The Unrecognized Burden of Osteoporosis-Related Vertebral Fractures in Patients With Heart Failure

Kristin J. Lyons, MDCM; Sumit R. Majumdar, MD, MPH; Justin A. Ezekowitz, MBBCh, MSc

Background—Heart failure (HF) is associated with several factors that contribute to both reduced bone mineral density and increased risk of osteoporosis-related fractures. Our objectives were to describe the prevalence and predictors of the most common osteoporotic fracture, vertebral compression fractures (VCF), in patients with HF.

Methods and Results—We conducted a cross-sectional study in a random sample of patients attending a tertiary care HF Clinic in Edmonton, Alberta, Canada. We collected sociodemographic, clinical, medication, and chest radiograph information. Primary outcome was board-certified radiologist–documented VCF on chest radiographs. Multivariable logistic regression was used to determine independent correlates of VCF. Overall, 623 patients with HF were included; 32% were over 75 years of age, 31% were women, 65% had ischemic cardiomyopathy, and 38% had atrial fibrillation. Prevalence of VCF was 77 of 623 (12%; 95% confidence interval, 10% to 15%), and 42 of 77 (55%) patients had multiple fractures. Only 15% of those with VCF were treated for osteoporosis. In multivariable analyses adjusted for age, female sex, weight, and medications, the only remaining predictors independently associated with fracture were atrial fibrillation (present in 42 of 77 [55%] of those with VCF versus 197 of 540 [36%] of those without; adjusted odds ratio, 2.1; 95% confidence interval, 1.2 to 3.6; \( P = 0.009 \)) and lipid-lowering drugs (used by 36 of 77 [47%] of those with VCF versus 342 of 540 [63%] of those without; adjusted odds ratio, 0.2; 95% confidence interval, 0.1 to 0.9; \( P = 0.03 \)).

Conclusions—About one-tenth of HF patients had a chest radiograph–documented VCF, and half of those with VCF had multiple fractures; most (85%) were not receiving an osteoporosis-specific therapy. A previously unrecognized risk factor—atrial fibrillation—was found to be independently associated with VCF. Chest radiograph reports may represent an important case-finding tool for osteoporosis-specific VCF, particularly in HF patients with atrial fibrillation. (Circ Heart Fail. 2011;4:419-424.)

Key Words: heart failure ■ osteoporosis ■ atrial fibrillation ■ epidemiology

Heart failure (HF) and osteoporosis are common conditions that each account for significant morbidity and mortality. HF has a prevalence of 8% in those \( \geq 75 \) years of age and is a leading cause of acute-care hospitalizations and mortality.1-3 The estimated annual cost for inpatient HF management in Canada is more than $1 billion, and the 1-year mortality rate after diagnosis ranges between 25% and 40%.4 Osteoporosis has a prevalence of 6% at 50 years of age and \( > 50 \% \) in those \( \geq 80 \) years of age.5 The estimated annual acute care costs attributable to osteoporosis in Canada are $1.3 billion, and about 20% of women and 40% of men die within 1 year of a hip fracture.5 With the aging of the population, the prevalence of both diseases is on the rise, and recent evidence suggests that HF patients are at increased risk of development of osteoporosis-related complications.6-10 Given the preventable morbidity and mortality associated with osteoporosis11,12 and the increasing life expectancy of HF patients, interventions to reduce fracture burden could improve overall quality and quantity of life in this frail, older population.

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Although hip fractures are the most devastating complication of osteoporosis, vertebral compression fractures (VCF) are by far the most common.13 Unfortunately, 60% to 70% of VCF are initially asymptomatic and thus escape clinical detection.14 Nevertheless, these “asymptomatic” VCF are associated with acute and chronic pain, deformity, disability, pulmonary complications, and even mortality.13 Furthermore, patients with osteoporosis-related VCF have at least a 5-fold increased risk of another vertebral fracture and a 3-fold increased risk of subsequent hip fracture.15 As a result, it is important to identify patients with VCF because appropriate treatment with a number of approved agents reduces the risk of future fractures by about 50%.12 Although population-based screening for osteoporosis-related VCF is not currently recommended,5 the chest radiograph may be a valuable case-finding tool in "at-risk" patients, such as those with HF. We have previously demonstrated that at least 60% of
clinically important VCF are recognized and reported in chest radiograph reports and that board-certified radiologists have a specificity for documenting VCF of 100%.16 Because most HF patients will invariably receive multiple chest radiographs over time, these radiographs may be useful for detecting VCF. Although this approach has been examined for older patients in general17 and for patients with chronic obstructive pulmonary disease,16,18 to our knowledge, there have been no studies examining the prevalence of VCF in HF.

