

Critical review and local audit of the prevalence of mental ill-health in heart failure patients

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Original Article

A CRITICAL REVIEW AND LOCAL AUDIT OF THE PREVALENCE OF MENTAL ILL-HEALTH IN HEART FAILURE PATIENTS

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ABSTRACT

Objective: To establish if depression results in poor adherence to therapy in patients with heart diseases.

Methods: This concept scoping study was conducted in two phases; the first was a systematic review of the literature, and the second part was local data analysis. Statistical analysis was performed using RevMan® V.5.3 (Cochrane Community).

Results: Patients who received multidisciplinary collaborative care showed significantly reduced major adverse cardiac outcomes in patients with cardiovascular diseases. They also demonstrated higher rates of self-reported remission of depression. The review also showed endpoint mortality after PCI was associated with patients having depression. Local population data showed that 26% of heart failure patients had mental ill health comorbidity, however, only 12% had a formal diagnosis recorded.

Conclusion: Depression is associated with poor cardiac outcomes in patients with coronary artery disease. It is widespread in patients with cardiovascular disease and must be screened for throughout the management plan.

Keywords: Independent prescribing pharmacist, Heart Failure, Depression, Anxiety, Primary Care, General Practice

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INTRODUCTION

Depression is widely reported to lead to adverse coronary heart disease (CHD) prognosis [1] poorer quality of life and increased healthcare costs [2]. The relationship has been widely examined and meta-analyses have demonstrated that depressive symptoms have an unfavorable impact on mortality and cardiovascular events in CHD or patients with post-MI [3].

Whilst there is much evidence of the link between these two conditions, previous pharmacological and psychological interventions explicitly implemented for this population have demonstrated lower levels of an effect than seen in other chronic diseases such as diabetes [4]. Furthermore, larger trials such as the Enhancing Recovery in CHD (ENRICH) [5] study did not demonstrate a significant reduction in major adverse cardiac events; they concluded that the cognitive behavioural therapy intervention provided, improved depression and social isolation, though the relative improvement in the psychosocial intervention group compared with the usual medical care group was less than expected, due to substantial improvement in usual care patients [5]. This led to the studies being questioned and the authors stating that managing this patient group remains a challenge as there is no conclusion about the best intervention to achieve positive outcomes [6].

Recent works explain that collaborative care has provided encouraging models of healthcare in patients with depression and anxiety. These collaborative care models have been associated with significant improvement in depression and anxiety outcomes compared with usual care [7].

Collaborative care is defined by a multidisciplinary approach to patient care; this is typically coordinated by the patient's General Medical Practitioner (GP) and another health professional, such as a counsellor. The process involves a structured patient management platform, with planned interventions, reviews and follow-ups, which include inter-professional communication between the different team members [8]. The number of viable RCTs that specifically assessed heart failure and depression is limited, and this review presents the available data, including broadened search terms [9].

The success of collaborative multidisciplinary care depends on the communication between healthcare professionals and their efforts to follow-up with patients on a regular basis.

METHODS

This study aims to explore if depression results in adverse outcomes in patients with coronary heart disease by review of the available data and to understand the current interventions employed to improve coronary heart disease prognosis with depression comorbidity. Also, to systematically review the evidence for the efficacy of multidisciplinary shared care approaches for depression in adults diagnosed with heart diseases. This concept scoping study was conducted in two phases; the systematic review and analysis of local data.

Part 1: a critical review

Review Manager (RevMan® V.5.3) (Cochrane community) was used for data assessment and analyses. Statistical analysis involved the assessment of the pooled data comparing collaborative multidisciplinary care and standard care. Also compared were patient outcomes in depressed and non-depressed individuals for the endpoint of adverse cardiovascular events. Dichotomous frequency data were extracted from the studies and the reported risk ratios (RR), standardized mean differences (SMD) for continuous variables and odds ratios (ORs) for dichotomous endpoints were reported with 95% Confidence Intervals (CI). Studies were compared based on the following aspects:

Inclusion criteria: Prospective study design; coronary heart disease patient population with depression co-morbidity; patients diagnosed with coronary artery disease who had received coronary stent implantation; used established assessment inventories to define depression and reported depression end-point scores or major adverse cardiac events.

Interventions: An RCT of multidisciplinary collaborative care, where patients received a structured management plan to deliver pharmacological or non-pharmacological interventions for depression and were followed up with inter-professional communications between members of a care team.

Control group: Patients receiving their usual care, or on the waiting list for treatment or no specific treatment for CHD and depression comorbidity.

