Comorbid Depression and Heart Failure: A Community Cohort Study

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Abstract

Objective
To examine the association between depression and clinical outcomes in heart failure (HF) in a community cohort.

Patients and Methods
HF patients in Minnesota, United States completed depression screening using the 9-item Patient Health Questionnaire (PHQ-9) between 1st Oct 2007 and 1st Dec 2011; patients with PHQ-9 ≥5 were labelled “depressed”. We calculated the risk of death and first hospitalization within 2 years using Cox regression. Results were adjusted for 10 commonly used prognostic factors (age, sex, systolic blood pressure, estimated glomerular filtration rate, serum sodium, ejection fraction, blood urea nitrogen, brain natriuretic peptide, presence of diabetes and ischaemic aetiology). Area under the curve (AUC), integrated discrimination improvement (IDI) and net reclassification improvement (NRI) compared depression as a predictor against the aforementioned factors.

Results
425 patients (mean age 74, 57.6% males) were included in the study; 179 (42.1%) had PHQ-9 ≥5. The adjusted hazard ratio of death was 2.02 (95% CI 1.34–3.04) and of hospitalization was 1.42 (95% CI 1.13–1.80) for those with compared to those without depression. Adding depression to the models did not appreciably change the AUC but led to statistically significant improvements in both the IDI (p = 0.001 and p = 0.005 for death and hospitalization, respectively) and NRI (for death and hospitalization, 35% (p = 0.002) and 27% (p = 0.007) were reclassified correctly, respectively).

Conclusion
Depression is frequent among community patients with HF and associated with increased risk of hospitalizations and death. Risk prediction for death and hospitalizations in HF patients can be improved by considering depression.
Introduction

Heart failure (HF) is a major health problem with high rates of mortality and hospitalization reported across Europe and North America [1–3]. Accurate prediction of prognosis in chronic HF patients is important for decision making and helps identify patients at risk who may benefit from closer monitoring [4,5]. Various risk prediction models have been proposed to predict mortality and hospitalization in HF [6–11]. A recently published systematic review by Ouwerkerk and colleagues has identified 11 of the most commonly used prognostic markers in the literature for risk prediction of chronic HF outcomes [6]. However, there are a number of drawbacks with currently available prognostic models, such as limited accuracy and scarcity of data available on predicting hospitalisation; hence, better prognostic markers are required for HF patients [7–10].

Depression has been found to be an independent predictor of mortality and hospitalization in HF [12–15]. However, the clinical utility of depression as a prognostic marker for HF outcomes has not been examined in comparison with some of the commonly used HF prognostic markers. Thus, the objective of this study was to examine if the presence of co-morbid depression provided incremental prognostic information for 2-year mortality and hospitalization risk prediction over the most commonly used prognostic markers in HF [6].

Methods

Study Setting

This was a prospective cohort study conducted in southeast Minnesota (with an approximate population of 185,000) [17] in the United States using the Rochester Epidemiology Project [18–20], a record linkage system which allows near complete capture of health care utilization for area residents. This is possible because the area is relatively isolated from other urban centers and has a small number of medical providers, including Mayo Clinic and Olmsted Medical Center, which deliver nearly all health care to local residents. This study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards.

Study Sample

Patients with either incident or prevalent HF were identified during an inpatient or outpatient visit using natural language processing of the electronic medical record. The diagnoses were manually validated by trained abstractors using the Framingham criteria, which has been described previously [14]. HF patients aged ≥18 years who resided in Olmsted, Dodge or Fillmore Counties in Minnesota were prospectively recruited between October 2007 and December 2011 and asked to complete a 9-item Patient Health Questionnaire (PHQ-9) [21] for depression. Written informed consent was obtained from all participants.