Accordingly, we performed a cross-sectional study of HF patients, with 2 main objectives: (1) to describe the prevalence of chest radiograph–documented VCF and (2) to determine the independent sociodemographic and clinical correlates of vertebral fracture.

Methods

Subjects and Setting
The University of Alberta Heart Function Clinic (HFC) in Edmonton, Alberta, Canada, has collected demographic and clinical characteristics of consecutive HF patients from 1989 onward using standardized data collection forms. Details of this clinic and the methodology have been previously published.19 This tertiary care clinic receives referrals from a region that has about 1000 primary care physicians and a catchment area of more than 1 million people with universal health coverage. The diagnosis of HF is made by the physicians in the HFC caring for the patient using the Framingham criteria.20

From a total cohort of 2231 patients with HF, we randomly selected 1000 patients for additional detailed review of chest radiographs and ancillary medical information. Inclusion criteria to this study were age ≥50 years, clinical history of HF, and available report from standard lateral chest radiographs performed and interpreted by a board-certified radiologist in our region within 6 months of the initial HFC visit. Of the 1000 patients screened from the HFC, we excluded 197 patients without a chest radiograph report from our region, 139 patients under the age of 50 years, and 41 patients without available charts for review. Thus, the final cohort included 623 patients. This study was approved by the University of Alberta Health Research Ethics Board.

Other Measurements
Baseline data were collected from the clinical chart using standardized forms as detailed previously.19 Briefly, demographic data, cardiovascular history, HF etiology and HF details, comorbid disease, investigations, laboratory values, and medications were abstracted after the baseline visit, where they were confirmed by the clinicians in the HFC. The physical examination and New York Heart Association class were performed by the HFC physician and recorded at each visit using a standardized template. Assessments of ejection fraction were taken from the most recent assessment prior to the HFC baseline visit and included an echocardiogram, nuclear imaging, or MRI. A history of arrhythmias including atrial fibrillation or flutter was confirmed by ECG.

Outcomes
The outcome of interest was the presence or absence of a recognized and documented VCF on chest radiography. These radiographs were interpreted independent from the current study, and the radiologists did not have access to any patient-level HF data. A fracture was considered to be present if there was any mention of vertebral fracture, deformity, compression, wedging, or loss of height reported in the body or summary of the official radiograph report.16–18 Most VCF involve the midthoracic (T7-T8) spine and thoracolumbar junction (T12-L1), and because these regions can be adequately visualized with standard chest radiographs, >80% of VCF could be identified.16–18 VCF are present when the above terms are used for reporting, fall into grade 2 (moderate) or grade 3 (severe) category of VCF, and are widely considered “clinically important.”16–18,21 The reliability and validity of this method of fracture recognition on chest radiography, compared with both a reference standard osteoporosis expert radiologist using semiquantitative methods as well as automated quantitative digital morphometry, have been extensively studied in our region.16,17 In summary, the true-positive rate of reporting by our center’s radiologists is 60% (95% confidence interval [CI], 48 to 71), with moderate inter-rater agreement (κ=0.64; 95% CI, 0.52 to 0.75); however, specificity for reporting of moderate to severe VCF is 100%,16,17

Statistical Analysis
Baseline characteristics are presented as number and proportions, means with standard deviations (SD), or medians with interquartile ranges (IQR), as appropriate. Multivariable logistic regression was used to assess the independent correlates of fracture. Age and sex were forced into the models, and individual covariates from Table 1 and Table 2 were then entered, based on clinical relevance, a univariate association (P<0.2), or presence of confounding (change in β-coefficient of >10%). All biologically plausible interaction terms were tested; none were statistically significant and so none are included in the final models. We used a missing indicator approach with dummy variables for missingness and direct maximum likelihood estimation methods. Adjusted odds ratios (OR) with their 95% CIs are reported; a probability value of ≤0.05 was considered statistically significant. In sensitivity analyses, we repeated our multivariable model without the presence of bisphosphonates, and a separate analysis restricted only patients with multiple fractures compared with no fractures. Analyses were performed using SPSS version 16.0 software (SPSS Inc, Chicago, IL), and graphs were created with STATA version 10.1 (Stata Corporation, College Station, TX).