Primary outcome: Major adverse cardiac events e. g. heart failure exacerbation, myocardial infarction, all-cause and/or CHD-related mortality or stroke or undergoing a revascularization procedure.

Secondary outcomes: Standardised measures using self-reporting questionnaires of depression, anxiety, quality of life (QOL) and cost-effectiveness, quality-adjusted life-years (QALY) and death.

Search strategy

The search strategy included keywords–coronary heart disease, heart failure and depression. Due to the lack of published RCTs on heart failure and depression; studies detailing CHD were also included to widen the search returns.

Electronic databases were searched using the Cochrane Central Register of Controlled Trials (CENTRAL) on The Cochrane Library,

MEDLINE, and EMBASE. The search yielded a small number of studies, as was found by Tully and Baumeister [9].

The search results identified 10 studies that were suitable to review. However, only 6 studies were initially included as they had a similarity that can be compared and 4 were excluded due to their different endpoint.

The 6 studies (table 1) [10-15] that were chosen covered a total of 1284 patients with CHD and depression/anxiety comorbidity, where 655 patients were randomized to the intervention group of collaborative care and 629 patients to control. For the purpose of studying the effect of collaborative multidisciplinary care on major adverse coronary outcomes, only 3 RCTs [11-12, 14] were included.

For the purpose of assessing the effect collaborative multidisciplinary care has on depression remission outcomes, 5 trials [11-15] met the inclusion criteria.

For the purpose of assessing the effects of depression on patients after a percutaneous coronary intervention (PCI), only four studies (table 2) were included.

Table 1: Randomised controlled trials reporting the difference between a collaborative care and standard care (Direct quotation)

Study	Study design	Length of intervention	Collaborative care intervention	Control group	Screening tool
TrueBlue [10]	Cluster randomised RCT	12 mo	Planned review every 3 mo to the practice nurse and their primary care practitioner over a 12-month period. Patient received referrals to mental health services.	Usual care; Practice nurse to monitor depression by screening at arranged interims	Patient Health Questionnaire (PHQ-9)
Bypassing the Blues [11]	Single-blind effectiveness RCT	8 mo	Planned telephone reviews led by a nurse and supervised by psychiatrist and primary care practitioner. Including shared decision making for depression. Psychoeducation was provided by way of bibliotherapy. Medication initiation/alteration and promotion of adherence for antidepressant medication was provided by the primary care practitioner. Referral to the community mental health team if needed. A combination of the above; or watchful-waiting	Usual care and given a brochure on depression and heart disease; primary care practitioner is informed of depression status	PHQ-2 and PHQ-9
CODIACS [12]	Single-blind effectiveness RCT	6 mo	Initial patient preference for problem-solving therapy by a problem-solving therapist (PST); treatment given via phone/internet and/or pharmacotherapy; or neither. Then a stepped-care approach every 6–8 w, with planned follow-up every week with PST, extended to longer intervals as needed	Usual care, primary care practitioner informed of depression status	Beck Depression Inventory (BDI)
MOSAIC [13]	Single-blind effectiveness RCT	6 mo	Psychiatrist and social workers provide tailored treatment-patient preference for pharmacotherapy or CBT (minimum of 6 sessions). Review and provided stepped-care along with planned telephone calls and follow-up to monitor symptoms, promote adherence and patient engagement	Enhanced usual care and primary care practitioner informed of psychiatric status	PHQ-2; Generalised Anxiety Disorder (GAD) assessment and item about panic attacks BDI
COPEs [14]	Single-blind effectiveness RCT	6 mo	Patient evaluated for preference for problem-solving therapy and/or pharmacotherapy; repeated assessments and a stepped-care approach if needed at 8 w intervals. Planned follow-up initially every week with PST or 1–2 and 3–5 w to titrate medication	Usual care	
SUCCEED [15]	Single-blind effectiveness RCT	3 mo	Psychiatrist and social worker providing patient centred depression treatment-based on history and patient preference e. g. pharmacological or psychotherapy. The study team advised the primary care practitioner and/or cardiologist with the treatment recommendations. Depression education and monitoring depression scores	Usual care; PCP informed of depression status	PHQ-2 and PHQ-9

Systematic review findings

The 6 RCTs that met the inclusion criteria to review the effects of collaborative care included 1284 patients with CHD with depression and anxiety comorbidities. Of these, a total of 655 patients were randomised to receive multidisciplinary collaborative care and 629

patients were controls. A description of the included trials is shown in table 1. In table 2, all four studies were included in the Forest Plot to statistically review the effect that depression has on patients post PCI. All the trials were from outside the UK, although the mental health screening questionnaires were well known and varied only minimally, using the Patient Health Questionnaire (PHQ) [20], the

