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The Real World Mental Health Needs of Heart Failure Patients Are Not Reflected by the Depression Randomized Controlled Trial Evidence

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Abstract

Introduction: International depression screening guidelines in heart failure (HF) are partly based on depression treatment efficacy from randomized controlled trials (RCTs). Our aim was to test the external validity of depression RCT criteria in a sample of real-world HF patients.

Methods: HF patients admitted to 3 hospitals in South Australia were referred to a HF psychologist if not already receiving current psychiatric management by psychologist or psychiatrist elsewhere. Screening and referral protocol consisted of the following; (a). Patient Health Questionnaire ≥10; (b). Generalized Anxiety Disorder Questionnaire ≥7); (c). positive response to 1 item panic attack screener; (d). evidence of suicidality. Patients were evaluated against the most common RCT exclusion criteria personality disorder, high suicide risk, cognitive impairment, psychosis, alcohol or substance abuse or dependency, bi-polar depression.

Results: Total 81 HF patients were referred from 404 HF admissions, and 73 were assessed (age 60.6±13.4, 47.9% female). Nearly half (47%) met at least 1 RCT exclusion criterion, most commonly personality disorder (28.5%), alcohol/substance abuse (17.8%) and high suicide risk (11.0%). RCT ineligibility criteria was more frequent among patients with major depression (76.5% vs. 46.2%, p<.01) and dysthymia (26.5% vs. 7.7%, p = .03) but not significantly associated with anxiety disorders. RCT ineligible patients reported greater severity of depression (M = 16.6±5.0 vs. M = 12.9±7.2, p = .02) and were higher consumers of HF psychotherapy services (M = 11.5±4.7 vs. M = 8.5±4.8, p = .01).

Conclusion: In this real-world sample comparable in size to recent RCT intervention arms, patients with depression disorders presented with complex psychiatric needs including comorbid personality disorders, alcohol/substance use and suicide risk. These findings suggest external validity of depression screening and RCTs could serve as a basis for level A guideline recommendations in cardiovascular diseases.

Introduction

Depression has gained widespread research attention with respect to prognosis of heart diseases including heart failure (HF) [1]. A meta-analysis by Rutledge et al. [2] suggested that the prevalence of clinical depression was 22% in HF, thus substantially higher than community prevalence estimates for populations free from heart failure [3]. It has been consistently shown that depression doubles the risk of major cardiac events and death in patients with documented HF [2,4,5], increases healthcare costs [6], significantly impairs quality of life [7–9], impairs self-care ability [10] and impacts upon participation in HF disease-management strategies [11]. Consequently, depression identification and management is emphasized in international cardiology

guidelines [12–15], HF treatment guidelines [16] and HF self-management recommendations [17].

Though a number of studies have applied routine depression screening protocols to improve recognition of depression [18–27] a paucity of information exists regarding the ensuing mental health management strategies initiated within cardiology settings from a positive depression-screen [22,28–31]. Thombs and colleagues systematic reviews confirm that a number of issues regarding routine screening remain unclear [28,29]. As the utility for depression screening alone in reducing depression and cardiovascular morbidity has not been established [22], randomised, controlled trials (RCTs) provide Level A empirical evidence to guide clinical practice for depression management in HF [2,32]. For example, the Safety and Efficacy of Sertraline for Depression

in Patients with Chronic Heart Failure trial was designed to facilitate easy translation into clinical practice [33]. Unfortunately, however, the extant depression RCT evidence in HF [32–36] has not been subjected to tests of external and ecological validity and therefore, the implications for clinical practice are not known [37]. Moreover, if external validity of depression RCTs is not established then unrealistic expectations regarding depression treatment response may be fostered among clinicians and patients alike [38]. Complicating these matters further, the American Heart Association guidelines recommend comprehensive assessment of other mental disorders such as anxiety [12] which are present in 30% of RCT patients with positive depression screen [39]. Yet Hasnain and colleagues [22] also emphasize the lack of guidance for individualized depression treatment plans when such comorbidity is present. Consequently, underestimation of the complexity of real-world mental health treatment needs may hamper concerted efforts to implement depression screening guidelines [12,13,16,17] and integrate depression management into HF clinical practice [19,40,41].

The topical nature of routine depression and anxiety screening [28,29] suggests it is timely to examine the practical implementation of integrated mental health care within real-world HF settings [30] subsequent to guideline based routine depression-screening initiatives. This study reports on referrals to a HF-specific psychologist generated from routine depression and anxiety screening in three public hospitals in Adelaide, South Australia. The following research questions will be answered:

1. To what extent are real-word HF-patients with depression covered by the inclusion and exclusion criteria of RCTs on depression in HF patients?

2. Do RCT ineligible patients differ from RCT eligible patients with respect to demographic and clinical characteristics?

3. What are the prevalence rates of various depression and anxiety disorders among HF patients referred for integrated mental health management after routine depression and anxiety screening?

Methods

Patient Selection

This study received ethics approval and all participants provided written and informed consent prior to assessment (Human Research Ethics Committee of The Queen Elizabeth Hospital, Lyell McEwin Hospital and Royal Adelaide Hospital #HREC/12/TQEHLMH/188). Between April 2011 and June 2012 patients with verified HF admission were managed by specialist HF nurses in a HF self-management program (HFSMP) [17] at three South Australian hospitals (Queen Elizabeth Hospital, Royal Adelaide Hospital, Lyell McEwin Hospital). During this period specialist HF nurses routinely screened patients with validated questionnaires and referred patients to the HFSMP psychologist when either of the following criteria were met; (a). depression symptoms were in the clinically significant range (Patient Health Questionnaire (PHQ-9) ≥10); (b). anxiety symptoms were in the clinically significant range (Generalized Anxiety Disorder (GAD-7) ≥7); (c). patients had evidence of panic attack (N.B. questionnaires described further below). (d). there was evidence of suicidality (PHQ or identified by nurse). Median time between referral and assessment was 20 days. A flow chart of participants through the study is shown in Figure 1.