Results

Patient Characteristics
Overall, the median age was 69 years, (IQR, 59 to 78 years), 32% of patients were ≥75 years of age, and 31% were women. In terms of HF, the mean left ventricular ejection fraction was 32% (SD, 16%), approximately half of the patients had New York Heart Association class III–IV symptoms, 38% had atrial fibrillation, and the majority (85%) of patients had ischemic cardiomyopathy (Table 1).

Prevalence of VCF
The overall prevalence of ≥1 VCF documented by chest radiography was 77 of 623 (12%; 95% CI, 10% to 15%), and more than half (55%; 95% CI, 43% to 65%) of these patients had multiple fractures.

Correlates of VCF
Patients with VCF were older (mean age, 72.6 years versus 68.4 years; P=0.002), more likely to be female (47% versus 29%; P=0.002), weighed less (mean weight, 75 kg versus 85 kg; P<0.001; Table 1), and were significantly more likely to have atrial fibrillation (55% versus 36%; P=0.002). In terms of medications, patients with VCF were less likely to be prescribed an angiotensin-converting enzyme inhibitor (65% versus 77%; P=0.02) and lipid-lowering agents (47% versus 63%; P=0.005) and more likely to be prescribed digoxin (25% versus 35%, P=0.05), but there were otherwise no significant differences in the use of other cardiovascular medications (Table 2). Patients with VCF were more likely to be taking osteoporosis-related medication (P<0.001), but
overall osteoporosis treatment was low, with only 14% of those with fractures treated with a bisphosphonate.

Multivariable Analysis
In models adjusted for older age, female sex, weight, and bisphosphonate use, the only independent correlates of VCF were use of lipid-lowering agents and the presence of atrial fibrillation (Table 3). Lipid-lowering agents were associated with a lower prevalence of VCF (adjusted OR, 0.2; 95% CI, 0.1 to 0.9; \( P = 0.03 \)). Conversely, atrial fibrillation was associated with an increased prevalence of fracture. Patients with atrial fibrillation had twice the risk of fracture (adjusted OR, 2.1; 95% CI, 1.2 to 3.6; \( P = 0.009 \)) compared with those without atrial fibrillation.

Sensitivity Analyses
The final model was repeated without the inclusion of bisphosphonates; no impact on either the magnitude or statistical significance of the included variables was seen (data not shown). Furthermore, in analyses in which the definition of fracture was restricted to patients with \( \geq 2 \) VCF (thereby excluding 35 patients with a single fracture), patients with atrial fibrillation tended to have more fractures when compared with patients without (50% versus 36%, \( P = 0.12 \)), but in adjusted analysis, this did not reach statistical significance (OR, 1.7; 95% CI, 0.8 to 3.4; \( P = 0.17 \); Table 3).

Discussion
In our study of patients with chronic HF treated in a tertiary-care HF clinic, we found that >1 in 10 had a...
clinically important, moderate-to-severe VCF documented on their initial chest radiograph. About half of these patients had multiple VCF, and only 14% were receiving appropriate treatment for osteoporosis. Of note, in analyses adjusted for older age, female sex, weight, and bisphosphonate use, only the use of lipid-lowering agents and the presence of atrial fibrillation were independent correlates of fracture.

Previous studies examining the prevalence of osteoporosis-related fractures in HF populations vary because of the heterogeneity of study designs and patient populations. In a large Canadian population-based study including more than 16,000 patients with cardiovascular disease age ≥65 years, the 1-year incidence of fracture requiring hospital admission was 4.6%. A recent US cohort study revealed that over 11.5 years of follow-up, the incidence of a hip fracture in patients with heart failure was 10%. The 12% prevalence in our study is possibly due to the asymptomatic nature of most VCF, whereas many upper-extremity fractures and all hip fractures result in hospitalization. Interestingly, the prevalence of VCF (n=5 patients, 15%) found in a study of 33 male HF patients with a low ejection is similar to our estimate of 12%.

Regardless of the exact estimate of prevalence, however, it is apparent throughout the available literature that HF patients are at increased risk of osteoporosis-related fractures when compared with those without HF. In 2 previous population-based studies, patients with HF had a 4-fold increased risk of any fractures and a 6-fold increased risk of hip fractures compared with patients with a non-HF cardiovascular diagnosis and a 4-fold increased risk of hip fracture when compared with those without a cardiovascular diagnosis. It would be expected that such fracture burden would have a significant functional and survival impact; in the above cohort study of Sennery et al, an HF patient with an incident hip fracture had a 2-fold increased risk of dying compared with HF patients without incident fractures. Possible explanations for the association between osteoporotic fractures and HF include shared risk factors (ie, age, female sex, renal disease, smoking), vitamin D deficiency, select medications that increase (eg, furosemide, vitamin K antagonists) or decrease (eg, β-blockers, statins) fractures, low body weight, and frailty.