Beck Depression Inventory (BDI) [21], the Hospital Anxiety Depression Scale (HADS) [22], and the Mini-International Neuropsychiatric Interview (MINI) [23]. For studies assessing multidisciplinary collaborative care pathways, interventions were provided for from 3 to 12 mo, with the median duration being 6 mo. Interventions were delivered by nurses in the Bypassing the Blues and TrueBlue trials; allied healthcare teams in the COPES and CODIACS trials and by social workers in the MOSAIC and SUCCEED trials. Pharmacists were not involved with any of these interventions.

Psychotherapy was delivered as part of the multidisciplinary collaborative care interventions and included problem-solving therapy in the COPES and the CODIACS studies, telephone-delivered CBT in the MOSAIC study and referral to community mental health services in the TrueBlue and Bypassing the Blues studies and a mixture of interventions in the SUCCEED study.

Pharmacological interventions varied for each study and included selective serotonin reuptake inhibitors (SSRIs), bupropion and, serotonin and norepinephrine reuptake inhibitors (SNRIs).

The risk of bias differed in each of the trials; each trial rated blinding to the subjective endpoints as high. However, on review of the study results, some studies employed selective reporting and other studies had uncertain allocation concealments. There was also missing trial information for some of the studies.

Multidisciplinary collaborative care was also reported to reduce major adverse cardiac outcomes significantly (fig. 1). Such outcomes were only reported in the COPES, CODIACS and the Bypassing the Blues trials. However, these studies only demonstrated a reduction in cardiac events in short and medium timeframes (RR=0.54; 95% CI 0.31 to 0.95 and p=0.03). No association was made with mortality rates (RR 1.38; 95% CI 0.53 to 3.58 and p=0.51).

Table 2: Studies used in metaanalysis

Reference	Screening tool used	Conclusions
[16]	Hospital Anxiety and Depression Scale (HADS)	Anxiety at baseline was associated with an increased 10-year mortality rate after PCI. Depression was also associated with higher 10-year mortality
[17]	HADS	The prevalence of depression and anxiety was 24.8% and 27.7%, respectively. The cumulative all-cause mortality rate in depressed patients was 37% versus 20% in non-depressed patients. Depression is associated with an increased risk of 77% for all-cause mortality, 10 y post-PCI, independently of anxiety. Although anxiety was associated with all-cause mortality, it has no additional value in the case of co-occurring depression
[18]	HADS	All-cause mortality rates differed significantly between depressed and non-depressed patients at 2-year follow-up, as 6 out of 98 subjects with elevated HADS-D scores (6.1 %), but only 8 out of 364 (2.2 %) patients with normal HADS-D scores had died [odds ratio = 2.9, 95 % confidence interval (95 % CI) = 1.0-8.6, p = 0.044]. In CHD patients, self-rated depressive symptoms at baseline were negatively linked to survival at 2-year follow-up but failed to predict mortality 3 y later. Thus, in contrast to other well-established risk factors, the prognostic value of depression for predicting adverse outcome may be temporarily limited. The mechanisms behind this transient effect need further study
[19]	Mini-International Neuropsychiatric Interview (MINI)	Patients with post-procedure depression had a higher rate of major adverse cardiac event (27.3 vs. 13.0%, P<0.001), mortality (5.8 vs. 2.0%, P=0.044). post-procedure depression was seen to be an independent predictor of 3-year major adverse cardiac event

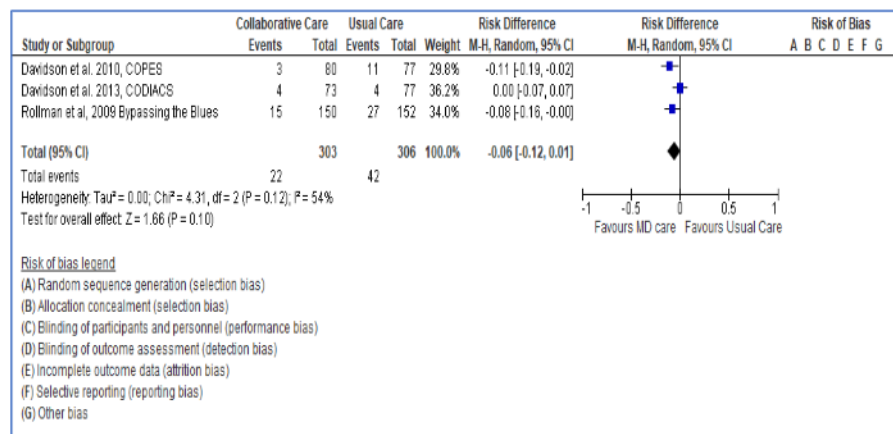


Fig. 1: Comparison of major adverse cardiac events following multidisciplinary/collaborative care and usual care