Depression Assessment

Depression symptoms were assessed using the PHQ-9 administered by a registered nurse in person, within 6 weeks of enrolment. A PHQ-9 score of 5 or more denotes mild depression, while a score of 10 or more is indicative of major depressive disorder [21]. Hence, a score of PHQ-9 ≥5 was used to define “presence of depressive symptoms”, while a score of PHQ-9 ≥10 was used to define “presence of moderate to severe depression”. All clinical variables were either obtained electronically or from patient records.
Measurement of Clinical Variables

Systolic blood pressure in mm Hg was obtained within 30 days of recording PHQ-9. Estimated glomerular filtration rate (eGFR) was estimated using the closest serum creatinine value within 1 year of administering PHQ-9 using the Modification of Diet in Renal Disease Study equation [22]. Left ventricular ejection fraction (EF) measured in % was obtained using the closest value from an echocardiogram within 6 months prior to 2 months after the patient’s diagnosis of HF (inpatient or outpatient) that identified them for recruitment into our study. Serum sodium (measured in mmol/l), blood urea nitrogen (measured in mg/dl), B-Type natriuretic peptide (BNP) (measured in pg/ml) and N-Terminal pro-BNP (NT-BNP) (measured in pg/ml) values were obtained within 1 year of administering PHQ-9. BNP values were used only when NT-BNP values were not available. Because of the need to use both BNP and NT-BNP data, we dichotomized them into raised vs. not raised. Raised BNP was defined as values more than 400 pg/ml. Raised NT-BNP was defined as values more than 450 pg/ml for age <50, more than 900 pg/ml for age 50–75, and more than 1800 pg/ml for age >75 [23].

Measurement of Clinical Outcomes

Participants were followed for 2 years after administering PHQ-9 for all-cause death and all-cause hospitalization. Deaths were obtained from inpatient and outpatient medical records and death certificates received from the state of Minnesota. Hospitalizations were ascertained using data from the Rochester Epidemiology Project. For patients hospitalized at the time of their HF, only subsequent hospitalizations were included in the analysis. In-hospital transfers or transfers between Olmsted Medical Center and Mayo Clinic were analysed as a single hospitalization event.

Statistical Analysis

Baseline patient characteristics were reported as a frequency (%) for categorical variables and mean (standard deviation [SD]) or median (25th percentile, 75th percentile) for continuous variables. Two-sample t-tests and χ² tests were used to test differences in baseline characteristics between patients with and without depressive symptoms for continuous and categorical variables, respectively. A Kaplan-Meier survival plot was constructed to illustrate the association between depression and all-cause mortality. A cumulative incidence plot was constructed for first hospitalization treating death as a competing risk. Cox proportional hazards regression models were used to examine the associations between presence of depressive symptoms with all-cause mortality and first hospitalization. The proportional hazards assumption was tested for both outcomes and found to be valid. Results were reported as hazard ratios (HR) with 95% confidence intervals (CI).

Ten of the 11 most commonly used prognostic markers for chronic HF outcomes identified from the published literature by Ouwerkerk and his colleagues were included in the model as confounding factors [6]; we chose this model as it distinguishes between prognostic markers for acute and chronic HF patients. Information on the New York Heart Association (NYHA) functional classification [24] was not consistently available and thus was not included in the model. Age, systolic blood pressure, estimated glomerular filtration rate, serum sodium and blood urea nitrogen were included in multivariable models as confounders and modelled as continuous variables. Ejection fraction was log transformed and included as continuous variables in the multivariable models. Gender, presence of diabetes, ischaemic aetiology and elevated B-Type natriuretic peptide (BNP) or N-Terminal pro-BNP (NT-BNP) were included as categorical variables. The 10 confounding factors identified by Ouwerkerk and colleagues were included in all multivariable models.
The prognostic utility of presence of depressive symptoms for 2-year mortality and hospitalization risk prediction was compared against a base model consisting of the 10 prognostic markers described above using three different statistical methods: area under the receiver operating characteristic curve (AUC), integrated discrimination improvement (IDI) and a continuous version of the net reclassification improvement (NRI) [25,26]. The IDI indicates if adding presence of depressive symptoms to the prediction model improves the discrimination slope, defined as the average predicted probability of outcome for those who experienced the outcome versus those who did not. The IDI is the difference in the discrimination slopes for the models with and without presence of depressive symptoms. The NRI assesses net improvement in risk classification. Individuals are divided into those who experienced the outcome and those who did not. The predicted probability of the outcome is calculated for each individual, first using the base prediction model and then after adding presence of depressive symptoms to the model. The NRI is a measure of the number of individuals who experienced the outcome who were reclassified upward and the number of individuals who did not experience the outcome who were reclassified downward after adding presence of depressive symptoms to the model. Outcomes within the first 2 years after HF were included in the analyses. Because the NRI and IDI analyses require that the outcome be known, patients who were lost to follow-up before 2 years and who were known to be alive at the last follow-up were excluded from the analyses. In predicting all-cause mortality and hospitalization, values of AUC were reported for the base model and after adding presence of depressive symptoms. A p-value of less than 0.05 was used to assess statistical significance. Sensitivity analyses included repeating the analyses for the presence of moderate to severe depression (PHQ-9 ≥10), and also repeating the analysis using PHQ-9 as a continuous variable. All analyses were performed using R 3.0.2 (The R Foundation for Statistical Computing) [27] and SAS version 9.3 (SAS Institute Inc., Cary, NC).