Table 3. Independent Correlates of the Presence of 1 or More Moderate to Severe Vertebral Fractures Versus Multiple Moderate to Severe Vertebral Fractures

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>One or More Fractures (n=77)</th>
<th></th>
<th></th>
<th>Multiple Fractures (n=42)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>P Value</td>
<td>OR</td>
<td>95% CI</td>
<td>P Value</td>
</tr>
<tr>
<td>Age, per year</td>
<td>1.01</td>
<td>0.98–1.03</td>
<td>0.67</td>
<td>1.02</td>
<td>0.98–1.05</td>
<td>0.27</td>
</tr>
<tr>
<td>Female</td>
<td>1.15</td>
<td>0.61–2.14</td>
<td>0.67</td>
<td>1.37</td>
<td>0.61–3.09</td>
<td>0.41</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2.07</td>
<td>1.19–3.59</td>
<td>0.009</td>
<td>1.75</td>
<td>0.84–3.86</td>
<td>0.14</td>
</tr>
<tr>
<td>Weight, per kg</td>
<td>0.98</td>
<td>0.97–1.0</td>
<td>0.01</td>
<td>0.98</td>
<td>0.96–1.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Lipid-lowering agents</td>
<td>0.22</td>
<td>0.05–0.95</td>
<td>0.04</td>
<td>0.22</td>
<td>0.03–1.67</td>
<td>0.14</td>
</tr>
<tr>
<td>Bisphosphonate</td>
<td>6.12</td>
<td>2.14–17.5</td>
<td>&lt;0.001</td>
<td>7.03</td>
<td>2.12–23.34</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Including older age, female sex, and atherosclerotic vascular disease, or may indeed be a risk factor for fracture itself. Conversely, treatments for osteoporosis (ie, the bisphosphonates) have been reported to lead to atrial fibrillation. However, this finding has been refuted by other studies, and we found that bisphosphonate use was neither associated with atrial fibrillation nor affected any of the other variables in our model. Given the observational nature of the study, we cannot assess cause and effect, and the interaction of atrial fibrillation, heart failure, and VCF must be further elucidated.

We speculate that hyperaldosteronism is a biologically plausible explanation for the relationship between chronic HF, osteoporosis, and atrial fibrillation. Hyperaldosteronism has been shown to play a role in animal models of osteoporosis-related fracture via magnesium and calcium wasting in the urine. Furthermore, in one case-control study, HF patients treated with spironolactone were significantly less likely to have a fracture than HF patients not treated with an aldosterone antagonist—a finding that we were unable to replicate but deserves further attention. In addition, increased levels of aldosterone lead to atrial fibrosis and subsequent atrial fibrillation, both of which can be reduced by treatment with spironolactone. Future studies exploring whether atrial fibrillation is a risk factor for fracture in populations across a spectrum of patients with available aldosterone levels are needed.

**Strengths and Limitations**

The present study has several strengths and limitations that must be considered. First, we did not undertake dedicated spinal radiographs or rereview chest radiographs to determine the most accurate prevalence of vertebral fracture. However, the methodology used in this study has been previously validated to be highly specific (100%) and moderately sensitive and therefore may underestimate the true prevalence. Second, actual measures of bone mineral density were not available. Nevertheless, >90% of patients over the age of 60 years with a VCF have low bone mass and current guidelines suggest that osteoporosis treatment could be initiated without direct measurement of bone mineral density. Third, frailty measures such as weight loss, poor energy, low physical activity, or falls risk were not available. Fourth, additional osteoporosis-related data such as a family or personal history of remote hip or other fractures or serum vitamin D and calcium levels were not available but are unlikely to materially alter our results.
Conclusions
More than one-tenth of HF patients had a chest radiograph–
documented VCF, 50% of those with VCF had multiple
fractures, and most (85%) were not treated for osteoporosis.
In analyses adjusted for age, female sex, low body weight,
and medications, atrial fibrillation (a previously unrecognized
risk factor) was strongly associated with the presence of VCF.
Future studies should attempt to confirm or refute both our
findings and our hypotheses related to hyperaldosteronism.
Our results also suggest that routine chest radiograph reports
may represent an important case-finding tool for VCF,
particularly in HF patients with atrial fibrillation. Strategies to
improve osteoporosis treatment in this easily identified pop-
ulation are needed to avoid future osteoporosis-related
complications.

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Disclosures
None.

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