To evaluate whether depression in percutaneous coronary intervention (PCI) patients is associated with a higher risk of adverse outcomes was also examined.

The four studies that are included in the Forest plot in fig. 3, demonstrate that endpoint mortality outcomes after PCI, are associated with a substantially higher risk of death in patients with depression (RR=1.43, 95% CI 1.24 to 1.65). Overall, patients with depression demonstrated a significantly higher risk for the primary endpoint of a major adverse cardiac event, and for the secondary endpoint of death.

With regards to the self-reported depression scores, in short timeframes, all the studies demonstrated an improvement in mood (fig. 2).

Multidisciplinary collaborative care has shown to be considerably associated with depression remission (OR=1.77; 95% CI 1.28 to 2.44, p=0.0005). However, only the COPES trial demonstrated ongoing depression responses at a medium length of time, using the Beck Depression Inventory (OR 2.26; 95% CI 1.14 to 4.46, p=0.02). Collectively, all depression remission data in the trials indicated similar results.

In previous systematic reviews, it was found that antidepressant medication and psychotherapy yielded similar results of depression remission in patients with coronary heart disease [4].

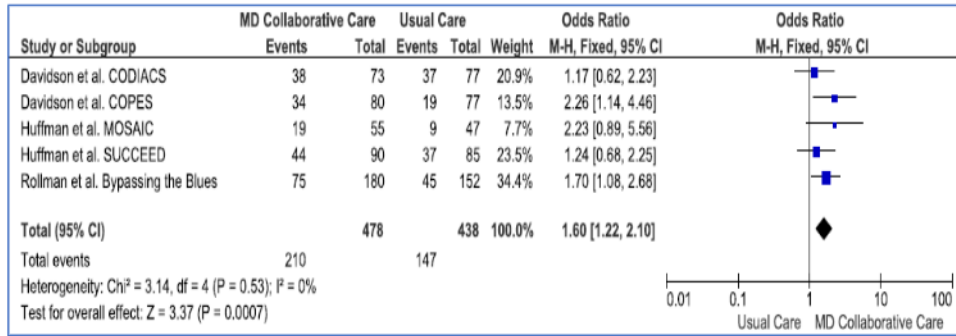


Fig. 2: Comparison: multidisciplinary (MD) collaborative care vs usual care, outcome: depression remission

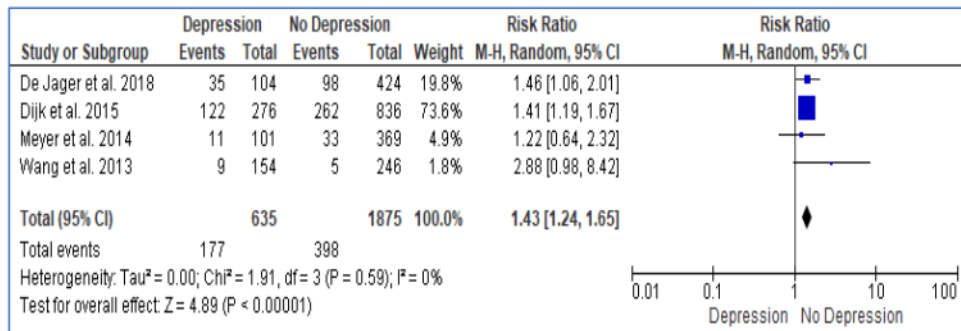


Fig. 3: Forest plot of depression and mortality endpoint as an outcome following PCI; Outcomes; Favour depression or favours no depression

RESULTS AND DISCUSSION

CONCLUSION

Systematic Review Conclusion

The 3 studies included in the analysis of the major adverse cardiac event in multidisciplinary collaborative care and usual care; COPES, CODIACS and Bypassing the Blues, demonstrated a reduction in major adverse cardiac outcomes in patients receiving multidisciplinary collaborative care. When reviewing patients' post-PCI, studies demonstrated a significant reduction in major adverse cardiac events and death in patients with no depression compared to patients who were diagnosed with depression. The COPES, CODIACS, MOSAIC, SUCCEED, Bypassing the Blues and True-blue studies demonstrated short term positive outcomes in depression remission and an improvement in depression scores when patients received multidisciplinary collaborative care, compared to receiving usual care. In the UK, there is no consensus on the optimal inventory tool to screen for depression in patients diagnosed with coronary heart disease.

