructive CAD.
Conclusion: Among women with signs and symptoms of ischemia undergoing coronary angiography for suspected obstructive CAD, HF hospitalization at 6-year follow-up was predominantly characterized by a preserved ejection fraction and not associated with obstructive CAD.

1. Introduction

Heart failure (HF) is one of the leading causes for hospital admission, especially in the aging population [1,2]. The association between obstructive coronary artery disease (CAD) and HF is well known but few studies have evaluated non-obstructive CAD and heart failure with preserved ejection fraction (HFpEF), which is becoming more prevalent than HF with reduced ejection fraction [3].

The National Heart Lung and Blood Institute sponsored Women's Ischemia Syndrome Evaluation (WISE) study focused on the mechanisms, prognosis and management of ischemic heart disease in women [4,5]. Based on this multicenter initiative, it is now clear that obstructive CAD is infrequent in women [6–8] and that the majority of women with signs and symptoms of ischemia have coronary microvascular dysfunction (CMD) [8]. It is also evident that women with signs and symptoms of ischemia without obstructive CAD have an elevated risk of major cardiovascular events, including HF [9–11], raising the question whether CMD is mechanistically linked with HFpEF [12–14].

To verify and characterize the HF hospitalization in WISE, we performed a retrospective chart review. Given that the majority of patients with HFpEF are women [15,16], and the majority of non-obstructive CAD patients are women [7–8], we hypothesized that women WISE women would predominantly present with HFpEF.

2. Methods

A retrospective chart review for characterization of HF hospitalization was performed on a cohort of 223 women enrolled at a single site

Abbreviations: HF, heart failure; EF, ejection fraction; HFpEF, heart failure with preserved ejection fraction; CAD, coronary arterial disease; CMD, coronary microvascular dysfunction.

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(University of Florida, Gainesville) in the NHLBI-sponsored WISE study and who were followed for a period of 6 years ± 2.6 years. Heart failure hospitalization was verified by a diagnosis of HF in the medical chart. Preserved EF was defined as ≥55% or a clinician's chart note of "normal" or "preserved" or "not reduced EF". All participants provided written informed consent prior to enrollment.

Inclusion and exclusion criteria, along with detailed descriptions of each of the study end-point measurements, have previously been published [7,11,17]. Briefly, the WISE subjects were all women with signs and symptoms of ischemia and objective evidence of ischemia on stress testing and who underwent coronary angiography. A WISE core laboratory (Rhode Island Hospital, Providence, RI, USA), blinded to clinical data, analyzed all angiograms to characterize the presence and extent of CAD [11]. Obstructive CAD was defined as ≥50% stenosis in any epicardial coronary artery, non-obstructive CAD was defined as ≥20 but <50%, and no CAD was <20%.

Statistical analysis included descriptive statistics to represent categorical and continuous variables with numbers and percentages or means and standard deviations. Fisher's exact test was used for statistical analysis to compare the rate of HF among patients with obstructive CAD and non-obstructive CAD.

3. Results

Baseline characteristics are reported in Table 1. The average age of subjects at the time of enrollment was 57 ± 11 years, and all subjects had a normal EF (63 ± 11%). The majority of patients (66%) had a family history of CAD, 63% had a history of hypertension, 53% had dyslipidemia and 30% had a history of diabetes.

Consistent with previous reports from other WISE investigations [6,10,11,15], 11% (n = 25) of our cohort were hospitalized for HF; 56% (n = 14) of whom reported recurrent hospitalization visits (>2 hospitalizations). Medical records were available for 13 of the 25 patients hospitalized for HF, with information on 17 separate hospital admissions. HF hospitalization was verified for all patients. Ejection fraction measured during hospitalization was preserved in 12/13 (92%) patients.

To address whether HF hospitalization was related to obstructive CAD, we stratified the HF hospitalizations by the presence of obstructive CAD. Among the 13 subjects with HF verified hospitalizations, HF hospitalization was not related to obstructive CAD vs non-obstructive CAD (4/13 [31%] vs 9/13 [69%] respectively, p = ns). The distribution of HFpEF and HFrEF according to obstructive, non-obstructive and no CAD is depicted in Fig. 1.

Table 1
Baseline characteristics.[a]

Characteristic	(n = 223)
Age (years ± SD)	57 ± 11
LVEF (%)	63 ± 11
Family history of CAD	66%
Hypertension	63%
Diabetes mellitus	30%
Dyslipidemia	53%
Use of lipid lowering medications	22%
Antihypertensive medication use	
ACE inhibitors	30%
ARB	2%
Diuretic	27%
Vasodilator	6%
Beta blocker	32%
Calcium channel blocker	13%
Aspirin use	53%
Obstructive CAD	36%
No or non-obstructive CAD	64%

Abbreviations: LVEF = left ventricular ejection fraction; ACE = angiotensin converting-enzyme; ARB = angiotensin receptor blocker; CAD = coronary artery disease.
[a] Data expressed as mean ± SD or percentage.

4. Discussion

We previously observed that women with signs and symptoms of ischemia and preserved ejection fraction had an unexpectedly high incidence of HF hospitalization [10]. Verification of HF and the type of HF (i.e. HFrEF vs. HFpEF) in this cohort has not been well characterized. The current study results verify the hospitalizations as HF and find that the majority (92%) of verified HF hospitalizations were HFpEF, consistent with our hypothesis.

Consistent with our original publication [10], we show a similar prevalence of HF (11% vs. 6%, respectively). That the majority of verified HF hospitalizations were classified as no or non-obstructive CAD (69%) is also consistent with this prior investigation [10]. We now extend this previous work by demonstrating that the majority of HF cases are characterized as having a preserved EF. Taken together, the data allow us to speculate that women with ischemic heart disease, non-obstructive CAD and preserved ejection fraction are at increased risk for developing HFpEF.

The mechanism for HF hospitalization remains incompletely understood. Taqueti et al. [18] previously demonstrated that low coronary flow reserve (CFR) was associated with increased rates of adverse clinical events including cardiovascular death or HF admission. We have consistently found that as many as 50% of women with signs and symptoms of ischemia, but not obstructive CAD, have coronary microvascular dysfunction. Given the small number of event rates in the present investigation, we were not adequately powered to test this specific question. Future studies in a larger population are needed to determine the relationship between coronary microvascular dysfunction and heart failure hospitalization – particularly those presenting with preserved ejection fraction.

Our results are limited by record availability only in a slight majority (52%) of HF hospitalizations. Furthermore, the WISE cohort by design includes only women and may not be generalizable to other populations.

5. Conclusions

Among women with signs and symptoms of ischemia, no obstructive CAD and preserved ejection fraction at enrollment, HF hospitalizations are most often HFpEF. Further work is needed to determine the mechanistic relationship between ischemic heart disease in women and the development of HFpEF.

Disclosures

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