Results

Patient Population and Characteristics

A total of 1147 patients with chronic HF diagnosed between October 2007 and December 2011 were approached to participate in the study and 663 (58.0%) patients consented. The patients who were approached but refused to participate were significantly older (mean age 78.6 ± 12.2 vs. 74.1 ± 13.3, respectively, p<0.001) and significantly more likely to be female (54.3% vs 45.4% respectively, p = 0.003) than study participants. Of those, 546 (82.0%) completed the PHQ-9 at a median time of 39 days (25th, 75th percentile: 27, 58) after enrolment. Eleven patients were excluded because they were lost to follow-up before the end of 2 years and 110 were excluded due to missing covariate values, resulting in 425 patients (mean age (SD) 73.5 (13.2); 57.6% men) included in the analyses (Fig 1). Among the study participants, 179 (42.1%) patients had depressive symptoms based on a PHQ-9 score ≥5, while 61 (14.4%) patients were classified as having moderate to severe depression based on a PHQ-9 score ≥10. The 10 clinical measures included in the base prognostic model are presented for patients with and without depressive symptoms in Table 1. No statistically significant differences were observed between the two patient groups, with the exception of age as patients with depressive symptoms were younger.

Presence of Depressive Symptoms, All-cause Mortality and Hospitalization

At the end of 2 years, 99 (23.3%) patients had died and 299 (70.4%) patients had at least 1 hospitalization. Patients with depressive symptoms had worse survival and hospitalization-free
survival over 2 years of follow-up (Fig 2). Presence of depressive symptoms was associated with 
more than a 2-fold increased risk of all-cause mortality within 2 years, unadjusted and after 
adjusting for the 10 most commonly used prognostic factors (Table 2). The unadjusted and 
adjusted risk of hospitalization was almost 50% higher among HF patients with depression 
compared to those without it.

Prognostic Utility of Depression in Prediction of All-cause Mortality and 
First Hospitalization

Table 3 compares the prognostic utility of adding depressive symptoms to the base model in 
predicting all-cause mortality and hospitalization within 2 years. The difference between the 
two models was not statistically significant for AUC values for either of the two outcomes. 
However, the IDI and NRI values showed statistically significant improvement for predicting

Table 1. Established prognostic factors at baseline in chronic heart failure patients with and without depressive symptoms.

|                                    | Patients with depressive symptoms (N = 179) | Patients without depressive symptoms (N = 246) | p-value |
|------------------------------------|--------------------------------------------|-----------------------------------------------|---------|
| Age (years), mean (SD)             | 71.77 (13.50)                              | 74.79 (12.77)                                 | 0.02    |
| Male                               | 108 (60.34%)                               | 137 (55.69%)                                  | 0.34    |
| Systolic BP (mm Hg), mean(SD)      | 123.00 (23.12)                             | 124.57 (23.04)                                | 0.49    |
| Estimated glomerular filtration rate, mean (SD) | 56.32 (25.29)                             | 57.70 (21.16)                                  | 0.54    |
| Ejection fraction (%), median (25th, 75th 
percentile) | 45.33 (31.00, 60.00)                     | 50.00 (33.20, 60.00)                           | 0.26    |
| Serum sodium (mmol/l), median (25th, 75th 
percentile) | 140.00 (137.00,141.00)                  | 139.00 (137.00,141.00)                         | 0.88    |
| Elevated level of BNP/NT-BNP       | 126 (70.39%)                               | 177 (71.95%)                                  | 0.73    |
| Ischemic etiology                  | 76 (42.46%)                                | 105 (42.68%)                                  | 0.96    |
| Prior diabetes mellitus            | 76 (42.46%)                                | 87 (35.37%)                                   | 0.14    |