HFSMP and Consent Process

Referred patients were contacted by telephone to schedule the initial mental health assessment and all facets of HFSMP care was provided at no cost. The HFSMP was community based, delivered flexibly at home visit, hospital site, or prior to weekly HFSMP exercise classes at Hampstead Rehabilitation Hospital. Ineligibility criteria for psychologist referral was not having cardiologist verified HF or currently receiving psychology and/or psychiatrist support elsewhere.

Patients who consented to standard HFSMP psychology assessment were free to refuse treatment at any time in accordance with ethical guidelines and government primary health care protocols. Patients not desiring the HFSMP psychology assessment (n = 5) were provided with alternative counselling arrangements including psychiatrist referral, local psychologist support and tele-counselling. Refusal did not impinge on standard cardiology care. HFSMP psychology was withdrawn in cases when patients transitioned to a palliative care team and the associated mental health supports. Patients requiring acute psychiatric care were managed by the treating psychologist in collaboration with the 24 hour South Australian Mental Health Emergency Triage Service for Community and Older Persons (Acute Crisis Intervention Service).

Psychological Assessment

Referred patients repeated the depression and anxiety questionnaire at the psychologist intake assessment and again before each subsequent psychologist appointment to verify symptom response to treatment. The PHQ-9 [42] is a 9 item depression questionnaire covering major depression disorder criteria demarcated by DSM-IV [3]. Respondents endorse items based on the previous two-weeks on a scale of 0 "not at all" to 3 "nearly every day." PHQ scores ≥10 warrant further evaluation according to the American Heart Association guidelines [12] and have favorable sensitivity and specificity for detection of depression disorder in heart disease populations [43].

Patients also completed an 8 item questionnaire regarding anxiety (Generalized Anxiety Disorder-7, 7 items (GAD-7); and a one-item panic screener "In the last 4 weeks, have you had an anxiety attack – suddenly feeling fear or panic?") [44–46]. The GAD-7 is a 7 item anxiety questionnaire covering Generalized Anxiety Disorder criteria demarcated by DSM-IV [3] and GAD-7 scores ≥7 warrant further evaluation [46]. The single-item panic disorder screener also showed favorable sensitivity and specificity in detection of panic disorder amongst medical and psychosomatic medicine populations [47]. The anxiety measures were selected in addition to depression screening as the American Heart Association [12] guidelines advocate comprehensive assessment of anxiety disorders. Also, anxiety disorders are highly prevalent in heart diseases and predict higher rates of cardiovascular morbidity and mortality in patients with heart disease [48–54].

Patients were assessed with the Structured Clinical Interview for DSM-IV Axis-I and AXIS-II disorders [55,56]. The SCID is a widely validated interview with favourable psychometric properties. Psychologist diagnoses were verified by two senior clinical psychologists once per month.

Comparison with RCT Exclusion Criteria

Comparison of the present community treatment sample against RCT exclusion criteria focussed on depression interventions as there are no known anxiety disorder interventions in HF patients. Ineligibility for RCT was determined from the recent systematic review of depression interventions in HF reported by Woltz and colleagues [32]. Woltz et al. [32] evaluated 23
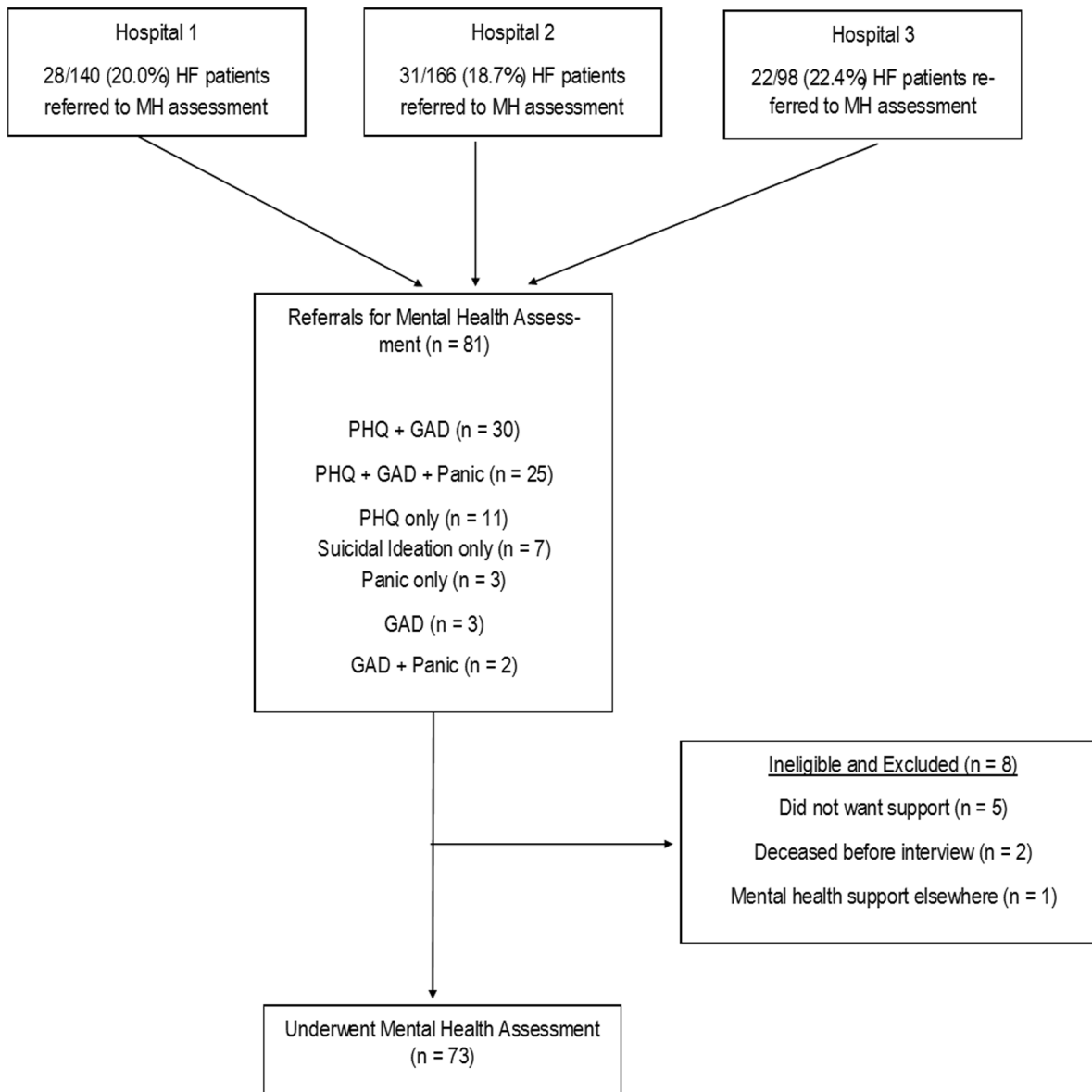
Figure 1. Flow chart of patients through the study.
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experimental and quasiexperimental HF trails (Total N = 3,564 patients) reporting depression symptom change from a range of interventions. Here we focussed solely on the six RCTs that evaluated either antidepressant or psychotherapy (i.e. cognitive-behavioural therapy, relaxation, mindfulness stress reduction) [33,36,57–61]. Ineligibility of our real world patients was determined against the six most common RCT exclusion criteria extracted from the included trials in Woltz et al [31]:

1. personality disorder [33,36,58,61]: SCID diagnosis of a personality disorder

2. suicide risk [33,36,57,59]; score of PHQ item 9≧2, verified at structured interview

3. cognitive impairment [33,36,57,61]: Mini Mental State Examination ≦23, verified dementia or developmental disorder

4. current or past psychosis [33,36,57,59,61]: SCID diagnosis of a psychotic episode/disorder

5. active alcohol/substance abuse or dependency [33,57,59–61]: SCID diagnosis of alcohol/substance abuse or dependency

6. current or past bi-polar [33,59,61]: SCID diagnosis of bi-polar disorder

Statistical Analyses

Data analysis was performed with SPSS® 19.0 (SPSS Inc., Chicago, IL). Descriptive comparisons between RCT eligible and ineligible groups employed the independent samples t-test, and the chi-square statistic with Fisher's exact test as appropriate. All statistical tests were two-tailed, an alpha value $p<.05$ was considered statistically significant. This exploratory study pertains to RCT criteria validation and we have therefore not adjusted for multiple comparisons [62].

Results

During the study period 81 patients were referred to HF mental health care, 8 were not included (did not want support (n = 5), HF death prior to mental health assessment (n = 2), receiving psychology treatment elsewhere (n = 1). This left a sample of 73 patients whom underwent mental health assessment and psychotherapy as appropriate (Flow Chart shown in Figure 1.).

Prevalence of RCT Eligibility by Depression Criteria

Nearly half (46.6%) of assessed patients would be excluded from RCTs according to the six standard exclusion criteria (Table 1). The most common RCT exclusion criterions were personality disorder (28.8%), alcohol/substance abuse or dependency (17.8%) and suicide risk (11.0%). Analysis comparing the proportion of each RCT eligibility criteria between patients with depression disorder (major depression or dysthymia ± any anxiety) with those without depression disorder showed that patients with a mood disorder were more likely to meet at least 1 RCT exclusion criteria (60.4% vs. 29%, p<.001), particularly personality disorder (41.7% vs. 4.0%, p<.001) and alcohol/substance abuse or dependency (25.0% vs. 4.0%, p = .03). The proportion of RCT exclusion criteria by depression diagnosis is depicted in Figure 2.

Demographic Descriptives According to RCT Eligibility

Comparison of the RCT eligible and ineligible patients with respect to demographics and comorbidities is shown in Table 2 (age M = 60.6±13.4, 47.9% female, 8.2% Indigenous Australian). RCT ineligible patients were more likely to have chronic pain documented in medical records (29.4% vs. 10.3%, p = .04). Ineligible patients were also less likely to have had a prior myocardial infarction (32.4% vs. 59.0%, p = .03), and there were no other significant differences.
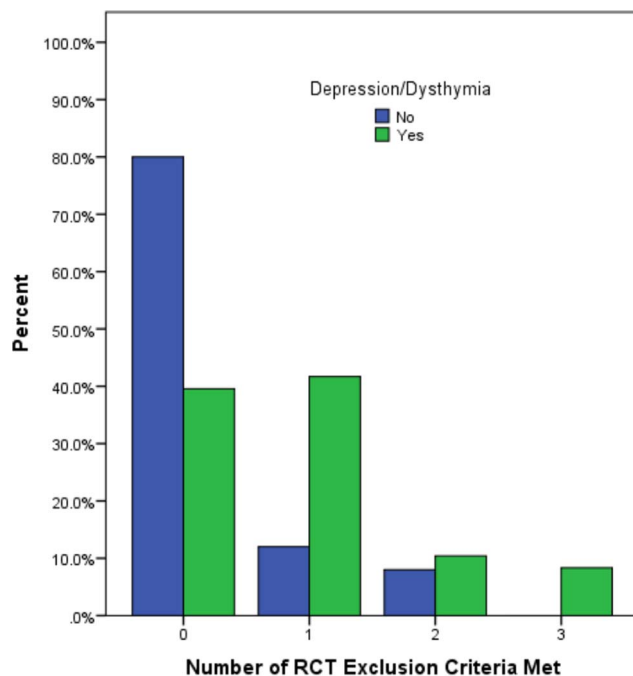
Figure 2. Proportion of standard RCT exclusion criteria met by HF patients according to depression status (yes vs. no).
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Psychosocial Descriptives According to RCT Eligibility

Comparison of the RCT eligible and ineligible patients with respect to clinical psychiatric factors is shown in Table 3. RCT ineligible patients were more likely to receive anti-depressant treatment including amitriptyline (58.8% vs. 23.1%, p<.01) and reported greater severity of depression (PHQ M = 16.6±5.0 vs. 12.9±7.2, p = .02). RCT ineligible patients were also higher consumers of psychotherapy sessions during the HFSMP (M = 11.5±4.7 vs. 8.5±4.8, p = .01).

Mental Health Prevalence Rates

The prevalence of depression and anxiety disorders is shown in Table 4 and stratified according to RCT eligibility. The most common disorders were major depression (60.3%), GAD (57.5%), panic disorder (52.1%) and social phobia (27.4%). Among the patients with a major depression or dysthymia diagnosis, 8/48 did not meet comorbid anxiety diagnosis. Comparison of patients based on RCT ineligibility showed an association with major depression (76.5% vs. 46.2%, p<.01) and dysthymia (26.5% vs. 7.7%, p = .03) and was not significantly associated with anxiety disorders.