Only one study utilised a clinical interview to diagnose depression in the form of the Mini-International Neuropsychiatric Interview (MINI) [23]. The remaining 9 studies utilised PHQ [20], BDI [21] and

HADS [22] self-reporting tools. This meta-analysis demonstrates that depression is associated with poor cardiac outcomes in patients with coronary artery disease. Depression is widespread in patients with cardiovascular disease and must be screened for throughout the management plan to ensure that their mental health does not have an impact on their cardiovascular outcomes [24]. Systematic review of the available data, combined with statistical analysis, demonstrated that multidisciplinary collaborative care reduces major adverse cardiac outcomes significantly in patients with cardiovascular diseases (CVD). The review also revealed that end point mortality outcomes after PCI are associated with a substantially higher risk of death in patients with depression. With regards to the self-reported depression scores in short timeframes, all studies included in the review demonstrated an improvement in mood.

Part 2-Comparison with local experience

The local practice population consists of 6500 patients; of these, 50 patients are included on the heart failure register. A total of 884 patients have a diagnosis of depression.

The table below details relevant treatment and diagnoses for all patients with heart failure at one medical practice in the United Kingdom (UK) (fig. 4).

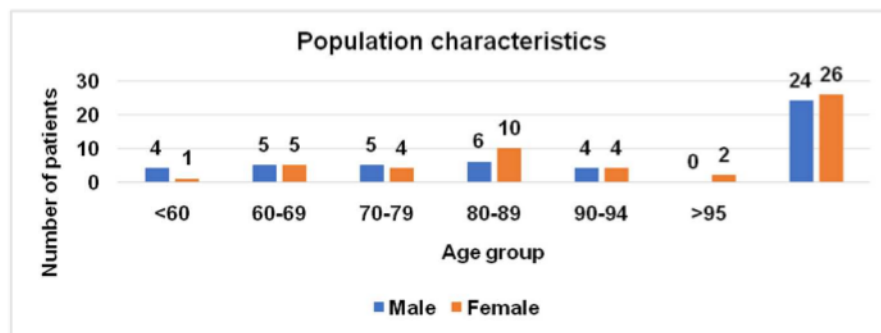


Fig. 4: Local practice heart failure patients population by age and gender

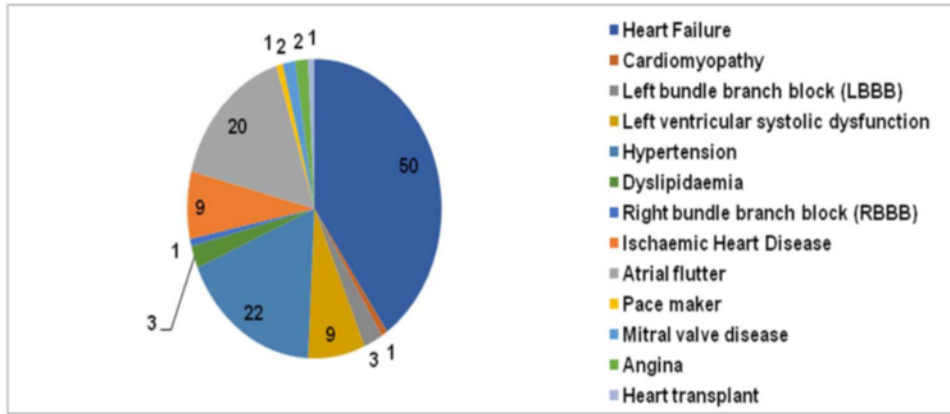


Fig. 5: Cardiovascular comorbidity in the local practice population

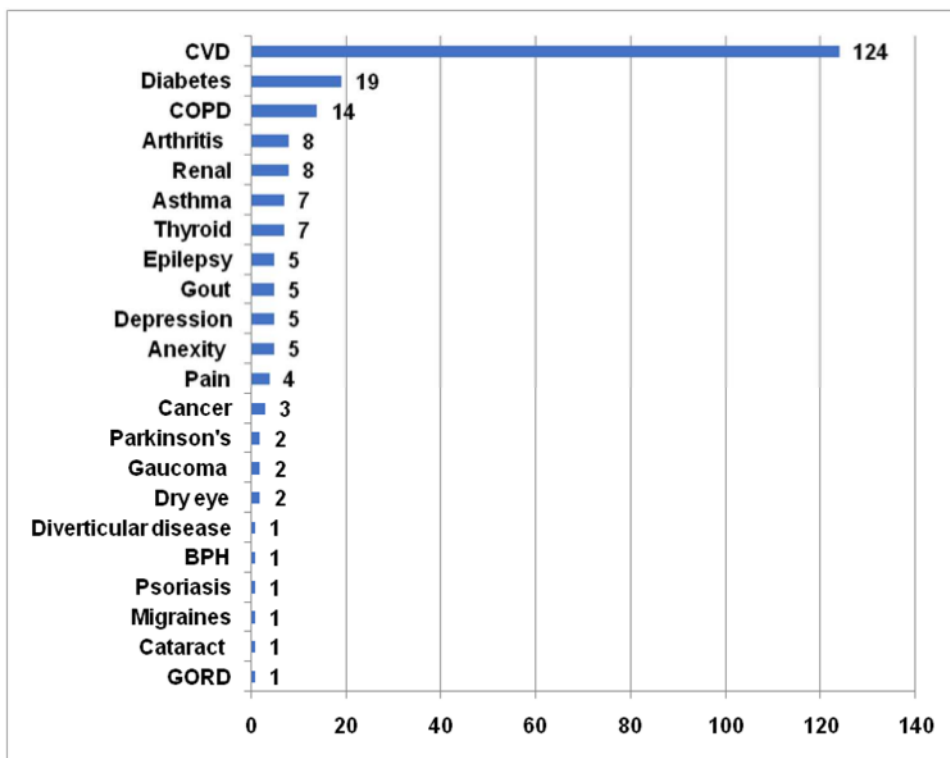


Fig. 6: Local practice population medical conditions

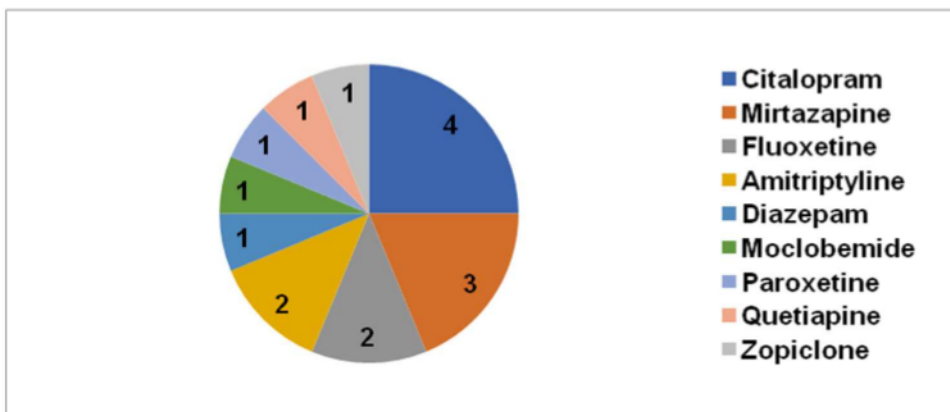


Fig. 7: Mental ill-health medications included in local practice heart failure population medication lists