Legend: Results are reported as n (%) unless otherwise noted. Presence of depressive symptoms defined as 9-item Patient Health Questionnaire (PHQ-9) ≥5. BNP = B-Type natriuretic peptide; BP = blood pressure; NT-BNP = N-Terminal pro-BNP; PHQ-9 = 9-item Patient Health Questionnaire; SD = standard deviation.
all-cause mortality after adding depressive symptoms. Regarding hospitalizations, the IDI and NRI-continuous showed statistically significant improvement after adding depressive symptoms to the model.

Sensitivity Analysis
Results of sensitivity analyses are presented in S1 File. A stronger association was observed between presence of moderate to severe depression (PHQ-9≥10) and all-cause mortality and hospitalization, when compared to mild or no depressive symptoms. Additionally, the NRI and IDI values improved significantly in predicting death and hospitalization, while there was no significant change in the AUC values. Furthermore, when analysing the PHQ-9 score as a continuous variable, a 10% increase in all-cause death and a 5% increase in hospitalization were observed per point increase in PHQ-9 score after adjustment for the 10 most commonly used prognostic factors.

Discussion
In a community cohort in the US, patients with chronic HF were found to have a high prevalence of depressive symptoms. Depression was associated with a higher risk of death and hospitalization compared to those without depression. These findings remain unchanged after adjusting for the 10 most commonly used prognostic factors in risk prediction for HF outcomes. Finally, adding depression to an existing prognostic model improved the prognostic utility in predicting death and hospitalization.

Table 2. Hazard ratios for all-cause death and first hospitalization within 2 years after HF for chronic heart failure patients with vs without depressive symptoms.

|                  | All-Cause Death | Hospitalization |
|------------------|-----------------|-----------------|
| Number of patients| 425             | 425             |
| Number of events  | 99              | 299             |
| Unadjusted HR (95% CI) | 1.87 (1.26, 2.78) | 1.48 (1.18, 1.86) |
| Adjusted* HR (95% CI) | 2.02 (1.34–3.04) | 1.42 (1.13–1.80) |

Legend: Presence of depressive symptoms defined as 9-item Patient Health Questionnaire (PHQ-9) ≥5. CI = Confidence interval; HR = Hazard Ratio.

*Adjusted for age, sex, systolic blood pressure, estimated glomerular filtration rate, blood urea nitrogen, serum sodium, elevated B-Type natriuretic peptide (BNP) or N-Terminal pro-BNP, ejection fraction, ischaemic aetiology and prior diabetes.

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Published results on the prevalence of depression in HF are varied. In our cohort, the prevalence of depression was 40.7% based on a symptom questionnaire, which is congruent with the reported prevalence of 33.6% in a meta-analysis [15]. HF patients with co-existing depression were approximately twice as likely to die in our study, which is consistent with previous findings [15]. Depression was also associated with an increase in the risk of hospitalization, which is again consistent with previous findings [14,15,28–31].

Two previous studies have assessed the prognostic utility of depression; however they have used “history of previous depression” as opposed to “current depression” as was used in our study [32,33]. Herein, addition of depression did not improve AUC values from the base model for predicting death and hospitalization. The lack of sensitivity of AUC in judging prognostic utility of a new marker has been discussed previously and the present study underscores the importance of incorporating methods such as IDI and NRI in risk prediction [26,34].