Discussion

This study reports the mental health status subsequent to depression and anxiety screening among HF patients. Psychological assessment suggested that patients commonly presented with emotional disorders other than depression including GAD and panic disorder, consistent with other research [54,63–67]. However, psychiatric history would preclude nearly half of these HF patients from participation in contemporary depression RCTs based on six standard exclusion criteria identified from Woltz et al's [32] systematic review. RCT ineligibility was highest amongst patients with depression disorders. Also, RCT ineligible patients reported greater severity of depression, chronic pain and were higher consumers of psychotherapy. Together the findings indicate that routine depression screening protocols may underestimate or not align with the real world psychiatric needs in HF. Consequently the extant depression treatment evidence may not even apply to half of cardiovascular patients referred for further psychiatric assessment.

A number of effective treatments for depression have been reported [68] though effects on suicidality are less clear [69]. The results here belie the assumption that depression is the only psychosocial factor for which HF patients require mental health care. These findings thus support the recent examples of routine anxiety screening in general cardiovascular patients [18,64,65]. Hasnain and colleagues [22] highlighted the absence of clinical guidance for individualized treatment plans when comorbid anxiety is present. The extent to which comorbid anxiety affects depression treatment response is unknown even though 30% of cardiac patients with a positive depression screen in a recent RCT met anxiety disorder criteria [39]. Clearly a limitation to mental health service provision and routine screening protocols among cardiovascular patients is the paucity of evidence-based treatments for individual anxiety disorders. Encouragingly, Shemesh et al showed that brief imaginal exposure and cognitive-behavioural therapy for PTSD after a cardiovascular event was associated with no marked increase in blood pressure, pulse and mean arterial pressure [70]. However safety of exposure-based anxiety treatments has not been demonstrated for GAD or panic [53]. These anxiety disorders were among the most common anxiety disorders prevalent here and elsewhere [54,63] and may raise cardiovascular risk [71]. Nevertheless, psychotropic agents are utilized in early psychiatric intervention for anxiety disorders and also those

Table 1. Psychiatric RCT ineligibility in heart failure patients referred for psychiatric care according to depression status.

Psychiatric RCT exclusions	Total N(%) N = 73	No Depression (N = 25)	Depression (N = 48)	P
Personality disorder	21 (28.8)	1 (4.0)	20 (41.7)	.001*
High suicide risk	8 (11.0)	3 (12.0)	5 (10.4)	1.0
Cognitive impairment	3 (4.1)	2 (8.0)	1 (2.1)	.27
Current or past psychosis	2 (2.7)	0	2 (4.2)	.54
Active alcohol/substance abuse or dependency	13 (17.8)	1 (4.0)	12 (25.0)	.03*
Current or past bi-polar	2 (2.7)	0	2 (4.2)	.54
Met any RCT exclusion criteria	34 (46.6)	5 (20.0)	29 (60.4)	.001*
Number of RCT exclusion criteria met				<.01*
1	23 (31.5)	3 (12.0)	20 (41.7)	
2	7 (9.6)	2 (8.0)	5 (10.4)	
3	4 (5.5)	0	4 (8.3)	

RCT, randomized controlled trial.
*p<.05.
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Table 2. Comparison of RCT eligible and ineligible patients on demographics and medical comorbidity.

	Total N(%) N = 73	RCT Eligible N = 39	RCT Ineligible N = 34	P
Demographic and comorbidity factors				
Female	35 (47.9)	18 (46.2)	17 (50.0)	.74
Age, M(SD)	60.6 (13.4)	60.7 (13.9)	60.6 (13.1)	.98
Lives on own	19 (26.0)	8 (20.5)	11 (32.4)	.25
Disability Pension	22 (30.1)	11 (28.2)	11 (32.4)	.70
Indigenous Australian	6 (8.2)	4 (10.3)	2 (5.9)	.68
Current divorce/bereavement	8 (11.0)	3 (7.7)	5 (14.7)	.46
NYHA Class II	26 (35.6)	17 (43.6)	9 (26.5)	.35
III	39 (53.4)	18 (46.2)	39 (53.4)	
IV	8 (11.0)	4 (10.3)	8 (11.0)	
Left ventricular ejection fraction	33.9 (12.1)	34.2 (11.6)	33.5 (12.9)	.82
Prior myocardial infarction	34 (46.6)	23 (59.0)	11 (32.4)	.03*
Atrial fibrillation	25 (34.2)	11 (28.2)	14 (41.2)	.24
Coronary artery bypass	19 (26.0)	13 (33.3)	6 (17.6)	.13
Valve repair/replacement	12 (16.4)	4 (10.3)	8 (23.5)	.13
Biventricular pacemaker	11 (15.1)	7 (17.9)	4 (11.8)	.46
Implanted cardiac defibrillator	19 (26.0)	13 (33.3)	6 (17.6)	.13
Stroke/cerebrovascular accident	9 (12.3)	6 (15.4)	3 (8.8)	.40
Chronic obstructive pulmonary disease	22 (30.1)	11 (28.2)	11 (32.4)	.70
Renal disease	26 (35.6)	15 (38.5)	11 (32.4)	.59
Diabetes	38 (52.1)	21 (58.3)	17 (45.9)	.29
Hypertension	50 (68.5)	27 (75.0)	23 (62.2)	.24
Hypercholesterolemia	34 (46.6)	15 (41.7)	19 (51.4)	.41
Tobacco Smoking	31 (42.5)	18 (46.2)	13 (38.2)	.50
Body mass index kg/m^2 >35	25 (24.2)	11 (28.2)	14 (41.2)	.24
Sleep apnea	13 (17.8)	5 (12.8)	8 (23.5)	.23
Chronic Pain	14 (9.2)	4 (10.3)	10 (29.4)	.04*

NYHA, New York Heart Association; RCT, randomized controlled trial.
*p<.05.
doi:10.1371/journal.pone.0085928.t002

Table 3. Comparison of RCT eligible and ineligible patients on clinical psychiatric characteristics.

