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The prognostic impact and optimal timing of the Patient Health Questionnaire depression screen on 4-year mortality among hospitalized patients with systolic heart failure

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ABSTRACT

Objective: An American Heart Association (AHA) Science Advisory recommends patients with coronary heart disease undergo routine screening for depressive symptoms with the two-stage Patient Health Questionnaire (PHQ). However, little is known on the prognostic impact of a positive PHQ screen on heart failure (HF) mortality.
Methods: We screened hospitalized patients with systolic HF (left ventricle ejection fraction≤40%) for depression with the two-item Patient Health Questionnaire (PHQ-2) and administered the follow-up nine-item Patient Health Questionnaire (PHQ-9) both immediately following the PHQ-2 and by telephone 1 month after discharge. Later, we ascertained vital status at 4-year follow-up on all patients who completed the inpatient PHQ-9 and calculated mortality incidence and risk by baseline PHQ.
Results: Of the 520 HF patients we enrolled, 371 screened positive for depressive symptoms on the PHQ-2. Of these, 63% scored PHQ-9≥10 versus 24% of those who completed the PHQ-9 1 month later ($P<.001$). PHQ-2 positive status was an independent predictor of 4-year all-cause mortality (HR: 1.50; $P=.04$), and mortality incidence was similar by baseline PHQ-9 score.
Conclusions: Among hospitalized patients with systolic HF, a positive PHQ-2 screen for depressive symptoms is an independent risk factor for increased 4-year all-cause mortality. Our findings extend the AHA's Science Advisory for depression to hospitalized patients with systolic HF.

1. Introduction

Heart failure (HF) is a common and growing health problem. Over 5 million people in the United States have HF, with approximately 915,000 new cases and 300,000 deaths annually. Yet despite recent therapeutic advances in care, HF remains the only major cardiovascular disease whose mortality rate has remained essentially unchanged over the past decade [1]. One potential contributor to these persistently poor outcomes is depression. Approximately half of HF patients report elevated levels of depressive symptoms, and they are more likely to report reduced health-related quality of life, poorer adherence with evidence-based care and increased cardiovascular morbidity and mortality than nondepressed HF patients even after adjustment for disease severity [2–4].

Based on the accumulating evidence linking depression with worse cardiovascular outcomes, the American Heart Association (AHA) issued a Science Advisory that recommended patients with coronary heart disease to undergo routine screening and treatment for depression [5]. Specifically, the Advisory suggested a two-stage approach beginning with the two-item Patient Health Questionnaire (PHQ-2) depression screen [6], followed by administration of the nine-item Patient Health Questionnaire (PHQ-9) [7] to screen-positive patients to assess symptom severity and guide treatment decisions. However, the Science Advisory did not specify the timing of the follow-up PHQ-9. Indeed, if the PHQ-9 is administered during hospitalization, then patients' "depressive symptoms" may be misattributed to such commonly experienced symptoms of hospitalization as fatigue, disturbances in sleep and appetite that are likely to resolve soon after discharge home [2,8]. However, waiting to administer the follow-up PHQ-9 to PHQ-2 screen-positive patients until after hospital discharge may delay the start of effective care for depression and increase suffering.

We previously reported that hospitalized patients with systolic HF who expressed depressive symptoms on the PHQ-2 [PHQ-2 (+)] experienced an increased rate of all-cause and cardiovascular mortality at 1 year following discharge compared to those who did not expressive depressive symptoms [PHQ-2 (−)] even after adjustment for known

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predictors of HF mortality [9]. However, the prognostic durability of the PHQ-2 beyond 1 year is presently unknown. Furthermore, we did not report on the pragmatic consequences of waiting to administer the follow-up PHQ-9 until after discharge to allow time for the potential "symptoms" of hospitalization to resolve. We now examine these issues in that study cohort we enrolled to inform development of an effectiveness trial to treat depression in patients with HF that we are presently conducting (ClinicalTrials.gov: NCT02044211).

2. Methods

Following a study protocol detailed previously [9] and approved by the Institutional Review Board of the University of Pittsburgh, study nurse-recruiters obtained Health Insurance Portability and Accountability Act (HIPAA) consent to approach patients hospitalized for any reason with a left ventricular ejection fraction (LVEF) ≤40% on the medical and cardiac wards at four Pittsburgh-area acute care hospitals between December 2007 and April 2009. We targeted enrollment of 372 PHQ-2 (+) study subjects to have sufficient power to conduct six receiver operating curve analyses to determine the ideal PHQ-9 cutoff score that best predicted 6-month mortality risk separately for each New York Heart Association (NYHA) class (II-IV) by gender to inform our proposed clinical trial. Given the substantial mortality risk among nondepressed HF patients [10], we also planned to enroll 100 HF patients to serve as a nondepressed control cohort [PHQ-2 (−)]. To operationalize this, our study nurses requested HIPAA consent from hospital staff who suspected that their patients with a qualifying LVEF might be depressed.