Limitations, Strengths and Implications
Depressive symptoms were measured only at enrolment and we cannot account for changes during follow-up. Some of the symptoms of depression overlap with common symptoms of HF, such as fatigue, low energy, psychomotor retardation, and sleep disturbances [13]. While the NYHA functional status was not consistently available in our cohort, evidence suggests inconsistency and high inter-operator variability in clinical recordings of NYHA in practice, which illustrates the practical problems in using it as a prognostic marker [35]. Further, depression has been shown to predict death and hospitalization in HF independent of NYHA functional status [28]. Finally, the population of southeast Minnesota is chiefly white and thus, our results should be examined in other racial groups.

Our study has a number of notable strengths. The participants were recruited from a community cohort, including both inpatients and outpatients, which is of optimal clinical relevance. Depression was prospectively ascertained using a validated instrument and follow-up was complete for critical outcomes in HF. Analytically, we used robust and complementary risk prediction methods which optimize our ability to assess the prognostic value of depression.

Despite the high prevalence of depressive symptoms in HF [15], it remains under recognized [36], and no study to date, to the best of our knowledge, has demonstrated the benefits of routine depression screening [37]. Indeed, treatment with anti-depressants has not shown any clear benefit in reducing depressive symptoms, deaths and hospitalization in HF [38–40].

Table 3. Comparison of the prognostic utility of adding depressive symptoms to the base model in predicting all-cause mortality and hospitalization within 2 years after heart failure in chronic heart failure patients.

| Outcome          | Model                          | AUC (95% CI)      | IDI, % (95% CI) | NRI-continuous, % (95% CI) | p-value |
|------------------|--------------------------------|-------------------|----------------|-----------------------------|---------|
| All-cause Death  | Base model*                    | 0.781 (0.729–0.834)| 3.10 (1.28–4.92) | 35.04 (12.80–57.27) | 0.06    |
|                  | Base model + depressive symptoms| 0.800 (0.748–0.852)| 0.06           | 0.001                       | 0.002   |
| Hospitalization  | Base model*                    | 0.667 (0.609–0.724)| 1.73 (0.53–2.93) | 27.23 (7.34–47.11) | 0.36    |
|                  | Base model + depressive symptoms| 0.679 (0.621–0.736)| 0.005          | 0.007                       | 0.007   |

Legend: Presence of depressive symptoms defined as 9-item Patient Health Questionnaire (PHQ-9) ≥5. AUC = area under curve; CI = confidence interval; IDI = integrated discrimination improvement; NRI = net re-classification improvement.

*Base model includes age, sex, systolic blood pressure, estimated glomerular filtration rate, blood urea nitrogen, serum sodium, elevated B-Type natriuretic peptide (BNP) or N-Terminal pro-BNP, ejection fraction, ischaemic aetiology and prior diabetes.

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There is some conflicting evidence about the use of cognitive behavioural therapy (CBT) in reducing depressive symptoms in HF patients, with a review suggesting no benefit [41], while some of the recent studies showing improvement in depressive symptoms with CBT [42,43]. On the other hand, other psychological interventions such as mindfulness-based stress reduction [44] have been shown to have the potential to improve depressive symptoms in HF patients. The recent guidelines published by the American Heart Association and the American College of Cardiology guidelines discuss the importance of depression as an important co-morbidity in heart failure patients and its association with reduced poor quality of life and poor health outcomes [4]. Some research suggests that lack of perceived social support may be an important mediator of poor prognosis associated with depression in HF patients [45,46], which in turn is potentially modifiable [47]. Further research should address these knowledge gaps.

It is important to underscore that ascertaining depression relies on a clinical assessment, which is efficient and not costly. We demonstrated the incremental information conferred by depression over well-established clinical factors, thereby indicating that assessing mental health and depression should be part of the holistic clinical evaluation of patients living with HF.

**Conclusion**

In HF, depression is frequent and is associated with an increase in deaths and hospitalizations. Depression increases the prognostic value of established and commonly used factors in HF patients. Further research is needed to determine the role of depression screening and ascertain the best strategies for managing depressive symptoms in HF patients.