Clinical Psychiatric Factors	Total N(%) N = 73	RCT Eligible N = 39	RCT Ineligible N = 34	P
Psychotherapy sessions	9.8 (4.8)	8.5 (4.8)	11.5 (4.7)	.01*
Past suicide attempt	13 (17.8)	5 (12.8)	8 (23.5)	.23
No past psychiatric care	53 (72.6)	30 (76.9)	23 (67.6)	.44
Medical records depression	15 (20.5)	5 (12.8)	10 (29.4)	.08
Medical records missing depression diagnosis[a]	39 (53.4)	18 (46.2)	21 (61.8)	.18
Anti-depressant	29 (39.7)	9 (23.1)	20 (58.8)	<.01*
PHQ-9 total M(SD)	14.7 (6.5)	12.9 (7.2)	16.6 (5.0)	.01*
Any SCID anxiety disorder	52 (71.2)	26 (66.7)	26 (76.5)	.36
Medical records missing anxiety diagnosis[a]	42 (57.5)	21 (53.8)	21 (61.8)	.50
Current anxiolytic	21 (28.8)	8 (20.5)	13 (38.2)	.10
GAD-7 M(SD)	12.6 (6.7)	12.3 (7.1)	13.0 (6.4)	.67
Panic-Screener	28 (38.4)	13 (33.3)	15 (44.1)	.35

GAD, Generalized Anxiety Disorder; PHQ, Patient Health Questionnaire; RCT, randomized controlled trial.
*p<.05.
[a]Medical records depression and medical records anxiety inclusive of diagnoses that conflicts with psychologist SCID assessment. Medical records missing depression or anxiety diagnosis evaluates medical record comorbidity lists and hospital discharge summaries in preceding 6 months prior to assessment with the SCID diagnosis.
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psychiatric disorders which were RCT exclusions (i.e. alcohol/substance abuse, psychosis and bi-polar depression).

The current findings should not detract from the importance of prior RCT studies [32–36] and aspects of methodological rigour other than the six external validity criteria evaluated here. Application of appropriate exclusion criteria are essential to maintain internal validity. Other reasons justifying exclusion based on psychiatric criteria include ethical access to more appropriate treatment and reducing heterogeneity [72]. Diagnostic comorbidity also serves as a source of bias in depression treatment efficacy RCTs [73].

The current findings should thus serve to raise awareness regarding psychiatric illness complexity and comorbidity, particularly as treatment-resistant depression increases cardiovascular risk [74,75]. Here, RCT ineligibility was primarily associated with depression disorders. Patients with mood disorder were significantly more likely to have personality disorders and active alcohol/substance abuse or dependency. Recently it was also documented that treatment seeking panic disorder patients also reported high rates of active alcohol/substance abuse and personality disorders [76]. The findings support the necessity of

comorbidity assessment by qualified professionals after a positive depression screen [12]. Indeed, the clinical importance of such assessments are bolstered by findings that the functional aspects of HF do not correlate with suicide risk [77], whereas personality disorders, anxiety and depression are more established factors that increase suicide risk [78,79].

The strength of this study was comprehensive psychological assessment after a routine depression and anxiety screening initiative in ambulatory HF patients thus facilitating mental health care tailored to individual patient needs. This study is presented with several limitations that temper the generalizability of these findings. Firstly, the use of anxiety questionnaires may have elicited more referrals for patients with comorbid anxiety-depression such as GAD and panic disorder [64,65]. The referral of panic disorder in particular may correspond to the tendency to focus on dyspnea symptoms in HF treatment [80]. Secondly, ethical constraints precluded an evaluation of HF patients that were not routinely screened and/or not referred. Thus there was no comparison of the prevalence of those constituent variables for RCT eligibility in the general HF population. Reports also suggest approximately 27% of cases are not examined in international routine depression screening

Table 4. Prevalence of depression and anxiety disorders in heart failure patients referred for psychiatric care.

SCID Diagnosis	Total N(%) N = 73	RCT Eligible N = 39	RCT Ineligible N = 34	P
Major Depression	44 (60.3)	18 (46.2)	26 (76.5)	<.01*
Dysthymia	12 (16.4)	3 (7.7)	9 (26.5)	.03*
Panic +- agoraphobia	38 (52.1)	17 (43.6)	21 (61.8)	.12
Generalized anxiety disorder	42 (57.5)	19 (48.7)	23 (67.6)	.10
Post-traumatic stress disorder	14 (19.2)	5 (12.8)	9 (26.5)	.14
Obsessive-compulsive disorder	5 (6.8)	3 (7.7)	2 (5.9)	1.0
Social phobia	20 (27.4)	8 (20.5)	12 (35.3)	.16
Adjustment disorder	14 (19.2)	9 (25.0)	5 (13.5)	.21

RCT, randomized controlled trial; SCID, Structured Clinical Interview.
*p<.05.
doi:10.1371/journal.pone.0085928.t004

protocols [19]. Thirdly, it was not known whether there was a selection bias in referrals given the under-representation of patients with cognitive impairment [81]. Fourthly, the sample size, comparable or larger than most intervention arms in recent depression RCTs evaluated by Woltz et al [32], was potentially too small to draw broad conclusions regarding the psychiatric treatments needs and screening suggestions of HF patients generally. Fifthly, the pragmatic aspects of routine screening in HF need to be considered within the regional context by contrast to other cardiology settings and international experiences [18,19,22,30,64,65,82]. These findings from the current HFSMP may not generalise to other hospitals and it is unknown whether depression screening in conjunction with other management strategies in HF might beneficially impact depression remission rates. Finally, the potential for Type I errors is a limitation and as such will require confirmation in independent cohorts.

In conclusion, implementation of routine depression screening protocols in cardiology settings may underestimate the severity and complexity of psychiatric needs in HF such as comorbid personality disorders, alcohol/substance use, suicide risk and anxiety disorders. Application of six standard exclusion criteria

suggested that the extant RCT evidence may not apply to half of HF patients referred for psychiatric care. Further investigation into external validity of depression RCTs in cardiology settings is recommended to better reflect typical HF patient needs [83]. These findings make the case for a specific focus on external validity of RCTs and depression screening protocols as basis for level A guideline recommendations.