Protocol-eligible patients were also required to report NYHA functional class level II-IV cardiac symptoms and to have no history of psychotic illness, bipolar disorder or current alcohol dependency or substance abuse disorder. After obtaining informed consent, study nurses collected sociodemographic and clinical information via patient interview, administered the PHQ-2 screen followed by the PHQ-9 and conducted a medical chart review to confirm protocol eligibility to continue in our cohort study. If so confirmed, the study nurses administered the 12-item Medical Outcomes Study Short Form to determine mental and physical health-related quality of life [11] and the PRIME-MD Anxiety Module to determine the presence of an anxiety disorder [12]. At 1 month following hospital discharge, another research assessor who was blinded as to patients' baseline PHQ-2 status and PHQ-9 score telephoned the patient to readminister the PHQ-9. We immediately notified the attending physician or primary care physician when their patient endorsed suicidal ideations on either the inpatient or 1 month follow-up PHQ-9.

2.1. PHQ-2 and PHQ-9 assessments

As recommended by the AHA Science Advisory [5], we defined a positive PHQ-2 screen for depression [PHQ-2 (+)] when a patient responded "yes" to one or both of the following questions: Over the preceding 2 weeks, how often have you been bothered by: (1) "little interest or pleasure in doing things" or (2) "feeling down, depressed or hopeless". We defined a negative PHQ-2 screen when the patient replied "not at all" to both items and was not taking an antidepressant (90% sensitivity and 69% specificity for major depressive disorder) [13]. To indicate at least a moderately severe level of depressive symptoms, we used the generally accepted PHQ-9 cutoff score of ≥10 (52% sensitivity and 91% specificity at detecting major depression among patients with cardiac disease) [13].

2.2. Vital status

To determine vital status and cause of death for up to 4 years following the date of recruitment, we used our medical center's electronic medical records system, the Social Security Death Index, online obituary notices and telephone calls with patients' predesignated secondary contacts and primary care physicians. Afterwards, two study physicians blinded as to patients' baseline PHQ-2 status independently classified the cause of each confirmed death as "cardiovascular" (e.g., HF, arrhythmia, myocardial infarction, stroke) or "noncardiovascular" (e.g., infection, cancer, trauma).

2.3. Statistical analyses

We compared patients' baseline sociodemographic and clinical characteristics by PHQ-2 status using *t* tests for continuous data and chi-square tests for categorical data, and we used the Hochberg method to control for multiple comparisons [14]. All tests were two-tailed and *P* values ≤.05 were considered significant; all analyses were performed with SAS statistical software version 9.3 (SAS Institute Inc., Cary, NC).

We used Kaplan–Meier survival analysis to calculate the incidence of all-cause and cardiovascular mortality by PHQ-2 status, with log-rank tests to evaluate differences for statistical significance. To control for possible confounders of the relationship between mood and mortality, we adjusted for several recognized of HF mortality [15,16] including diabetes, anemia (hemoglobin<10 g/dl), hyponatremia (sodium<136 mEq/L), renal insufficiency (creatinine>1.7 mg/dl), blood pressure and use of an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker medication, as well as coumadin using Cox proportional-hazard models. We also performed sensitivity analyses to assess the potential impact of missing information on the cause of death on our findings. First, we assumed that patients whose cause of death was undetermined had died of a cardiovascular cause and then, since antidepressant use may affect mortality risk [17,18], we repeated our analyses excluding patients who self-reported use of an antidepressant at baseline.

We dichotomized the PHQ-2 so that >0 on either of the two questions was considered a positive screen as the instrument is more likely to be utilized in this manner by busy staff in routine clinical practice settings. We categorized inpatient PHQ-9 data into groups using established PHQ-9 severity levels [7] and then applied Kaplan–Meier survival analyses to calculate the incidence of all-cause and cardiovascular mortality at yearly follow-up intervals. Next we adjusted for possible confounders of the relationship between depressive symptoms and HF morbidity and mortality using Cox models. To examine for bias, we compared baseline sociodemographic and clinical characteristics of patients missing 1-month PHQ-9 scores to those with complete data.

3. Results

3.1. Study recruitment and follow-up

As portrayed in Fig. 1, hospital medical staff identified 857 HF patients with HF who provided HIPAA consent for one of our nurse-recruiters to approach. Of these, 589 (69%) agreed to undergo our screening procedure, and 69 were ineligible as they reported NYHA class I symptoms. Of the remaining 520 who provided signed informed consent and completed the PHQ-2, 401 were PHQ-2 (+) and 119 PHQ-2 (−), and 471 met all protocol eligibility criteria and completed the PHQ-9 [371 PHQ-2 (+) and 100 PHQ-2 (−)]. Later, 316 PHQ-2 (+) and 83 PHQ-2 (−) study subjects completed the 1-month follow-up PHQ-9 by telephone, and we confirmed vital status on all 471 (100%) at 4 years following enrollment of the last recruited patient (June 2013). Afterwards, we identified 202 deaths [164 PHQ-2 (+) and 38 PHQ-2 (−); 43%] and were able to categorize a cause of death on 194 (96%), of which we classified 134 (69%) as cardiovascular-related.

3.2. Baseline patient characteristics

Compared with HF patients who screened PHQ-2 (−) at baseline, PHQ-2 (+) patients were younger and more likely to have comorbid anxiety, report more depressive and NYHA functional class symptoms