**Supporting Information**

S1 File. Sensitivity Analysis.
(DOCX)

S2 File. Dataset.
(XLSX)

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**Author Contributions**

Conceived and designed the experiments: BJ VR SW FM AC. Analyzed the data: BJ SW RJ AC. Wrote the paper: BJ FM VR SW RJ AC.

**References**

1. Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. Nat Rev Cardiol. 2011; 8: 30–41. doi:10.1038/nrcardio.2010.165 PMID: 21060326

2. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Executive summary: heart disease and stroke statistics—2013 update: a report from the American Heart Association. Circulation. 2013; 127: 143–52. doi: 10.1161/CIR.0b013e318262ab8f PMID: 23283859

3. Guha K, McDonagh T. Heart failure epidemiology: European perspective. Curr Cardiol Rev. 2013; 9: 123–7. PMID: 23997298

4. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013; 62: e147–239. doi: 10.1016/j.jacc.2013.05.019 PMID: 23747642
5. Steyerberg E. Clinical Prediction Models. A Practical Approach to Development, Validation, and Updating Series. NY: Springer; 2012.

6. Ouwerman AH. Factors influencing the predictive power of models for predicting mortality and/or heart failure hospitalization in patients with heart failure. JACC Heart Fail. 2014; 2: 429–36. doi: 10.1016/j.jchf.2014.04.006 PMID: 25194294

7. Betham AV, Davidson PM, Newton PJ, Frost SA, MacDonald PS, Stewart S. What are the factors in risk prediction models for rehospitalisation for adults with chronic heart failure? Aust Crit Care. 2012; 25: 31–40. doi: 10.1016/j.aucc.2011.07.004 PMID: 21889883

8. Kansagara D, Englander H, Salaniro A, Kagen D, Theobald C, Freeman M, et al. Risk prediction models for hospital readmission: a systematic review. JAMA. 2011; 306: 1688–98. doi: 10.1001/jama.2011.1515 PMID: 22009101

9. Nutter AL, Tanawuttiwat T, Silver MA. Evaluation of 6 prognostic models used to calculate mortality rates in elderly heart failure patients with a fatal heart failure admission. Congest Heart Fail. 2010; 16: 196–201. doi: 10.1111/j.1751-7133.2010.00180.x PMID: 20887615

10. Giamouzis G, Kalogeropoulos A, Georgiopoulou V, Laskar S, Smith AL, Dunbar S, et al. Hospitalization epidemic in patients with heart failure: risk factors, risk prediction, knowledge gaps, and future directions. J Card Fail. 2011; 17: 54–75. doi: 10.1016/j.cardfail.2010.08.010 PMID: 21872655

11. Rahimi K, Bennett D, Conrad N, Williams TM, Basu J, Dwight J, et al. Risk prediction in patients with heart failure: a systematic review and analysis. JACC Heart Fail. 2014; 2: 440–6. doi: 10.1016/j.jchf.2014.04.008 PMID: 25194291

12. Frasure-Smith N, Lespérance F, Habra M, Talajic M, Khairy P, Dorian P, et al. Elevated depression symptoms predict long-term cardiovascular mortality in patients with atrial fibrillation and heart failure. Circulation. 2009; 120: 134–40, 3p following 140. doi: 10.1161/CIRCULATIONAHA.109.851675 PMID: 19564557

13. Joynt KE, Whellan DJ, O’connor CM. Why is depression bad for the failing heart? A review of the mechanistic relationship between depression and heart failure. J Card Fail. 2004; 10: 258–71. PMID: 15190537

14. Moraska AR, Chamberlain AM, Shah ND, Vickers KS, Rummans TA, Dunlay SM, et al. Depression, healthcare utilization, and death in heart failure: a community study. Circ Heart Fail. 2013; 6: 387–94. doi: 10.1161/CIRCHEARTFAILURE.112.000118 PMID: 23512984

15. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. J Am Coll Cardiol. 2006; 48: 1527–37. doi: 10.1016/j.jacc.2006.06.055 PMID: 17045884