Author Contributions

Conceived and designed the experiments: PJT GAW TS HB. Performed the experiments: PJT TS. Analyzed the data: PJT GAW TS HB. Wrote the paper: PJT GAW TS HB.

References

1. Ferrari AJ, Charlson FJ, Norman RE, Patten SB, Freedman G, et al. (2013) Burden of Depressive Disorders by Country, Sex, Age, and Year: Findings from the Global Burden of Disease Study 2010. PLoS Med 10: e1001547.
2. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ (2006) Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. J Am Coll Cardiol 48: 1527–1537.
3. American Psychiatric Association (2000) Diagnostic and statistical manual of mental disorders: DSM-IV-TR. Washington, D.C.: American Psychiatric Association.
4. Jiang W, Alexander J, Christopher E, Kuchibhatla M, Gaulden LH, et al. (2001) Relationship of depression to increased risk of mortality and rehospitalization in patients with congestive heart failure. Arch Intern Med 161: 1849–1856.
5. O'Connor CM, Jiang W, Kuchibhatla M, Mehta RH, Clary GL, et al. (2008) Antidepressant use, depression, and survival in patients with heart failure. Arch Intern Med 168: 2232–2237.
6. Smith DH, Johnson ES, Blough DK, Thorp ML, Yang X, et al. (2012) Predicting costs of care in heart failure patients. BMC Health Serv Res 12: 434.
7. Baumeister H, Hutter N, Bengel J, Härter M (2011) Quality of life in somatically ill persons with comorbid mental disorders: a systematic review and meta-analysis. Psychother Psychosom 80: 275–286.
8. Jaarsma T, Johansson PJ, Ågren S, Strömberg A (2010) Quality of life and symptoms of depression in advanced heart failure patients and their partners. Curr Opin Supp Pall Care 4: 233–237.
9. Samartzis L, Dimopoulos S, Tziongourou M, Nanas S (2013) Effect of psychosocial interventions on quality of life in patients with chronic heart failure: A meta-analysis of randomized controlled trials. J Card Fail 19: 125–134.
10. Holzapfel N, Lowe B, Wild B, Schellberg D, Zugck C, et al. (2009) Self-care and depression in patients with chronic heart failure. Heart Lung 38: 392–397.
11. Jaarsma T, Lesman-Leegte I, Hillege HL, Veeger NJ, Sanderman R, et al. (2010) Depression and the Usefulness of a Disease Management Program in Heart Failure. Insights From the COACH (Coordinating study evaluating Outcomes of Advising and Counseling in Heart failure) Study. J Am Coll Cardiol 55: 1837–1843.
12. Lichtman JH, Bigger JT, Jr., Blumenthal JA, Frasure-Smith N, Kaufmann PG, et al. (2008) Depression and coronary heart disease: recommendations for screening, referral, and treatment: a science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Psychiatric Association. Circ 118: 1768–1775.
13. Chronic Heart Failure Guidelines Expert Writing Panel (2011) Guidelines for the prevention, detection and management of chronic heart failure in Australia. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand.
14. Orth-Gomer K, Albus C, Bages N, DeBacker G, Deter HC, et al. (2005) Psychosocial considerations in the European guidelines for prevention of cardiovascular diseases in clinical practice: Third Joint Task Force. Int J Behav Med 12: 132–141.
15. Albus C, Jordan J, Herrmann-Lingen C (2004) Screening for psychosocial risk factors in patients with coronary heart disease-recommendations for clinical practice. Eur J Cardiovasc Prev Rehabil 11: 75–79.
16. McMurray JJV, Adamopoulos S, Anker SD, Auricchio A, Böhm M, et al. (2012) ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. Eur J Heart Fail 14: 803–869.
17. Lainscak M, Blue L, Clark AL, Dahlström U, Dickstein K, et al. (2011) Self-care management of heart failure: practical recommendations from the Patient Care Committee of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 13: 115–126.
18. Luttik MLA, Jaarsma T, Sanderman R, Fleer J (2011) The advisory brought to practice. Routine screening on depression (and anxiety) in coronary heart disease; consequences and implications. Eur J Cardiovasc Nurs 10: 228–233.
19. Smolderen KG, Buchanan D, Amin A, Gosch K, Nugent K, et al. (2011) Real-World Lessons From the Implementation of a Depression Screening Protocol in Acute Myocardial Infarction Patients: Implications for the American Heart Association Depression Screening Advisory. Circ Cardiovasc Qual Outcomes 4: 283–292.
20. Shemesh E, Annunziato RA, Rubinstein D, Sultan S, Malhotra J, et al. (2009) Screening for depression and suicidality in patients with cardiovascular illnesses. Am J Cardiol 104: 1194–1197.
21. Caro MA, Sowden GL, Mastromauro CA, Mahnks S, Beach SR, et al. (2012) Risk factors for positive depression screens in hospitalized cardiac patients. J Cardiol 60: 72–77.
22. Hasnain M, Vieweg WVR, Lesnefsky EJ, Pandurangi AK (2011) Depression screening in patients with coronary heart disease: A critical evaluation of the AHA guidelines. J Psychosom Res 71: 6–12.
23. Holzapfel N, Zugck C, Müller-Tasch T, Löwe B, Wild B, et al. (2007) Routine Screening for Depression and Quality of Life in Outpatients With Congestive Heart Failure. Psychosomatics 48: 112–116.
24. Yeager KR, Binkley PF, Saveanu RV, Golden-Kreutz DM, Dembe AE, et al. (2011) Screening and Identification of Depression Among Patients with Coronary Heart Disease and Congestive Heart Failure. Heart Fail Clin 7: 69–74.
25. Sowden G, Mastromauro CA, Januzzi JL, Fricchione GL, Huffman JC (2010) Detection of depression in cardiac inpatients: feasibility and results of systematic screening. Am Heart J 159: 780–787.
26. Burton C, Simpson C, Anderson N (2013) Diagnosis and treatment of depression following routine screening in patients with coronary heart disease or diabetes: a database cohort study. Psychol Med 43: 529–537.
27. Jani BD, Purves D, Barry S, Cavanagh J, McLean G, et al. (2013) Challenges and Implications of Routine Depression Screening for Depression in Chronic Disease and Multimorbidity: A Cross Sectional Study. PLoS ONE 8: e74610.
28. Thombs BD, de Jonge P, Coyne JC, Whooley MA, Frasure-Smith N, et al. (2008) Depression screening and patient outcomes in cardiovascular care: a systematic review. J Am Med Assoc 300: 2161–2171.
29. Thombs BD, Roseman M, Coyne JC, de Jonge P, Delisle VC, et al. (2013) Does Evidence Support the American Heart Association's Recommendation to Screen Patients for Depression in Cardiovascular Care? An Updated Systematic Review. PLoS ONE 8: e52654.
30. Herrmann-Lingen C (2011) Steps towards integrated psychosomatic medicine–the example of psychocardiology. J Psychosom Res 70: 111–115.
31. Annunziato RA, Rubinstein D, Sheikh S, Maurer M, Cotter G, et al. (2008) Site matters: winning the hearts and minds of patients in a cardiology clinic. Psychosomatics 49: 386–391.
32. Woltz PC, Chapa DW, Friedmann E, Son H, Akintade B, et al. (2012) Effects of interventions on depression in heart failure: a systematic review. Heart Lung 41: 469–483.
33. Jiang W, O'Connor C, Silva SG, Kuchibhatla M, Cuffe MS, et al. (2008) Safety and efficacy of sertraline for depression in patients with CHF (SADHART-