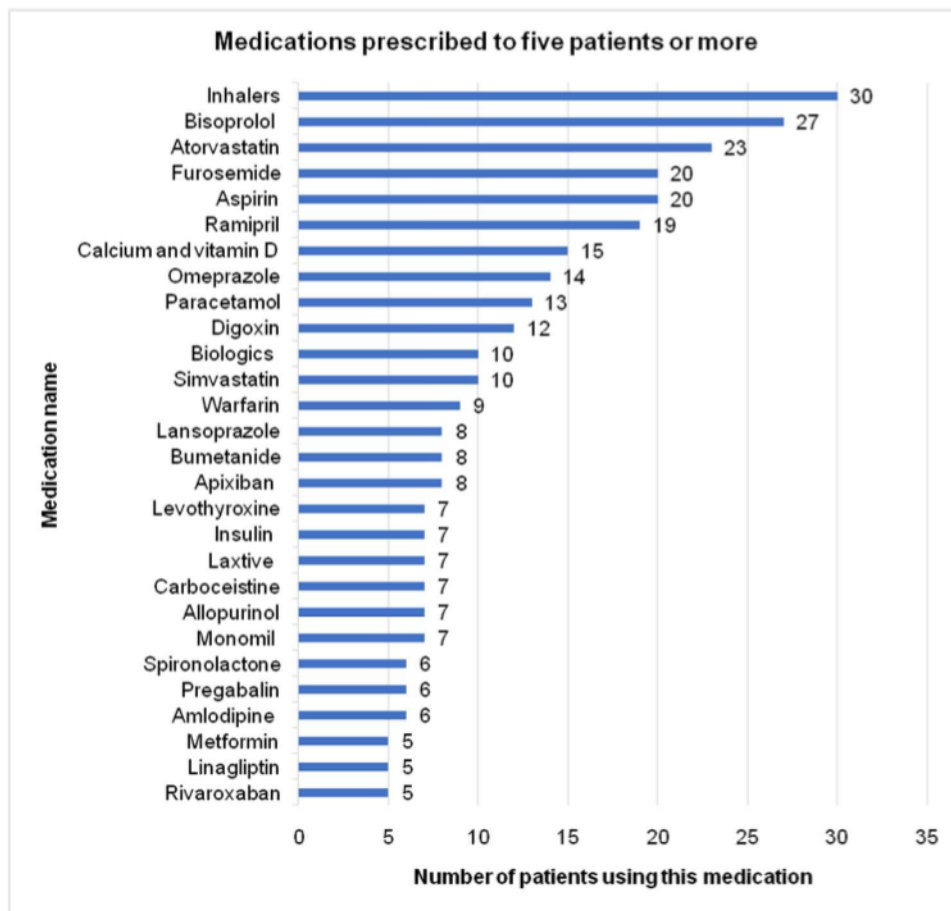


Fig. 8: Most used medications in the local practice population

From the 50 patients with heart failure, 6 patients have had a documented diagnosis of depression and/or anxiety. Out of all patients, there were 124 with documented cardiovascular conditions (fig. 5), with the most common comorbidities of diabetes and chronic obstructive pulmonary disease (COPD) (fig. 6).

There were 16 prescriptions for medications used in the treatment of mental ill-health (fig. 7), but only 6 patients had a documented diagnosis.

The most used medications (in 5 patients or more) were Simvastatin, 'Biologics,' Digoxin, Paracetamol, Omeprazole, Calcium and vitamin D, Ramipril, Aspirin, Furosemide, Atorvastatin, Bisoprolol, Inhalers (fig. 8).

Local Audit Conclusion

Based on the finding from the local population information, it was clear that while a high percentage of heart failure patients (26% of all patients) are prescribed medications for mental illness, only 12% of all patients had a documented diagnosis, which is lower than the general UK heart failure population (13%). This finding indicates that the national prevalence of mental illness in heart failure patients may be underestimating the actual problems in this population. It is recommended that primary care health professionals:

- Medically review all patients diagnosed with heart failure for mental ill-health.
- Use a standardised algorithm to assess for depression or anxiety.
- Document any diagnoses on the PMR.
- Follow-up patients with depression and anxiety in line with the clinical and local guidelines.
- Clarify all diagnoses in patients receiving medications that could be used for depression and/or anxiety.

- Ensure all patients receiving medication for mental ill health have the option of receiving psychotherapy.

AUTHORS CONTRIBUTIONS

Conceptualization, Methodology, Validation of the Analysis, Investigation, Mariam Ahmed, Hana Morrissey and Patrick Ball; Writing—Original Draft Preparation, Mariam Ahmed; Writing—Review and Editing, Mariam Ahmed and Patrick Ball; Supervision, Mariam Ahmed and Patrick Ball; Project Administration, Mariam Ahmed.

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CONFLICTS OF INTERESTS

The authors declare no conflict of interest.

REFERENCES

1. Rugulies R. Depression as a predictor for coronary heart disease: a review and meta-analysis. *Am J Prev Med* 2002;23:51–61.
2. Samartzis L, Dimopoulos S, Tziogourou M, Nanas S. Effect of psychosocial interventions on quality of life in patients with chronic heart failure: a meta-analysis of randomized controlled trials. *J Card Fail* 2013;19:125–34.
3. Meijer A, Conradi H, Bos E, Thombs B, Van Melle J, De Jonge P. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis of 25 y of research. *Gen Hosp Psychiat* 2011;33:203–16.
4. Baumeister H, Hutter N, Bengel J. Psychological and pharmacological interventions for depression in patients with diabetes mellitus—a systematic cochrane review. *Diabetic Med* 2014;31:773–86.