16. Sherwood A, Blumenthal JA, Trivedi R, Johnson KS, O’connor CM, Adams KF, et al. Relationship of depression to death or hospitalization in patients with heart failure. Arch Intern Med. 2007; 167: 367–73. doi: 10.1001/archinte.167.4.367 PMID: 17325299

17. United States Census Bureau. Population Estimates. In: Minnesota: 2010 [Internet]. 2012 [cited 5 Apr 2016]. Available: http://www.census.gov/prod/cen2010/cph-2-25.pdf

18. Rocca WA, Yawn BP, St Sauver JL, Grossardt BR, Melton LJ. History of the Rochester Epidemiology Project: half a century of medical records linkage in a US population. Mayo Clin Proc. 2012; 87: 1202–13. doi: 10.1016/j.mayocp.2012.08.012 PMID: 23199802

19. St Sauver JL, Grossardt BR, Leibson CL, Yawn BP, Melton LJ, Rocca WA. Generalizability of epidemiological findings and public health decisions: an illustration from the Rochester Epidemiology Project. Mayo Clin Proc. 2012; 87: 151–60. doi: 10.1016/j.mayocp.2011.11.009 PMID: 22305027

20. St Sauver JL, Grossardt BR, Yawn BP, Melton LJ, Rocca WA. Use of a medical records linkage system to enumerate a dynamic population over time: the Rochester epidemiology project. Am J Epidemiol. 2011; 173: 1059–68. doi: 10.1093/aje/kwq482 PMID: 21430193

21. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001; 16: 606–13. PMID: 11556941

22. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006; 145: 247–54. PMID: 16908915

23. Maisel A, Mueller C, Adams K, Anker SD, Aspromonte N, Cieles G, et al. State of the art: using natriuretic peptide levels in clinical practice. Eur J Heart Fail. 2008; 10: 824–39. doi: 10.1016/j.ejheart.2008.07.014 PMID: 18760965

24. The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. Human Biology. 1994. doi: 10.3738/027.083.0506
25. Pencina MJ, D’Agostino RB, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. Stat Med. 2011; 30: 11–21. doi: 10.1002/sim.4085 PMID: 21204120

26. Pencina MJ, D’Agostino RB, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med. 2008; 27: 157–72; discussion 207–12. doi: 10.1002/sim.2929 PMID: 17569110

27. Team RC. R Core Team (2012). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0. http://www.R-project.org/. [Internet]. 2012. p. -. Available: http://www.r-project.org/

28. Jiang W, Alexander J, Christopher E, Kuchibhatla M, Gaulden LH, Cuffe MS, et al. Relationship of Depression to Increased Risk of Mortality and Rehospitalization in Patients With Congestive Heart Failure. Arch Intern Med. 2001; 161: 1849. doi: 10.1001/archinte.161.15.1849 PMID: 11493126

29. Fulop G, Strain JJ, Stetin G. Congestive heart failure and depression in older adults: clinical course and health services use 6 months after hospitalization. Psychosomatics. 2003; 44: 367–73. doi: 10.1176/appi.psych.44.5.367 PMID: 12954910

30. Koenig HG. Depression in hospitalized older patients with congestive heart failure. Gen Hosp Psychia-

31. Faris R, Purcell H, Henein MY, Coats AJ.S. Clinical depression is common and significantly associated with reduced survival in patients with non-ischaemic heart failure. Eur J Heart Fail. 2002; 4: 541–551. doi:10.1016/S1388-9842(02)00101-0 PMID: 12167395

32. O’Connor CM, Abraham WT, Albert NM, Clare R, Gattis Stough W, Gheorghiade M, et al. Predictors of mortality after discharge in patients hospitalized with heart failure: an analysis from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). Am Heart J. 2008; 156: 662–73. doi: 10.1016/j.ahj.2008.04.030 PMID: 18926148

33. Amarasingham R, Moore BJ, Tabak YP, Drazner MH, Clark CA, Zhang S, et al. An automated model to identify heart failure patients at risk for 30-day readmission or death using electronic medical record data. Med Care. 2010; 48: 981–8. doi: 10.1097/MLR.0b013e3181e860d9 PMID: 20940649