CHF): a randomized, double-blind, placebo-controlled trial of sertraline for major depression with congestive heart failure. Am Heart J 156: 437–444.

34. Cully JA, Stanley MA, Deswal A, Hanania NA, Phillips LL, et al. (2010) Cognitive-behavioral therapy for chronic cardiopulmonary conditions: preliminary outcomes from an open trial. Prim Care Companion J Clin Psychiatry 12: PCC.09m00896.

35. O'Hea E, Houseman J, Bedek K, Sposato R (2009) The use of cognitive behavioral therapy in the treatment of depression for individuals with CHF. Heart Fail Rev 14: 13–20.

36. Gary RA, Dunbar SB, Higgins MK, Musselman DL, Smith AL (2010) Combined exercise and cognitive behavioral therapy improves outcomes in patients with heart failure. J Psychosom Res 69: 119–131.

37. Rothwell PM (2005) External validity of randomised controlled trials: ?To whom do the results of this trial apply? Lancet 365: 82–93.

38. van der Lem R, van der Wee NJ, van Veen T, Zitman FG (2012) Efficacy versus effectiveness: a direct comparison of the outcome of treatment for mild to moderate depression in randomized controlled trials and daily practice. Psychother Psychosom 81: 226–234.

39. Rollman BL, Belnap BH, LeMenager MS, Mazumdar S, Houck PR, et al. (2009) Telephone-delivered collaborative care for treating post-CABG depression: a randomized controlled trial. JAMA 302: 2095–2103.

40. Ruscio AM, Holohan DR (2006) Applying empirically supported treatments to complex cases: Ethical, empirical, and practical considerations. Clin Psychol: Science Pract 13: 146–162.

41. Collins PY, Insel TR, Chockalingam A, Daar A, Maddox YT (2013) Grand Challenges in Global Mental Health: Integration in Research, Policy, and Practice. PLoS Med 10: e1001434.

42. Spitzer RL, Kroenke K, Williams JB (1999) Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. JAMA 282: 1737–1744.

43. McManus D, Pipkin SS, Whooley MA (2005) Screening for depression in patients with coronary heart disease (data from the Heart and Soul Study). Am J Cardiol 96: 1076–1081.

44. Kroenke K, Spitzer RL, Williams JB (2001) The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 16: 606–613.

45. Spitzer RL, Kroenke K, Williams JB, Lowe B (2006) A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 166: 1092–1097.

46. Kroenke K, Spitzer RL, Williams JB, Lowe B (2010) The Patient Health Questionnaire Somatic, Anxiety, and Depressive Symptom Scales: a systematic review. Gen Hosp Psych 32: 345–359.

47. Löwe B, Gräfe K, Zipfel S, Spitzer RL, Herrmann-Lingen C, et al. (2003) Detecting panic disorder in medical and psychosomatic outpatients: Comparative validation of the Hospital Anxiety and Depression Scale, the Patient Health Questionnaire, a screening question, and physicians' diagnosis. J Psychosom Res 55: 515–519.

48. Pedersen SS (2001) Post-traumatic stress disorder in patients with coronary artery disease: a review and evaluation of the risk. Scand J Psychol 42: 445–451.

49. Doerfler LA, Paraskos JA (2005) Post-traumatic stress disorder in patients with coronary artery disease: screening and management implications. Can J Cardiol 21: 689–697.

50. Haworth JE, Moniz-Cook E, Clark AL, Wang M, Waddington R, et al. (2005) Prevalence and predictors of anxiety and depression in a sample of chronic heart failure patients with left ventricular systolic dysfunction. Eur J Heart Fail 7: 803–808.

51. Ballenger JC, Davidson JR, Lecrubier Y, Nutt DJ, Roose SP, et al. (2001) Consensus statement on depression, anxiety, and cardiovascular disease. J Clin Psych 62: 24–27.

52. Scherrer JF, Chrusciel T, Zeringue A, Garfield LD, Hauptman PJ, et al. (2010) Anxiety disorders increase risk for incident myocardial infarction in depressed and nondepressed Veterans Administration patients. Am Heart J 159: 772–779.

53. Tully PJ, Cosh SM, Baune BT (2013) A review of the affects of worry and generalized anxiety disorder upon cardiovascular health and coronary heart disease. Psychol Health Med 18: 627–644.

54. Tully PJ, Cosh SM (2013) Generalized anxiety disorder prevalence and comorbidity with depression in coronary heart disease: a meta analysis. J Health Psychol 18: 1601–1616.

55. First MB, Gibbon M, Spitzer RL, Williams JBW, Benjamin LS (1997) Structured Clinical Interview for DSM-IV Axis II Personality Disorders, (SCID-II). Washington, D.C.: American Psychiatric Press, Inc.

56. First MB, Williams JBW, Spitzer RL, Gibbon M (2007) Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Clinical Trials Version (SCID-I/P W/psychotic screen). New York: Biometrics Research.