5. Berkman L, Blumenthal J, Burg M, Carney M, Catellier D, Cowan J, *et al.* Enhancing recovery in coronary heart disease patients investigators (ENRICH). Effects of treating depression and low perceived social support on clinical events after myocardial infarction: The enhancing recovery in coronary heart disease patients (ENRICH) randomized trial. *J Am Med Assoc* 2003;289:3106-16.
6. Linden W. How many meta-analyses does it take to settle a question? *Psychosom Med* 2013;75:332-4.
7. Richards D, Hill J, Gask L, Lovell K, Chew-Graham C, Bower P, *et al.* Clinical effectiveness of collaborative care for depression in UK primary care (CADET): cluster randomised controlled trial. *Br Med J* 2013;347:f4913.
8. Sanchez K. Collaborative care in real-world settings: barriers and opportunities for sustainability. *Patient Prefer Adher* 2017;11:71-4.
9. Tully P, Baumeister H. Collaborative care for comorbid depression and coronary heart disease: a systematic review and meta-analysis of randomised controlled trials. *Br Med J Open* 2015;5:e009128.
10. Morgan M, Coates M, Dunbar J, Reddy P, Schlicht K, Fuller J. The true blue model of collaborative care using practice nurses as case managers for depression alongside diabetes or heart disease: a randomized trial. *Br Med J Open* 2013;3:e002171.
11. Rollman B, Belnap B, LeMenager M, Mazumdar S, Schulberg H, Reynolds C. The Bypassing the Blues treatment protocol: stepped collaborative care for treating post-CABG depression. *Psychosom Med* 2009;71:217-30.
12. Davidson K, Bigger J, Burg M, Carney R, Chaplin W, Czajkowski S, *et al.* Centralized, stepped, patient preference-based treatment for patients with post-acute coronary syndrome depression: CODIACS vanguard randomized controlled trial. *J Am Med Assoc Intern Med* 2013;173:997-1004.
13. Huffman J, Mastromauro C, Beach S, Celano C, DuBois C, Healy B, *et al.* Collaborative care for depression and anxiety disorders in patients with recent cardiac events: the management of sadness and anxiety in cardiology (MOSAIC) randomized clinical trial. *J Am Med Assoc Intern Med* 2014;174:927-35.
14. Davidson K, Rieckmann N, Clemow L, Schwartz J, Shimbo D, Medina V, *et al.* Enhanced depression care for patients with acute coronary syndrome and persistent depressive symptoms; coronary psychosocial evaluation studies randomized controlled trial (COPES). *Arch Intern Med* 2010;170:600-8.
15. Huffman J, Mastromauro C, Sowden G, Wittmann C, Rodman R, Januzzi J.A collaborative care depression management program for cardiac inpatients: depression characteristics and in-hospital outcomes (SUCCEED). *Psychosomat* 2011;52:26-33.
16. De Jager T, Dulfer K, Radhoe S, Bergmann M, Daemen J, Van Domburg R, *et al.* Predictive value of depression and anxiety for long-term mortality: differences in outcome between acute coronary syndrome and stable angina pectoris. *Int J Cardiol* 2018;250:43-8.
17. Van Dijk M, Utens E, Dulfer K, Al-Qezweny M, van Geuns R, Daemen J, *et al.* Depression and anxiety symptoms as predictors of mortality in PCI patients at 10 y of follow-up. *Eur J Prev Cardiol* 2016;23:552-8.
18. Meyer T, Hussein S, Lange H, Herrmann Lingen C. Transient impact of baseline depression on mortality in patients with stable coronary heart disease during long-term follow-up. *Clin Res Cardiol* 2014;103:389-95.
19. Wang Z, Guo M, Si TM, Jiang M, Liu S, Liu Y, *et al.* Association of depression with adverse cardiovascular events after percutaneous coronary intervention. *Coronary Artery Dis* 2013;24:589-95.
20. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001;16:606-13.
21. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiat* 1961;4:561-71.
22. Snaith RP. The hospital anxiety and depression scale. *Health Qual Life Outcomes* 2003;1:29.
23. Sheehan DV, Lecrubier Y, Sheehan KH. The mini-international neuropsychiatric interview (M. I. N. I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiat* 1998;59 Suppl 20:22-57.
24. Ahmed M, Morrissey H, Ball PA. Mental ill-health and heart failure comorbidity. *Int J Curr Pharm Res* 2019;11:34931.