34. Cook NR. Use and misuse of the receiver operating characteristic curve in risk prediction. Circulation. 2007; 115: 928–35. doi: 10.1161/CIRCULATIONAHA.106.672402 PMID: 17309939

35. Raphael C, Briscoe C, Davies J, Ian Whinnett Z, Manisty C, Sutton R, et al. Limitations of the New York Heart Association functional classification system and self-reported walking distances in chronic heart failure. Heart. 2007; 93: 476–482. PMID: 17005715

36. Cully JA, Jimenez DE, Ledoux TA, Deswal A. Recognition and treatment of depression and anxiety symptoms in heart failure. Prim Care Companion J Clin Psychiatry. 2009; 11: 103–9. PMID: 19617942

37. Ontario HQ. Screening and management of depression for adults with chronic diseases: an evidence-based analysis. Ont Health Technol Assess Ser. 2013; 13: 1–45.

38. Fraguas R, da Silva Telles RM, Alves TCTF, Andrei AM, Rays J, Iosifescu D V, et al. A double-blind, placebo-controlled treatment trial of citalopram for major depressive disorder in older patients with heart failure: the relevance of the placebo effect and psychological symptoms. Contemp Clin Trials. 2009; 30: 205–11. doi: 10.1016/j.cct.2009.01.007 PMID: 19470312

39. Chung ML, Dekker RL, Lennie TA, Moser DK. Antidepressants do not improve event-free survival in patients with heart failure when depressive symptoms remain. Heart Lung. 2013; 42: 85–91. doi: 10.1016/j.hrtlng.2012.12.003 PMID: 23306168

40. Jiang W, Krishnan R, Kuchibhatla M, Cuffe MS, Martsberger C, Arias RM, et al. Characteristics of depression remission and its relation with cardiovascular outcome among patients with chronic heart failure (from the SADHART-CHF Study). Am J Cardiol. 2011; 7: 127–41. doi: 10.1016/j.amjcard.2010.10.013 PMID: 21295172

41. Dekker RL. Cognitive therapy for depression in patients with heart failure: a critical review. Heart Fail Clin. 2011; 7: 127–41. doi: 10.1016/j.hfcl.2010.10.001 PMID: 21109215

42. Freedland KE, Carney RM, Rich MW, Steinmeyer BC, Rubin EH. Cognitive Behavior Therapy for Depression and Self-Care in Heart Failure Patients: A Randomized Clinical Trial. JAMA Intern Med. American Medical Association; 2015; 175: 1–10. doi: 10.1001/jamainternmed.2015.5220

43. Dekker RL, Moser DK, Peden AR, Lennie TA. Cognitive therapy improves three-month outcomes in hospitalized patients with heart failure. J Card Fail. 2012; 18: 10–20. doi: 10.1016/j.cardfail.2011.09.008 PMID: 22196836

44. Sullivan M, Wood L, Terry J, Brantley J, Charles A, Vicky M, et al. The Support, Education, and Research in Chronic Heart Failure Study (SEARCH): a mindfulness-based psychoeducational intervention improves depression and clinical symptoms in patients with chronic heart failure. Am Heart J. 2009; 157: 84–90. doi: 10.1016/j.ahj.2008.08.033 PMID: 19081401
45. Chung ML, Moser DK, Lennie TA, Frazier SK. Perceived social support predicted quality of life in patients with heart failure, but the effect is mediated by depressive symptoms. Qual Life Res. 2013; 22: 1555–63. doi: 10.1007/s11136-012-0294-4 PMID: 23076798

46. Chung ML, Lennie TA, Dekker RL, Wu J-R, Moser DK. Depressive symptoms and poor social support have a synergistic effect on event-free survival in patients with heart failure. Heart Lung. 2011; 40: 492–501. doi: 10.1016/j.hrtlng.2010.08.001 PMID: 21453972

47. Graven LJ, Grant J. The impact of social support on depressive symptoms in individuals with heart failure: update and review. J Cardiovasc Nurs. 2013; 28: 429–43. doi: 10.1097/JCN.0b013e3182578b9d PMID: 22728774