57. Gottlieb SS, Kop WJ, Thomas SA, Katzen S, Vesely MR, et al. (2007) A double-blind placebo-controlled pilot study of controlled-release paroxetine on depression and quality of life in chronic heart failure. Am Heart J 153: 868–873.

58. Lekakis J, Ikonomidis I, Papoutsi Z, Moutsatsou P, Nikolaou M, et al. (2010) Selective serotonin re-uptake inhibitors decrease the cytokine-induced endothelial adhesion molecule expression, the endothelial adhesiveness to monocytes and the circulating levels of vascular adhesion molecules. Int J Cardiol 139: 150–158.

59. Fraguas R, da Silva Telles RM, Alves TC, Andrei AM, Rays J, et al. (2009) 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 30: 205–211.

60. Sullivan MJ, Wood L, Terry J, Brantley J, Charles A, et al. (2009) 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 157: 84–90.

61. Yu DS, Lee DT, Woo J, Hui E (2007) Non-pharmacological interventions in older people with heart failure: effects of exercise training and relaxation therapy. Gerontol 53: 74–81.

62. Rothman KJ (1990) No adjustments are needed for multiple comparisons. Epidemiol 1: 43–46.

63. Serber ER, Todaro JF, Tilkemeier PL, Niaura R (2009) Prevalence and characteristics of multiple psychiatric disorders in cardiac rehabilitation patients. J Cardiopulm Rehabil Prev 29: 161–168; quiz 169–170.

64. Luukinen H, Jokelainen J, Hedberg P (2010) The relationships between high-sensitivity C-reactive protein and incident depressed mood among older adults. Scand J Clin Lab Invest 70: 75–79.

65. Hood KK, Lawrence JM, Anderson A, Bell R, Dabelea D, et al. (2012) Metabolic and inflammatory links to depression in youth with diabetes. Diabetes Care 35: 2443–2446.

66. Tully PJ, Baune BT (in press) Comorbid anxiety disorders alter the association between cardiovascular diseases and depression: the German National Health Interview and Examination Survey. Soc Psych Psych Epidemiol.

67. Edmondson D, Richardson S, Falzon L, Davidson KW, Mills MA, et al. (2012) Posttraumatic Stress Disorder Prevalence and Risk of Recurrence in Acute Coronary Syndrome Patients: A Meta-analytic Review. PLoS ONE 7: e38915.

68. Khan A, Faucett J, Lichtenberg P, Kirsch I, Brown WA (2012) A Systematic Review of Comparative Efficacy of Treatments and Controls for Depression. PLoS ONE 7: e41778.

69. Jakobsen JC, Hansen JL, Storebø OJ, Simonsen E, Gluud C (2011) The Effects of Cognitive Therapy versus 'No Intervention' for Major Depressive Disorder. PLoS ONE 6: e28299.

70. Shemesh E, Annunziato RA, Weatherley BD, Cotter G, Feaganes JR, et al. (2011) A randomized controlled trial of the safety and promise of cognitive-behavioral therapy using imaginal exposure in patients with posttraumatic stress disorder resulting from cardiovascular illness. J Clin Psychiatry 72: 168–174.

71. Kemp AH, Quintana DS, Felmingham KL, Matthews S, Jelinek HF (2012) Depression, comorbid anxiety disorders, and heart rate variability in physically healthy, unmedicated patients: Implications for cardiovascular risk. PLoS One 7: e30777.

72. Zetin M, Hoepner CT (2007) Relevance of exclusion criteria in antidepressant clinical trials: a replication study. J Clin Psychopharmacol 27: 295–301.

73. Mulder RT, Frampton C, Joyce PR, Porter R (2003) Randomized controlled trials in psychiatry. Part II: Their relationship to clinical practice. Aus NZ J Psych 37: 265–269.

74. Carney RM, Freedland KE (2009) Treatment-resistant depression and mortality after acute coronary syndrome. Am J Psych 166: 410–417.

75. Jiang W, Krishnan R, Kuchibhatla M, Cuffe MS, Martsberger C, et al. (2011) Characteristics of depression remission and its relation with cardiovascular outcome among patients with chronic heart failure (from the SADHART-CHF Study). Am J Cardiol 107: 545–551.

76. Hoertel N, Le Strat Y, De Maricourt P, Limosin F, Dubertret C (2013) Are subjects in treatment trials of panic disorder representative of patients in routine clinical practice? Results from a national sample. J Affect Disord 146: 383–389.

77. Lossnitzer N, Muller-Tasch T, Lowe B, Zugck C, Nelles M, et al. (2009) Exploring potential associations of suicidal ideation and ideas of self-harm in patients with congestive heart failure. Depress Anxiety 26: 764–768.

78. Sareen J, Cox BJ, Afifi TO, de Graaf R, Asmundson GJ, et al. (2005) Anxiety disorders and risk for suicidal ideation and suicide attempts: a population-based longitudinal study of adults. Arch Gen Psychiatry 62: 1249–1257.

79. Borges G, Nock MK, Haro Abad JM, Hwang I, Sampson NA, et al. (2010) Twelve-month prevalence of and risk factors for suicide attempts in the World Health Organization World Mental Health Surveys. J Clin Psychiatry 71: 1617–1628.

80. Dharmarajan K, Strait KM, Lagu T, Lindenauer PK, Tinetti ME, et al. (2013) Acute Decompensated Heart Failure Is Routinely Treated as a Cardiopulmonary Syndrome. PLoS ONE 8: e78222.

81. Vogels RL, Scheltens P, Schroeder-Tanka JM, Weinstein HC (2007) Cognitive impairment in heart failure: a systematic review of the literature. Eur J Heart Fail 9: 440–449.

82. Wade V, Cheok F, Schrader G, Hordacre AL, Marker J (2005) Depression after cardiac hospitalisation–the Identifying Depression as a Comorbid Condition (IDACC) study. Aus Fam Phys 34: 985–989.

83. Masoudi FA, Havranek EP, Wolfe P, Gross CP, Rathore SS, et al. (2003) Most hospitalized older persons do not meet the enrollment criteria for clinical trials in heart failure. Am Heart J 146: 250–257.